RĪGAS TEHNISKĀ UNIVERSITĀTE

Materiālzinātnes un lietišķās ķīmijas fakultāte

Organiskās ķīmijas tehnoloģijas institūts

Bioloģiski aktīvo savienojumu ķīmijas tehnoloģijas katedra

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mPGES-1 Inhibitoru dizains. Heteroaromātisko C–H saišu aminēšanas un oksidēšanas metožu izstrāde

Promocijas darbs

Zinātniskais vadītājs

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PROMOCIJAS DARBS
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APSTIPRINĀJUMS

Apstiprinu, ka esmu izstrādājis doto promocijas darbu, kas iesniegts izskatīšanai Rīgas Tehniskajā universitātē ķīmijas doktora grāda iegūšanai. Promocijas darbs nav iesniegts nevienā citā universitātē zinātniskā grāda iegūšanai.

Dmitrijs Lubriks …….(Paraksts)

Datums: ……

Promocijas darbs sagatavots kā vienots zinātnisko publikāciju un patentu kopums. To veido kopsavilkums, 3 publikācijas un 4 patenti.

SATURS

LIETOTIE SAĪSINĀJUMI

Å – angstrēms

AA – arahidonskābe

AcO – acetoksi-

Arg – arginīns

ArI – ariljodīds

Boc – *treš*-butoksikarbonil-

cPGES – citosola prostaglandīna sintāze

COX – ciklooksigenāze

EDCI – 1-(3-dimetilaminopropil)-3-etilkarbodiimīda hidrohlorīds

GSH – glutations

HSA – cilvēka seruma albumīns

IC_{50} – liganda koncentrācija, kas nodrošina enzīma aktivitātes 50% inhibēšanu

hWB – cilvēka pilnasins

LDA – litija diizopropilamīds

5-LO – 5-lipoksigenāze

LTA_4 – leikotriēns A_4

Me – metil

mPGES – mikrosomāla prostaglandīna sintāze

NPL – nesteroidālie pretiekaisuma līdzekļi

PGE_2 – Prostaglandīns E_2

PGF_{2a} – Prostaglandīns F_2

PGD_2 – Prostaglandīns D_2

PGH_2 – Prostaglandīns H_2

PGI_2 – Prostaglandīns I_2, Prostaciklīns

PLA_2 – Fosfolipāze A_2

Ph – fenil-

SAR – struktūras-aktivitātes likumsakarības

S_EAr – elektrofīlā aromātiskā aizvietošana

SEM – [2-(trimetilsilil)etoksi]metil–

SET – viena elektrona pārnese

QSAR – kvalitatīvās struktūras-aktivitātes kopsakarības

TXA_2 – Tromboksāns A_2

PROMOCIJAS DARBA VISPĀRĒJS RAKSTUROJUMS

1.1. Tēmas izklāsts, promocijas darba struktūra un apjoms

Farmaceitiskās industrijas, materiālzinātnes un citu starpdisciplināro zinātnes nozaru straujā attīstība pēdējās desmitgadēs ir būtiski ietekmējusi „tradicionālo" zinātnes nozaru pētījumu raksturu un virzienus. Tā, organiskajā ķīmijā pakāpeniski sāk dominēt pielietojama rakstura pētījumi, kuri vērsti uz citu, radniecīgo zinātnes nozaru problēmu risinājumiem. Tādējādi, līdztekus analītiskajai ķīmijai, arī organiskā ķīmija pakāpeniski pārvēršas par sava veida „instrumentu" jeb metodoloģiju kopumu starpdisciplināro zinātnes nozaru mērķu sasniegšanai. Piemēram, viens no svarīgākajiem organiskās ķīmijas pētījumu virzieniem ir jaunu sintēzes metodoloģiju izstrāde medicīnas ķīmijas, agroķīmijas un farmaceitiskās industrijas vajadzībām. Latvijā ķīmiski-farmaceitiskā nozare ir viens no prioritārajiem tautsaimniecības virzieniem, un tāpēc promocijas darbu izstrāde medicīnas ķīmijas jomā ir svarīgs ieguldījums nozares speciālistu sagatavošanā.

Promocijas darbu veido pielietojamo pētījumu kopums, un darbs veltīts medicīnas ķīmijas problēmu risināšanai. Viens no promocijas darbā iekļautajiem pētījumiem vērsts uz jauna darbības mehānisma nesteroidālo pretiekaisuma līdzekļu izstrādi, par farmakoloģisko mērķi izmantojot mikrosomālo prostaglandīna sintāzi 1 (mPGES-1). mPGES-1 sintāzes inhibitoru dizainā līdztekus tradicionālajiem struktūras-aktivitātes likumsakarību pētījumiem izmantota arī datormodelēšana. Farmakoforā datormodeļa izstrāde paātrināja potenciālo pretiekaisuma līdzekļu izstrādi, un darbs ir vainagojies ar vairākiem augsti efektīviem līdersavienojumiem tālākai virzībai *in vivo* pētījumos. Intelektuālais ieguldījums mPGES-1 inhibitoru izstrādē aizsargāts ar 4 starptautiskajiem patentiem.

Otrs promocijas darbā iekļautais pētījums vērsts uz jaunu organiskās sintēzes metožu izstrādi, kuras būtu piemērotas potenciālo zāļvielu struktūras modifikācijai sintēzes shēmas pēdējās stadijās. Strukturālās daudzveidības radīšana pētāmajā bāzes struktūrā sintēzes beigu posmā jeb t.s. „vēlīnā modifikācija" ievērojami paātrina struktūras-aktivitātes likumsakarību pētījumus un racionalizē sintētisko darbu. Promocijas darba ietvaros ir izstrādātas uz C-H saites aktivāciju balstītas aromātisko un heteroaromātisko savienojumu reģioselektīvas aminēšanas un oksidēšanas metodes. Metodes balstās uz viena reaktora secīgu reakciju virkni un iekļauj sākotnēju C-H saišu aktivāciju, izmantojot hipervalentos joda(III) savienojumus un tālāku λ^3-jodānu starpsavienojumu reakciju ar strukturāli daudzveidīgiem slāpekļa un skābekļa nukleofīliem. Izstrādātās metodes publicētas trijās zinātniskajās publikācijās.

Promocijas darbs sagatavots kā tematiski vienotu zinātnisko publikāciju un patentu kopums, un kopsavilkums sniedz paveiktā darba kopskatu. Publikācijas un patentu pieteikumi uzrakstīti angļu valodā.

1.2. Pētījuma mērķis un uzdevumi

Promocijas darbam ir divi savstarpēji saistīti **mērķi**:

1. plašas savienojumu bibliotēkas skrīninga rezultātā atrasto mPGES-1 sintāzes inhibitoru (*hit*) pārvērst par līdersavienojumu (*lead*) tā tālākai attīstībai par jauna darbības mehānisma nesteroidālo pretiekaisuma līdzekli;

2. izstrādāt jaunu sintēzes metodoloģiju potenciālo zāļvielu bāzes struktūras „vēlīnai modifikācijai". Sintēzes metodoloģijas izstrāde balstāma uz C–H saišu aktivācijas pieeju, kura neprasa bāzes struktūras iepriekšēju modifikāciju un ļauj veikt tiešu C–H saišu apmaiņu pret C–O un C–N saitēm.

Darba mērķu īstenošanai izvirzīti šādi **uzdevumi**:

1. sintezēt strukturāli daudzveidīgus aktīvā savienojuma (*hit*) analogus un uz to bāzes izstrādāt pirmās paaudzes mPGES-1 inhibitoru farmakoforo datormodeli;

2. uzlabot farmakoforo datormodeli un veikt struktūras –aktivitātes likumsakarību pētījumus;

3. izmantot optimizēto farmakoforo modeli virtuālo mPGES-1 inhibitoru aktivitātes prognozei; sintezēt prognozētos aktīvākos savienojumus un pārbaudīt to bioloģisko aktivitāti;

4. izstrādāt metodi elektroniem bagātu heteroaromātisko savienojumu reģioselektīvai C–H oksidēšanai, izmanojot hipervalentos joda(III) savienojumus;

5. izstrādāt metodi elektroniem bagātu heteroaromātisko savienojumu reģioselektīvai C–H azidēšanai un C–H aminēšanai, izmanojot hipervalentos joda(III) savienojumus un Cu(I) sāļu katalīzi.

1.3. Darba aprobācija un publikācijas

Promocijas darba rezultāti publicēti 4 PCT patentu pieteikumos un 3 zinātniskajos rakstos.

PCT patentu pieteikumi:

1. Doods, H.; Lubriks, D.; Arndt, K.; Roenn, R.; Stenkamp, D.; Klinder, K.; Kuelzer, R.; Mack, J.; Suna, E.; Pfau, R.; Pelcman, B.; Priepke, H. *3H-Imidazo[4,5-c]pyridine-6-carboxamides as anti-inflammatory agents.* WO 2010/100249 A1, September 10, 2010.

2. Priepke, H.; Doods, H.; Kuelzer, R.; Pfau R.; Stenkamp, D.; Pelcman, B.; Roenn, R.; Lubriks, D.; Suna, E. *2-(Arylamino)-3H-imidazo[4,5-b]pyridine-6-carboxamide derivatives and their use as mPGES-1 inhibitors.* WO 2012/022792 A1, February 23, 2012

3. Priepke, H.; Doods, H.; Kuelzer, R.; Pfau R.; Stenkamp, D.; Pelcman, B.; Roenn, R.; Lubriks, D.; Suna, E. *2-Aminobenzimidazole derivatives useful in the treatment of inflammation.* WO 2012/076672 A1, June 14, 2012.

4. Priepke, H.; Doods, H.; Kuelzer, R.; Pfau R.; Stenkamp, D.; Pelcman, B.; Roenn, R.; Lubriks, D.; Suna, E. *Imidazo[4,5-b]pyridine-6-carboxamides as anti-inflammatory agents.* WO 2012/076674 A1, June 14, 2012.

Zinātniskie raksti:

1. Lubriks, D.; Sokolovs, I.; Suna, E. Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles. *Org. Lett*. **2011**, *13*, 4324–4327.

2. Lubriks, D.; Sokolovs, I.; Suna, E. Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes. *J. Am. Chem. Soc.* **2012**, *134*, 15436-15442.

3. Sokolovs, I.; Lubriks, D.; Suna, E. Copper-Catalyzed Intermolecular C-H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes. *J. Am. Chem. Soc.* **2014**, *136*, 6920–6928.

PROMOCIJAS DARBA GALVENIE REZULTĀTI

2.1. Mikrosomālās prostaglandīna sintāzes 1 (mPGES-1) inhibitoru izstrāde

2004. Gadā aptiekas pārtrauca tirgot vairākus pretiekaisuma līdzekļus, piemēram, rofekoksibu, jo šī preparāta ilgstoša lietošana daudziem pacientiem izraisīja smagas, bieži pat letālas kardiovaskulāras komplikācijas. Jāatzīmē, ka rofekoksiba pārdošanas apjomi 2003. gadā sasniedza 2,5 miljardus ASV dolāru, liecinot par pretiekaisuma līdzekļu augsto pieprasījumu. Lai aizstātu no pārdošanas atsauktos preparātus, daudzas pasaules vadošās farmaceitiskās kompānijas uzsāka jaunas darbības mehānisma pretiekaisuma līdzekļu izstrādes pētījumus.

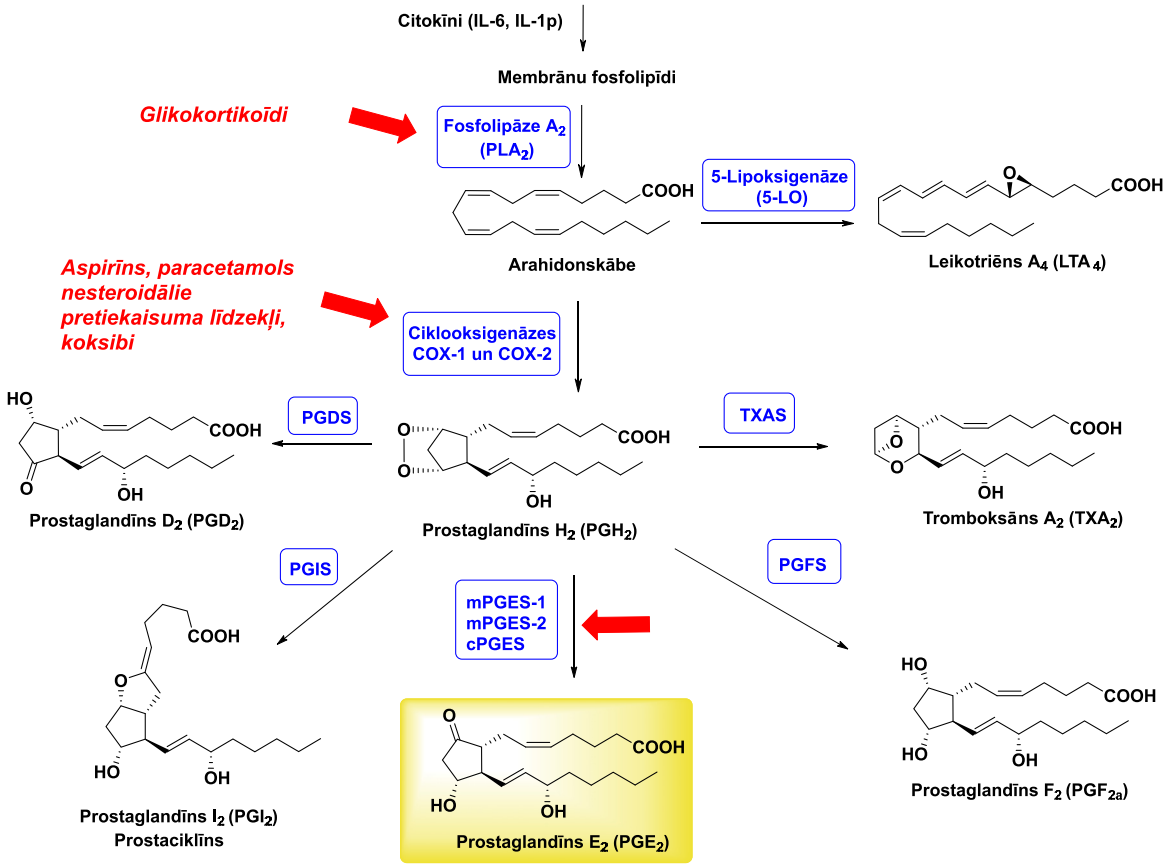
2.1.1. Arahidonskābes metabolisms

Vairumam no mūsdienās lietotajām nenarkotiskajām pretiekaisuma, pretdrudža un pretsāpju zāļvielām farmakoloģiskās darbības mehānisms ir saistīts ar prostaglandīna PGE_2 veidošanās inhibēšanu. Prostaglandīns PGE_2 ir nepiesātinātās taukskābes – arahidonskābes (AA) metabolīts, kurš audos pastiprināti veidojas dažādu kaitīgu faktoru (mehānisku, ķīmisku, termisku, neirālu vai humorālu) ietekmē. Prostaglandīna PGE_2 uzkrāšanās audos ir saistīta arī ar sāpju rašanos, jo PGE_2 paaugstina nociceptoru (sāpju receptoru) jutību pret kairinātājiem, līdz ar to izsaucot hiperalgēziju. PGE_2 Ietekmē notiek arī asinsvadu paplašināšanās, palielinās kapilāru sieniņu caurlaidība, un rodas tūska – pazīmes, kuras raksturīgas iekaisumam.[1] Tādēļ prostaglandīnu PGE_2 uzskata par iekaisuma mediatoru.

Prostaglandīna PGE_2 veidošanos principā iespējams kavēt dažādos arahidonskābes metabolisma posmos (1. att.). Piemēram, glikokortikoīdi (prednizolons, metilprednizalons 2. att.) ar proteīna lipokortīna-1 starpniecību bloķē Fosfolipāzi A_2 (PLA_2), tādējādi kavējot pašas arahidonskābes veidošanos. Vairums zāļvielu tomēr ir mērķētas uz ciklooksigenāžu, sevišķi iekaisuma jeb inducējamā izoenzīma COX-2 inhibēšanu (aspirīns, paracetamols, nesteroidālie pretiekaisuma līdzekļi (NPL), piemēram, *ibuprofēns*, *diklofenaks* kā arī t.s. koksibi – *celekoksibs* un *rofekoksibs*; sk. 2. att.). Interesanti, ka COX-2 darbojas kā mPGES-1 kokatalizators un mediators. Normālos fizioloģiskos apstākļos mPGES-1 līmenis ir ļoti zems. Turpretim, paaugstinoties COX-2 koncentrācijai, attiecīgi palielinās arī mPGES-1 koncentrācija, kas nodrošina strauju PGE_2 veidošanos.

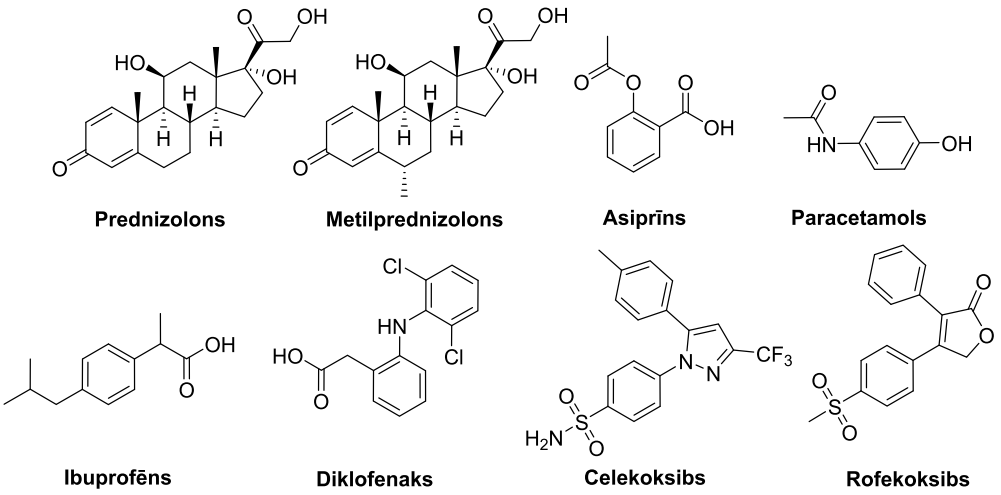
Būtiski, ka praktiski visām līdz šim lietotajām pretiekaisuma zāļvielām raksturīgas ievērojamas blaknes. To cēlonis ir citu arahidonskābes metabolītu – leikotriēnu (LTA_4), tromboksāna (TXA_2) un pārējo prostaglandīnu (PGF_{2a}, PGD_2 un PGI_2) biosintēzes inhibēšana. Arahidonskābes metabolīti ir bioregulatori daudzos fizioloģiski svarīgos procesos. Tie ietekmē sirds-asinsvadu, gremošanas, elpošanas un reproduktīvo sistēmu, un to biosintēzes kavēšana var

izraisīt nevēlamas fizioloģiskas sekas. Interesanti, ka arahidonskābes metabolītiem bieži ir pretēji fizioloģiskie efekti. Tromboksāns A_2 (TXA_2) sašaurina asinsvadu sieniņas un paaugstina arteriālo spiedienu, bet prostaglandīns I_2 (PGI_2) izraisa pretējo efektu – paplašina asinsvadus. TXA_2 un PGI_2 antagonistiskie efekti izpaužas arī iedarbībā uz asins sarecēšanu: TXA_2 ir spēcīgs trombocītu agregācijas induktors, bet PGI_2 kavē trombocītu agregāciju un adhēziju. Līdzīgi, prostaglandīni $PGF_{2\alpha}$ un PGD_2 izraisa bronhu sašaurināšanos, bet prostaglandīnam PGE_2 raksturīgs bronholītiskais efekts.



1. att. Arahidonskābes metabolisms

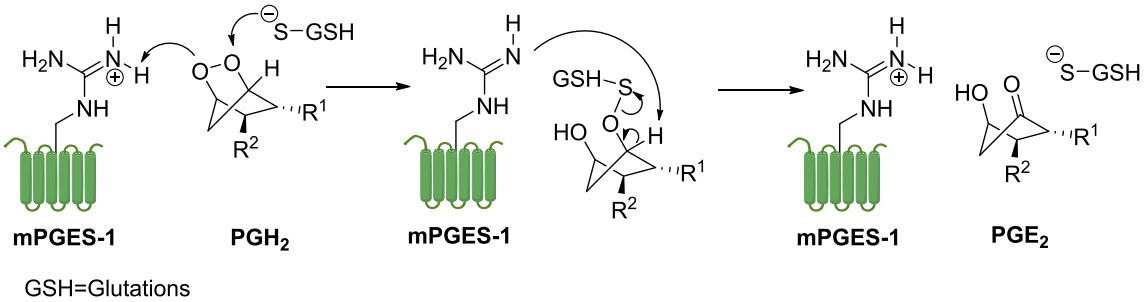
Ar prostaglandīna PGE_2 biosintēzes neselektīvo inhibēšanu saistītās blaknes ir bijušas par cēloni vairāku plaši lietotu pretiekaisuma un pretsāpju zāļvielu atsaukšanai no tirgus. Piemēram, 2004. gadā aptiekas pārtrauca tirgot COX-2 inhibitoru rofekoksibu, jo daudziem pacientiem šī preparāta ilgstoša lietošana izraisīja smagas, bieži pat letālas kardiovaskulāras komplikācijas.



2. att. Reprezentatīvi pretiekaisuma līdzekļi

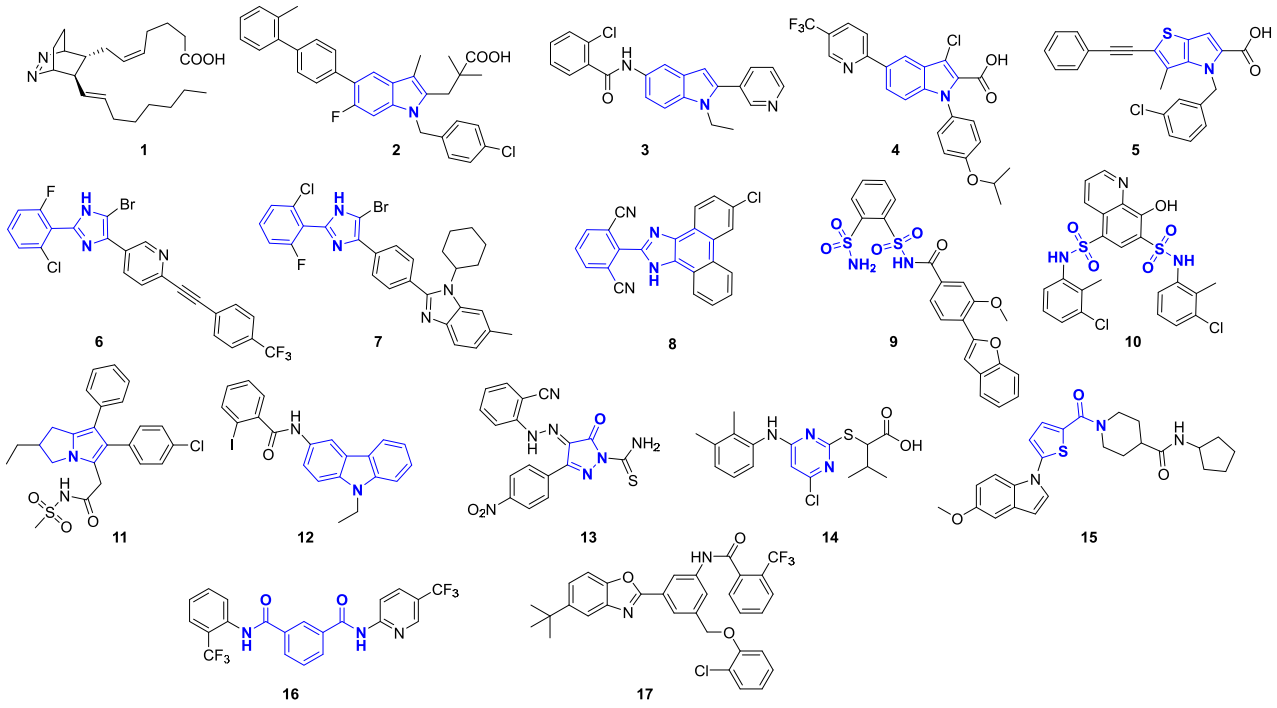
Arahidonskābes metabolisma kaskādes analīze (1. att.) rāda, ka iekaisuma mediatora PGE_2 biosintēzi var inhibēt selektīvi, iedarbojoties uz mPGES-1. PGES Fermentu grupu veido citosolā lokalizētais ferments cPGES un membrānsaistītie proteīni mPGES-1 un mPGES-2, kuri katalizē PGH_2 pārvēršanu par PGE_2. Jāatzīmē, ka cPGES un mPGES-2 ir pastāvīgi funkcionējošie enzīmi, kuri nodrošina homeostatisko PGE_2 līmeni. Turpretī mPGES-1 sintāze ir inducējamais enzīms, kura pastiprinātu ekspresiju izraisa COX-2 līmeņa paaugstināšanās iekaisuma faktoru ietekmē.[2] Tāpēc mPGES-1 ir piemērots terapeitiskais mērķis pretiekaisuma, pretdrudža un pretsāpju zāļvielu izstrādei.[3]

Cilvēka mPGES-1 sintāzes un glutationa (GSH) kompleksa struktūra ir noteikta ar rentgenstruktūras difrakcijas metodi (3.5 Å izšķirtspēja).[4] Cilvēka mPGES-1 sastāv no 3 vienādām subvienībām, un katru subvienību veido 4 transmembrānas spirāles. Kompleksa uzbūves noskaidrošana ļāva izprast mPGES-1 lomu PGH_2 pārvērtībā par PGE_2. Tā, sākotnēji notiek GSH tiolāta anjona uzbrukums PGH_2 endoperoksīda C–9 skābeklim. Uzbrukumam seko protona pārnese no mPGES-1 sintāzes (Arg–126) uz C-11 skābekli, un veidojas hidroksilgrupa. Kaskādes reakcijas noslēgumā mPGES-1 sintāze (Arg–126) deprotonē C–9 oglekli, veidojot ketonu un reģenerējot GSH tiolāta anjonu (3. att.).[4]



3. att. Postulētais mPGES-1 katalizētas PGE_2 veidošanās mehānisms

Uz PGE_2 biosintēzes mehānismu tika balstīts vairāku mPGES-1 inhibitoru dizains. Piemēram, prostaglandīnam PGH_2 strukturāli līdzīgajā modificētajā taukskābē **1** peroksīda cikls aizstāts ar biciklu (4. att.).[5] Tomēr lielākajai daļai no mPGES-1 inhibitoriem nav acīmredzamas strukturālas līdzības ar endogēno substrātu PGH_2. Starp visplašāk sastopamajiem mPGES-1 inhibitoru struktūrelementiem jāatzīmē indola un tam radniecīgā tienopirola heterocikli (Kanādas firmas *Merck Frosst* radītais indola atvasinājums **2**,[6] Itālijas uzņēmumā *Aziende Chimiche Riunite* izstrādātais savienojums **3**,[7] Zviedrijas uzņēmuma *Biolipox(Orexo)* un Latvijas OSI kopīgi izstrādātie indols **4**[8] un tienopirols **5**),[9] 2-arilimidazoli un 2-arilbenzimidazoli (imidazols **6**,[10] Vācijas uzņēmuma *Boeringer-Ingelheim* radītais diarilimidazola atvasinājums **7**,[11] benzimidazols **8**[12]), kā arī sulfonamīda funkcionālo grupu saturoši mPGES-1 inhibitori (Zviedrijas uzņēmumā *ASTRA ZENECA* izstrādātais bis-sulfonamīds **9**[13] un *Biolipox(Orexo)/LOSI* radītais bis-sulfonamīds **10**).[14] Starp patentētajiem mPGES-1 inhibitoriem jāpiemin arī trešajā klīnisko pētījumu fāzē esošais *licofelons* **11**,[15] karbazola atvasinājums **12**,[16] 2,4-dihidro-pirazolons **13**,[17] pirimidīna atvasinājums **14**,[18] tienilkarbonskābes amīds **15**,[19] Zviedrijas kompānijas *NOVA-SAID* izstrādātais izoftalskābes diamīds **16**[20] un benzoksazols **17**[21] (4. att.).



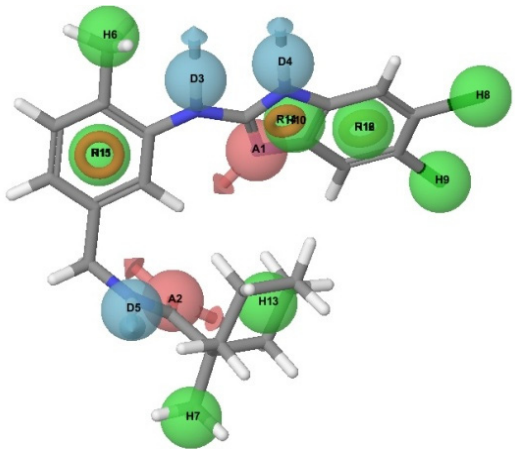
4. att. Patentētie mPGES-1 inhibitori

2.1.2. Farmakoforais modelis

Lai paātrinātu zāļvielu izstrādi un paaugstinātu sintēzes darba mērķtiecību, medicīnas ķīmijā plaši izmanto datormodelēšanu. Datormodeļi ļauj kvantitatīvi paredzēt ķīmisko savienojumu un mērķproteīna saistības efektivitāti un sniedz informāciju par mērķproteīna–liganda mijiedarbības telpiskajiem, fizikālajiem un ķīmiskajām raksturlielumiem. Datormodeļu izstrādei visbiežāk

izmanto savienojuma receptorsaistības (aktivitātes) raksturlielumus, kurus korelē ar savienojuma trīsdimensiju struktūru vai specifiski izvēlētiem struktūrelementiem, izmantojot matemātiko statistiku. Šādi iegūst t.s. kvalitatīvos struktūras-aktivitātes kopsakarību (*Quantitative Structure-Activity Relationship* jeb *QSAR*) modeļus. QSAR apzīmējums bieži tiek lietots plašākā nozīmē, ar to apzīmējot jebkuru „struktūras-īpašības" modeli. Starp plašāk lietotajiem QSAR modeļiem ir t.s. farmakoforie modeļi, kuri īpaši noderīgi nenoskaidrotas struktūras mērķproteīnu gadījumā.

Farmakoforā modeļa strukturelements ir farmakofors – zāļvielas fragments vai funkcionālā grupa, kura nodrošina receptorsaistību. Piemēram, farmakofors var būt spirta vai amīna funkcionālā grupa, aromātiskais cikls vai karboksilāta anjons. Katra farmakofora (un arī zāļvielu molekulas) stēriskās un elektroniskās īpašības apraksta ar deskriptoriem. Deskriptors ir, piemēram, ūdeņraža saites donora vai akceptora veidošanās virziens, hidrofobās virsmas laukums, aizvietotāja dipolmomenta vērsums, lādiņš, rezonanses formas, aromātiskās π-sistēmas esamība u.c. funkcijas. Vienam farmakoforam parasti cenšas atrast pēc iespējas vairāk dažādu deskriptoru, lai ar matemātiskās analīzes palīdzību atrastu visām analizējamajām zāļvielu molekulām kopīgos deskriptorus. Piemēram, aromātiskā π-sistēmas esamība ir deskriptors. Tomēr zināms, ka aromātiskiem gredzeniem piemīt hidrofobas īpašības, tādēļ aromātiskajos gredzenos kā papildus deskriptors tiek izmantota hidrofobā virsma (5. att.).



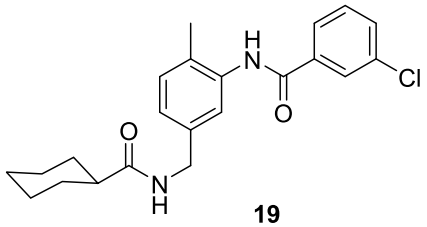
5. att. Farmakoforais modelis (aromātiskiem gredzeniem pievieno hidrofobo īpašību; zaļas-hidrofobas, sarkanas-protonu akceptoras, zilas-protonu donoras īpašības, oranžas-aromātiskā π-sistēmas esamība)

Farmakofora modeli parasti ģenerē, izmantojot ligandu kopumu ar eksperimentāli iepriekš noteiktu afinitāti pret mērķproteīnu. Viss ligandu kopums tiek nejaušā kārtībā sadalīts divās grupās: darba grupā un testa grupā (*training set*). Grupas var būt gan skaitliski vienādas, gan atšķirīgas. Darba grupu izmanto, lai izveidotu farmakoforo modeli, bet testa grupu – lai pārbaudītu izveidotā modeļa spēju prognozēt afinitāti. Sākotnēji katrai darba grupas molekulai tiek aprēķinātas zemākās enerģijas konformācijas, kuras pieņem par bioaktīvajām konformācijām. Turpmākā modeļa izstrādes mērķis ir atrast pēc iespējas vairāk deskriptorus, kuri raksturīgi visiem *aktīvajiem*

ligandiem, bet iztrūkst visām darba grupas *neaktīvajām* molekulām. Modeļa izstrādes gaitā tiek ģenerētas daudzas farmakoforu modeļu hipotēzes, kuru precizitātes pārbaudei izmanto testa grupu. Vislabākās farmakoforā modeļa hipotēzes spēj pareizi prognozēt testa grupā esošo molekulu saistības afinitāti 70-85% gadījumos, un tas ir ļoti labs rādītājs. Izveidoto farmakoforo modeli tālāk pielieto, lai prognozētu konstruējamo ligandu saistības afinitāti.

2.1.3. mPGES-1 Inhibitoru struktūras-aktivitātes likumsakarību pētījumi. Pirmās paaudzes farmakoforais modelis

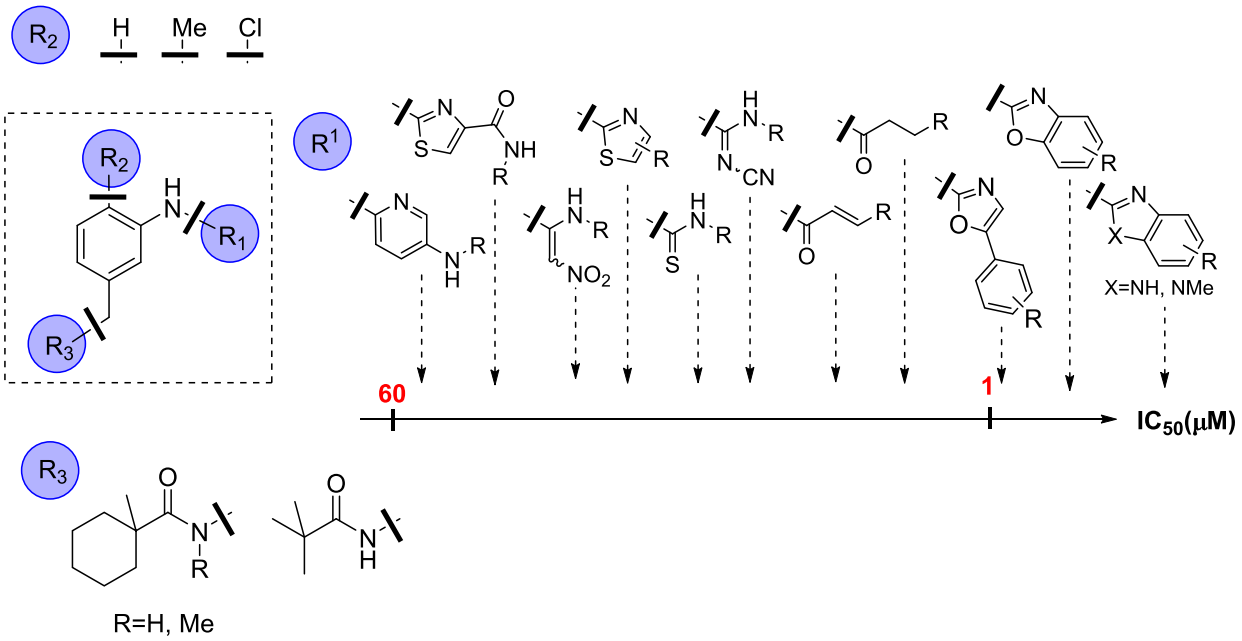
Jaunu patentspējīgu mPGES-1 inhibitoru izstrādes programmas pamatā bija plašas savienojumu bibliotēkas (~ 2 milj. individuālu ķīmisko vielu) skrīninga rezultātā atrasts aktīvs savienojums (*hit*) – acilēts aminometilanilīns **19** ar IC_{50}=832 mM inhibējošo aktivitāti pret mPGES-1 (6. att.). Augstas caurlaides spējas skrīnings tika veikts Vācijas uzņēmumā *Boehringer Ingelheim*. Lai atvieglotu un paātrinātu jaunu mPGES-1 inhibitoru izstrādi un paaugstinātu sintēzes darba mērķtiecību, aktīvā savienojuma attīstīšanai par t.s. „līdersavienojumu" jeb „*hit-to-lead*" programmai nolēmām pielietot kompleksu pieeju: tradicionālos struktūras-aktivitātes likumsakarību (SAR) pētījumus apvienojām ar datormodelēšanu. Tā kā darba uzsākšanas brīdī trūka informācijas par savienojuma **19** saistības vietu ar enzīmu, kā arī par mPGES-1 un liganda-enzīma kompleksa uzbūvi, no plašā QSAR datormodeļu klāsta izvēlējāmies farmakoforo modelēšanu, kura īpaši noderīga nenoskaidrotas struktūras mērķproteīnu gadījumā. Farmakofora modeļa izmantošana ļauj prognozēt inhibējošo aktivitāti un sniegt informāciju par enzīma–liganda mijiedarbību.



19

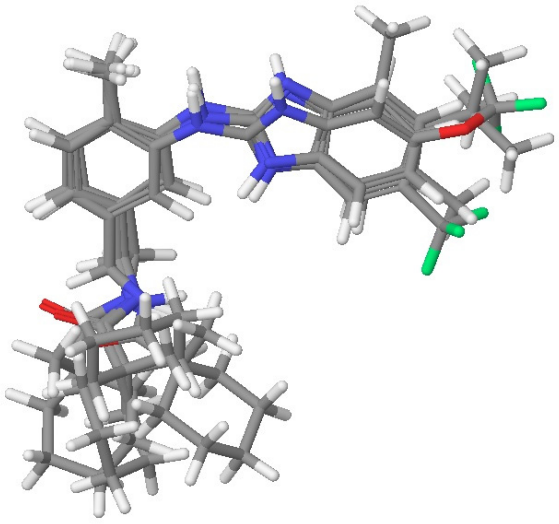
6. att. Savienojumu bibliotēkas aktivitātes pārbaudē atrastais aktīvais savienojums **19**

Farmakoforā modeļa izstrādei nepieciešams strukturāli daudzveidīgs ligandu klāsts ar eksperimentāli noteiktu katra liganda afinitāti pret mērķproteīnu. Tādēļ sākotnēji sintezējām plašu liganda **19** analogu klāstu ar dažādiem aizvietotājiem R^1, R^2 un R^3 centrālajā gredzenā. Kopumā sintezējām 120 savienojumus, kuriem noteiktā inhibējošā aktivitāte pret mPGES-1 bija robežās no IC_{50}=1 μM līdz pat IC_{50}=60 μM. Visaktīvākie ligandi ar submikromolāro inhibējošo koncentrāciju saturēja 2-aminooksazola, 2-aminobenzoksazola un 2-aminobenzimidazola struktūrelementus (7. att.).



7. att. Farmakoforā modeļa izveidei un sākotnējiem SAR pētījumiem sintezētie savienojumi

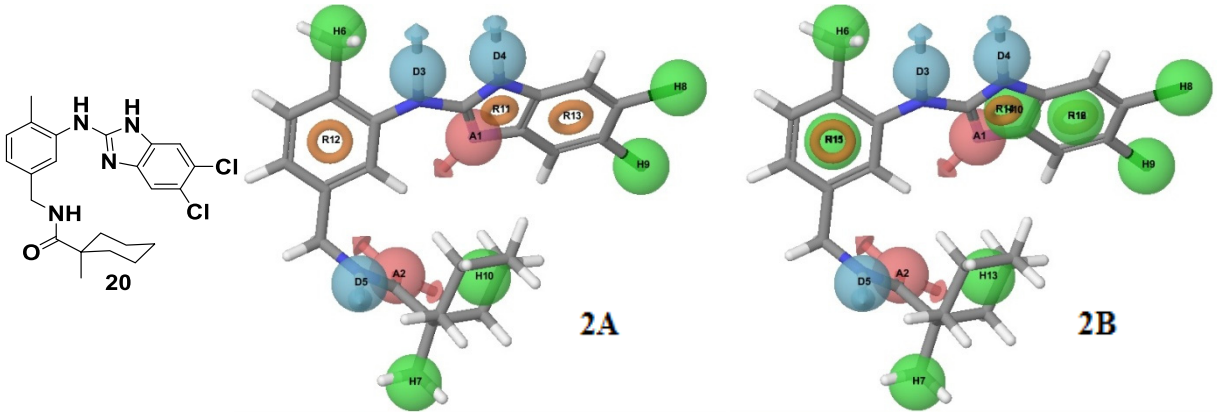
No sintezētā 120 savienojumu klāsta 60 savienojumi bija neaktīvi (IC_{50}>10 μM), 35 savienojumiem piemita vidēja inhibējošā aktivitāte (IC_{50} robežās no 1 līdz 10 μM), bet 25 ligandi bija aktīvi, jo to inhibējošā aktivitāte bija zemāka par 1 μM. Farmakoforā modeļa darba datubāzes izveidei izvēlējāmies 15 visaktīvākās struktūras un 15 visneaktīvākās. Ar *Schroedinger Suite 2012* programmu izvēlētajiem 30 savienojumiem aprēķinājām zemākās enerģijas konformācijas un veicām aprēķināto struktūru savietošanu, izmantojot *Schroedinger* programmu paketē iebūvēto *Maestro 9.3* superpozīcijas funkciju (8. att.).



8. att. Vairāku darba datubāzes struktūru superpozīcija

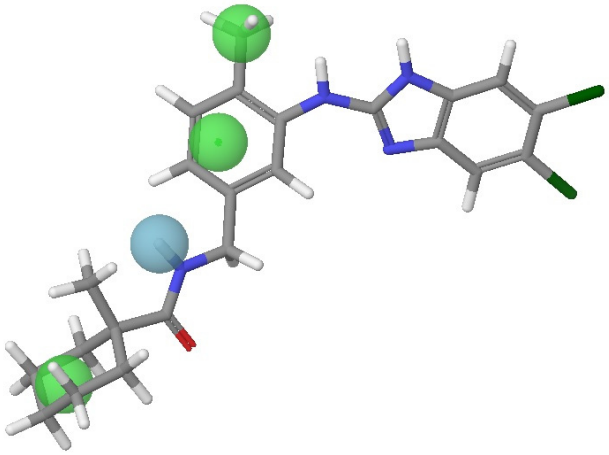
Tālāk, izmantojot *Phase* 3.7 moduli, katram savienojumam atradām farmakoforus, kuru īpašības aprakstam izmantojām deskriptorus (9. att.; ligandam **20** automātiski ģenerētais deskriptoru komplekts attēlots struktūrā **2A**). *Phase* modulī iebūvētais deskriptoru redaktors ļauj mainīt gan

programmas ģenerētos deskriptorus, gan arī pievienot jaunus. Aromātiskiem gredzeniem piemīt hidrofobās īpašības, un, lai uzlabotu aromātiska gredzena farmakofora efektivitāti, tā raksturošanai pievienojam hidrofobitāti kā jaunu deskriptoru (9. att., struktūra **2B**). Pēc darba datubāzes skenēšanas ieguvām jaunu datubāzi ar savienojumu farmakoforiem un to deskriptoriem.



9. att. Ligandam **20** atrastie deskriptori (zaļa krāsa–hidrofobitāte, sarkanā–protonu akceptors, zilā–protonu donors, oranžā-aromātiskā π-sistēma)

Pēc farmakoforu deskriptoru ģenerēšanas veicām statistiskos aprēķinus, lai atrastu pēc iespējas vairāk deskriptorus, kuri raksturīgi visiem *aktīvajiem* ligandiem, bet iztrūkst visām *neaktīvajām* molekulām. Modeļa izstrādes gaitā tika ģenerētas 240 farmakoforā modeļa hipotēzes. Tālāk modeļu hipotēzēm pārbaudījām spēju prognozēt savienojumu aktivitāti, proti, spēju sadalīt visus 120 sintezētos savienojumus 3 grupās: aktīvajos, vidēji aktīvajos un neaktīvajos savienojumos. Jo lielāks ir aktīvo savienojumu skaits, kuriem farmakoforu īpašības (rādiuss, vektors, tilpums) sakrīt ar analizējamā modeļa attiecīgo farmakoforu īpašībām un jo mazāka ir vidējā kvadrātiskā novirze no modeļa, jo labāks ir modelis. Pārbaudes rezultātā nonācām pie farmakoforā modeļa, kurš balstās uz četriem farmakoforajiem punktiem: vienu ūdeņraža saites donoru un trijām hidrofobā tipa mijiedarbībām (10. att.). Atrastais farmakofora modelis sintezēto 120 savienojumu klāstā identificēja visus 25 aktīvos savienojumus, tos atlasot no neaktīvajiem un vidēji aktīvajiem. Tomēr modelis nepareizi prognozēja 17 vidējās aktivitātes savienojumus un 5 neaktīvos savienojumus.

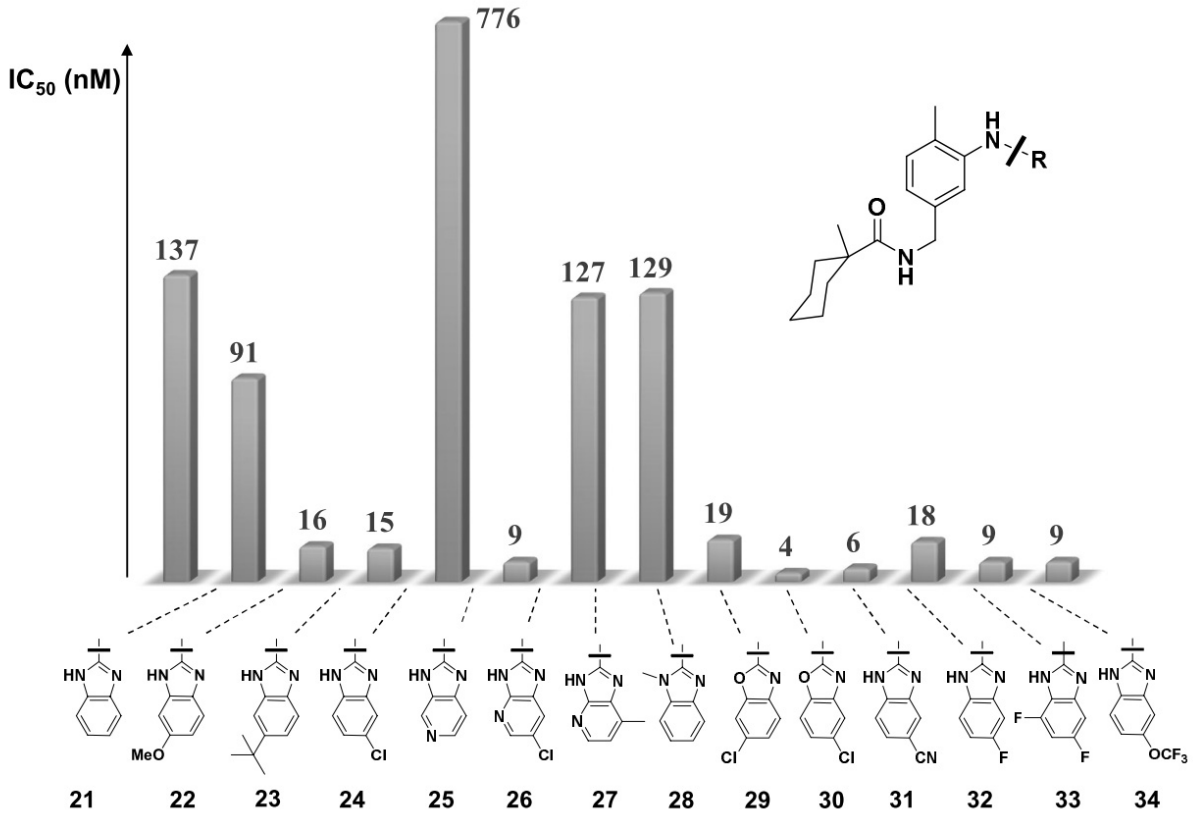


10. att. Pirmās paaudzes farmakoforais modelis

2.1.4. Otrās paaudzes farmakoforā modeļa izstrāde

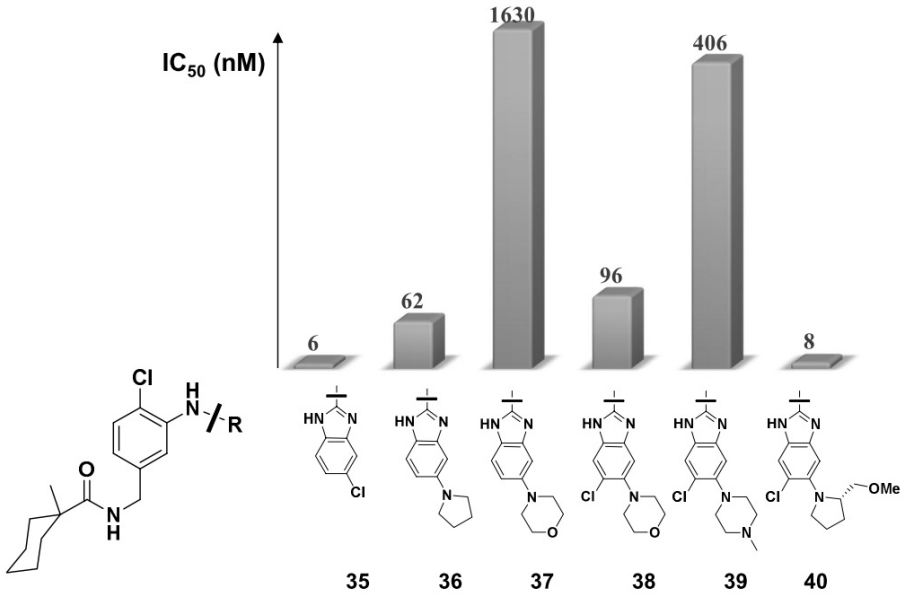
Izveidotā farmakoforā modeļa precizitātes uzlabošanai nolēmām ieviest papildus farmakoforus. Modeļa pilnveidošana ļautu precīzāk atlasīt neaktīvus un vidēji aktīvus ligandus. Jaunu farmakoforu identificēšana būtu jāveic heterocikla (benzimidazola, benzoksazola) daļā, kurā acīmredzami trūkst farmakoforo punktu (10. att.). Turklāt SAR likumsakarību analīze liecina, ka 2-aminobenzimidazola vai 2-aminobenzoksazola struktūrelementa ievadīšana ļauj iegūt mPGES-1 inhibitorus ar submikromolāru aktivitāti (7. att.). Tādēļ turpmākajā pētījumu posmā pievērsāmies benzazolu heterociklus saturošu ligandu sintēzei.

Sintezējot virkni 2-aminobenzimidazolu **21-34**, noskaidrojām, ka lipofīlu aizvietotāju ievadīšana benzimidazola 5. stāvoklī heterociklā uzlaboja mPGES-1 inhibējošo aktivitāti (savienojumi **23-24**, **32-34** salīdzinājumā ar neaizvietoto benzimidazolu **21**; sk. 11. att). Polārā slāpekļa atoma ievadīšana benzimidazola 5. pozīcijā samazināja inhibējošo aktivitāti (savienojums **25**), bet benzimidazoli ar slāpekļa atomu 4. pozīcijā saglabāja augsto inhibējošo aktivitāti (savienojums **26**, 11. att.). Noskaidrojām, ka ūdeņraža saites donora klātbūtne benzimidazola fragamentā neietekmē inhibējošo aktivitāti, kura *N*-H benzimidazoliem **21**, **24** un to struktūranalogiem – *N*-metilbenzimidazolam **28** un benzoksazoliem **29-30** praktiski ir vienāda.



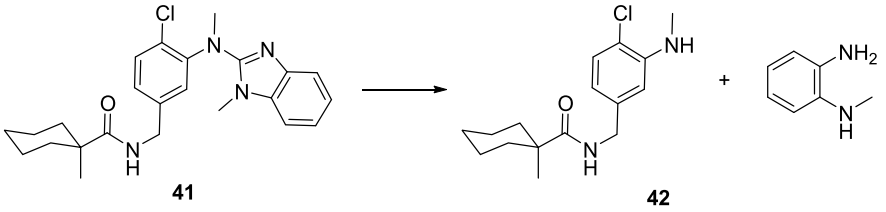
11. att. mPGES-1 inhibitoru struktūras-aktivitātes likumsakarības benzazolu **21-34** rindā

Telpiski lielāku lipofīlo aizvietotāju ievadīšana benzimidazolā kopumā saglabāja augsto inhibējošo aktivitāti (savienojumi **36**, **40**), liecinot par to, ka benzimidazolu 5. un 6. pozīcijas apgabalā enzīmā aktīvajā centrā ir salīdzinoši liela telpiskā brīvība (11. att.). Polārie heteroatomi ievērojami samazina inhibējošo aktivitāti (savienojumi **37**, **39** salīdzinot ar **36**, **38** un **40**), kas liecina par šajā apgabalā dominējošo lipofīlo sadabību starp ligandu un mPGES-1.



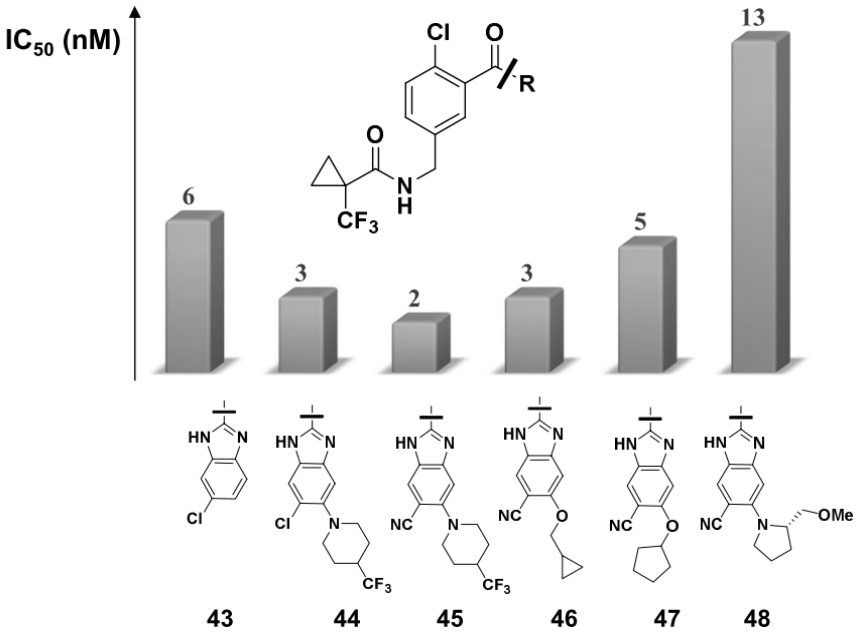
12. att. mPGES-1 inhibitoru struktūras-aktivitātes likumsakarības aminobenzimidazolu **35-40** rindā

Saskaņā ar pirmās paaudzes farmakoforā modeļa hipotēzi (10. att.) slāpekļa atoma tiltiņš starp centrālo benzola gredzenu un benzimidazola heterociklu nav farmakoforais elements, un tāpēc tā aizvietojuma pakāpei nebūtu jāietekmē mPGES-1 inhibējošā aktivitāte. Lai pārbaudītu farmakoforā modeļa pareizību, otrējo amīna grupu tiltiņā nolēmām aizstāt ar trešējo amīna grupu, kā arī ar ketogrupu. Diemžēl sintezētais trešējais amīns **41** izrādījās ārkārtīgi nestabils, un reakcijā ar gaisa mitrumu tas spontāni sadalījās par *N*-metilanilīnu **42** un *N*-metilfenilēndiamīnu (13. att.).



13. att. Aminobenzimidazola **41** sadalīšanās

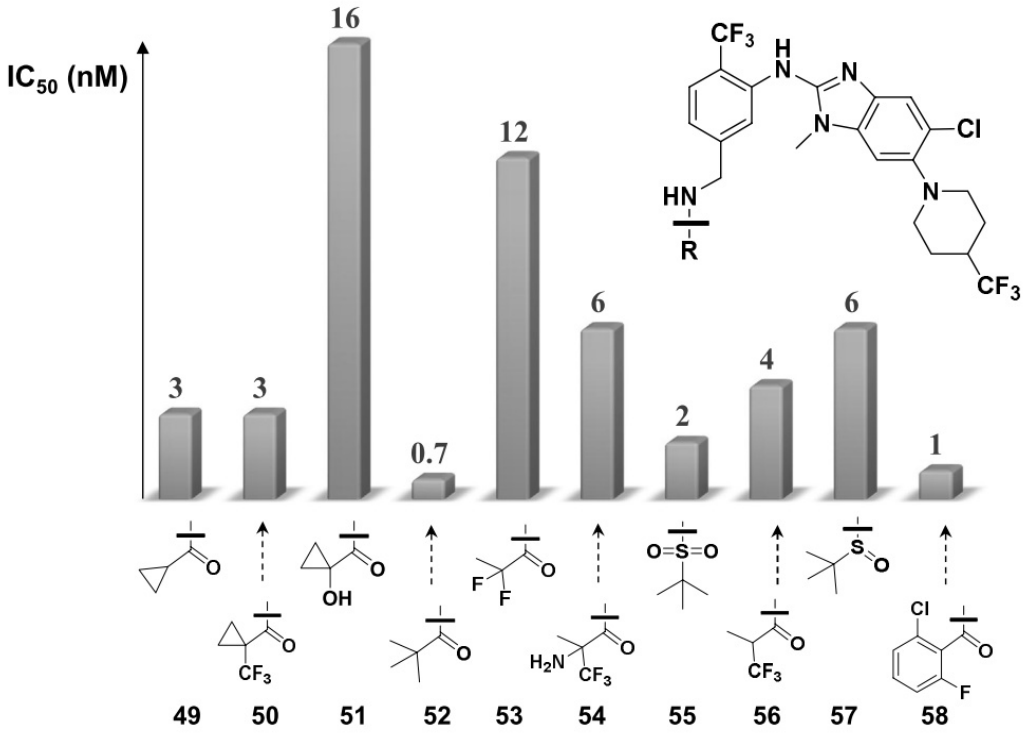
Savukārt ketogrupas tiltiņu saturošie savienojumi ir stabili, turklāt tie nodrošina nanomolārā līmeņa inhibēšanas aktivitāti (14. att.), kas apstiprina 1. paaudzes farmakoforā modeļa pareizību: tiltiņš starp centrālo gredzenu un benzimidazola fragmentu nenodrošina receptorsaistību un, tātad, nav farmakoforais elements. Aktīvākie sērijas savienojumi satur izteikti lipofīlus aizvietotājus benzimidazola gredzenā **43-48** (14. att.).



14. att. Ketoatvasinājumu **43-48** mPGES-1 inhibitorā aktivitāte

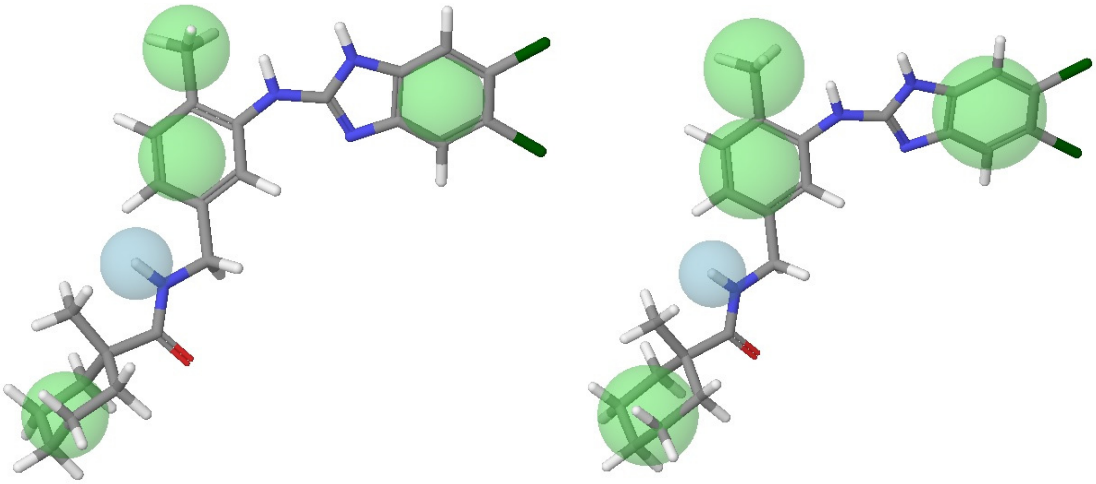
Diemžēl vairumam ketoatvasinājumu (14. att.) piemīt zema *in vitro* metaboliska stabilitāte ($t_{1/2}$ no 2 līdz 15 minūtēm), tāpēc ketogrupu saturošie inhibitori tālākajos pētījumos netika izmantoti. Zema metaboliskā stabilitāte raksturīga arī vairākiem aminobenzimidazola atvasinājumiem, piemēram, savienojumiem **26** ($t_{1/2}$=1 min), **30** ($t_{1/2}$=7 min), **31** ($t_{1/2}$=5 min), **34**

($t_{1/2}$=6 min), **35** ($t_{1/2}$=7 min), **40** ($t_{1/2}$=7 min) un **43** ($t_{1/2}$=4 min). Tika noskaidrots, ka zemā metaboliskā stabilitāte saistīta ar 1-metilcikloheksilgrupas oksidēšanos. Aktīvākie no sintezētajiem 1-metilcikloheksilgrupas analogiem **49-58** ar paaugstinātu metabolisko stabilitāti ir parādīti 15. attēlā.



15. att. mPGES-1 inhibitori **49-58** ar paaugstinātu metabolisko stabilitāti

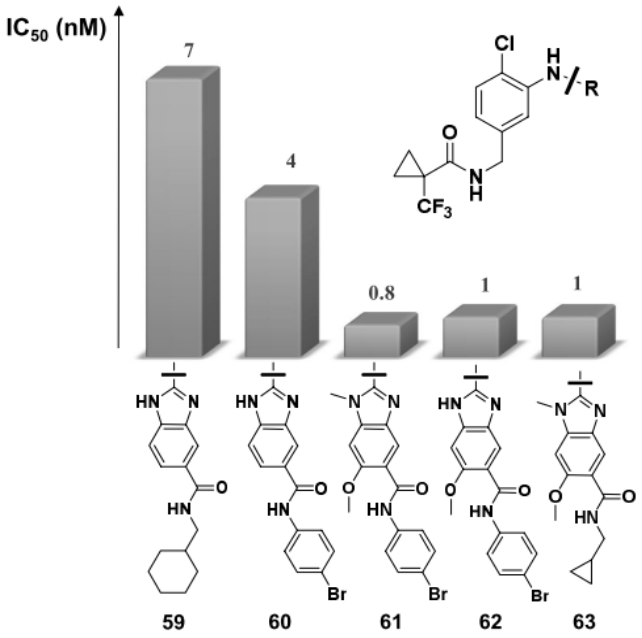
Pirmās paaudzes farmakoforā modeļa optimizācijai tika izmantoti visi papildus sintezētie mPGES-1 inhibitori, kopskaitā vairāk nekā 180 savienojumu. Pēc papildus farmakoforu deskriptoru ģenerēšanas un statistiskajiem aprēķiniem ieguvām 35 farmakoforā modeļa hipotēzes. No tām par otrās paaudzes farmakoforo modeli tika izvēlēta hipotēze ar 5 farmakoforiem: vienu ūdeņraža saites donoru un četrām hidrofobām mijiedarbībām (16. att.). Otrās paaudzes modelis spēja ievērojami precīzāk atlasīt aktīvākus savienojumus no neaktīviem, tomēr 4 vidēji aktīvi un 1 neaktīvs savienojums tika prognozēti kļūdaini. Farmakoforā modeļa tālākai uzlabošanai izvēlējāmies nesarežģīt modeli ar papildus farmakoforiem, bet izmainīt esošo farmakoforu sfēru rādiusus. Pārbaudot dažādus farmakoforu sfēru rādiusus, atradām, ka lipofīlo farmakaforu rādiusu palielināšana par 0.3 Å (no 1.0Å uz 1.3Å) un neliela attālumu izmainīšana starp farmakoforiem ļāva izveidot modeli, kurš veiksmīgi un gandrīz kvantitatīvi spēj atlasīt aktīvus savienojumus no neaktīvajiem un vidēji aktīvajiem (16. att.).



16. att. mPGES-1 inhibitoru otrās paaudzes farmakoforais modelis

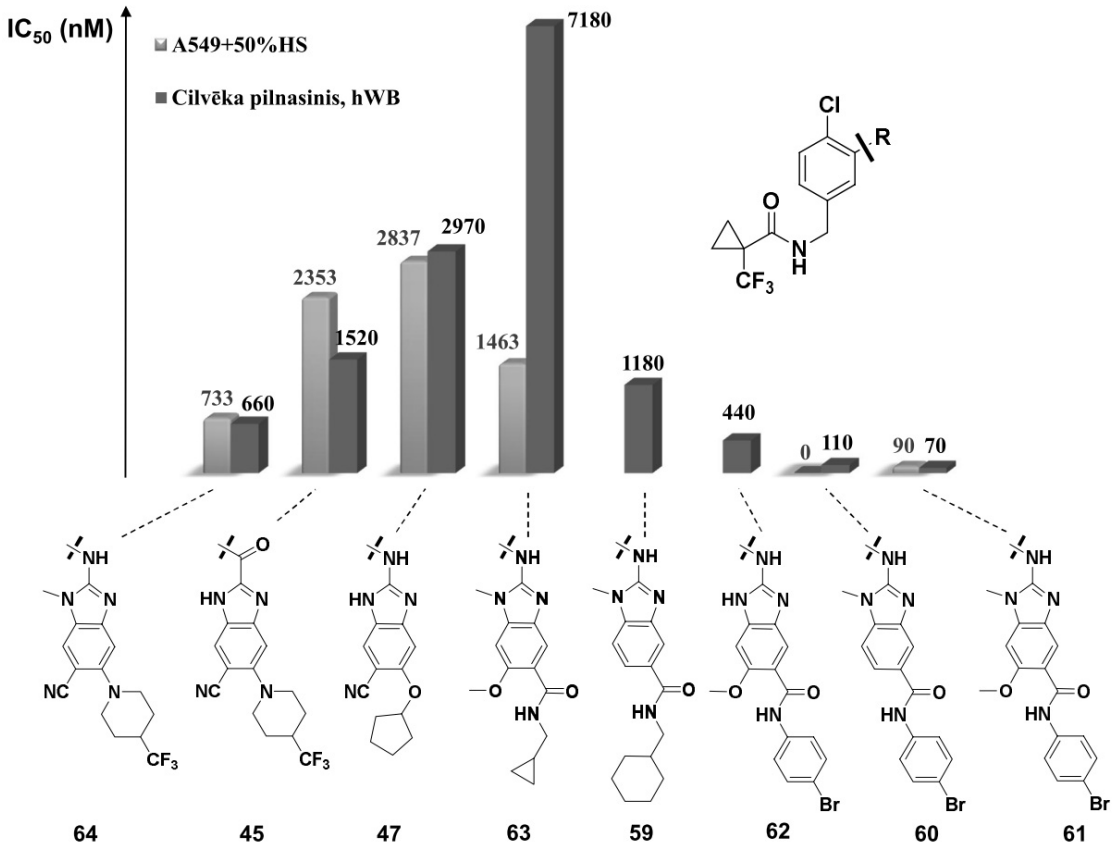
Farmakoforais modelis uzskatāmi rāda, ka mPGES-1 enzīma aktīvajā centrā benzimidazolu 5. un 6. pozīcijas apgabalā ir salīdzinoši maz telpisko apgrūtinājumu. Tas pavēra ceļu savienojumu inhibēšanas aktivitātes tālākajai paaugstināšanai, ievadot benzimidazola heterocikla 5. un 6. stāvokļos stēriski lielus hidrofobus aizvietotājus. Pamatojoties uz šo atziņu, izveidojām plašu hipotētisku inhibitoru struktūru klāstu, kuru ievietojām otrās paaudzes farmakoforajā modelī. Starp hipotētiskajām struktūrām augstu aktivitāti farmakoforais modelis prognozēja benzimidazola atvasinājumiem ar konformacionāli ierobežotu amīda grupu benzimidazola gredzena 5. stāvoklī (savienojumi **59–63**, 17. att.).

Visi savienojumi ar augstu prognozēto aktivitāti tika sintezēti, un eksperimentāli noteiktās ļoti augstās inhibējošās aktivitātes (17. att.) apstiprināja otrās paaudzes farmakoforā modeļa pareizību.



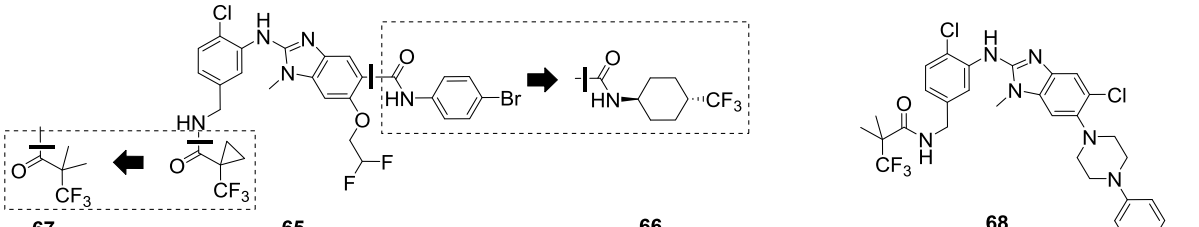
17. att. Amīda grupu saturošie benzimidazolu rindas mPGES-1 inhibitori **59–63**

Turklāt jāatzīmē, ka, atšķirībā no iepriekš iegūtajiem aktīvākajiem inhibitoriem **45**, **47** un **64**, amīda grupu saturošiem benzimidazola atvasinājumi **60-63** saglabā augstu inhibējošo aktivitāti arī cilvēka seruma albumīna klātbūtnē (”A549+50% HSA” tests) un cilvēka pilnasiņu parauga klātbūtnē (”hWB” tests) (18. att.). Tas liecina, ka savienojumiem **60-63** ir ievērojami zemāka afinitāte pret asins plazmas proteīniem un, tātad, potenciāli augstāka biopieejamība.



18. att. Izvēlētu mPGES-1 inhibitoru aktivitāte asins seruma un pilnasiņu parauga klātbūtnē

Aktīvāko amīdu **61-62** strūktūras papildus optimizācija ļāva uzlabot gan inhibitorās aktivitātes asins seruma un pilnasiņu parauga klātbūtnē, gan arī būtiski paaugstināt savienojumu metabolisko stabilitāti. Darba rezultātā tika izveidoti četri līdersavienojuma kandidāti **65–68** tālākai izmantošanai *in vivo* pētījumos (19. att.).



67
IC_{50} (nM) = 0,4
IC_{50} (A549+50% HS, nM) = 5
IC_{50} (hWB, nM) = 9
Met. stab.: >90 min

65
IC_{50} (nM) = 0,5
IC_{50} (A549+50% HS, nM) = 7
IC_{50} (hWB, nM) = 10
Met. stab.: $t_1/_2$>90 min

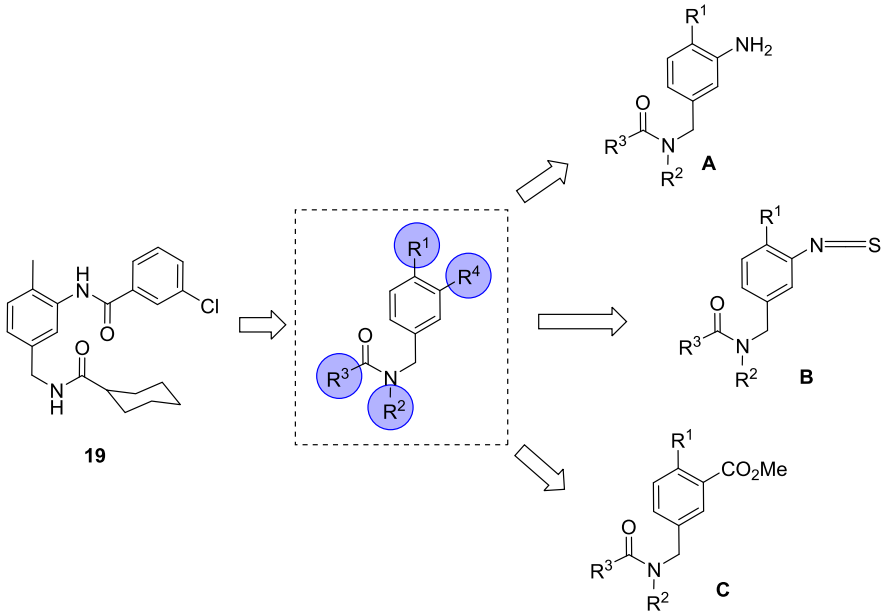
66
IC_{50} (nM) = 0,6
IC_{50} (A549+50% HS, nM) = 89
IC_{50} (hWB, nM) = 350
Met. stab.: >90 min

68
IC_{50} (nM) = 0,7
IC_{50} (A549+50% HS, nM) = 175
IC_{50} (hWB, nM) = 220
Met. stab.: 70 min

19. att. Identificētie līdersavienojumu kandidāti mPGES-1 inhibitoru rindā

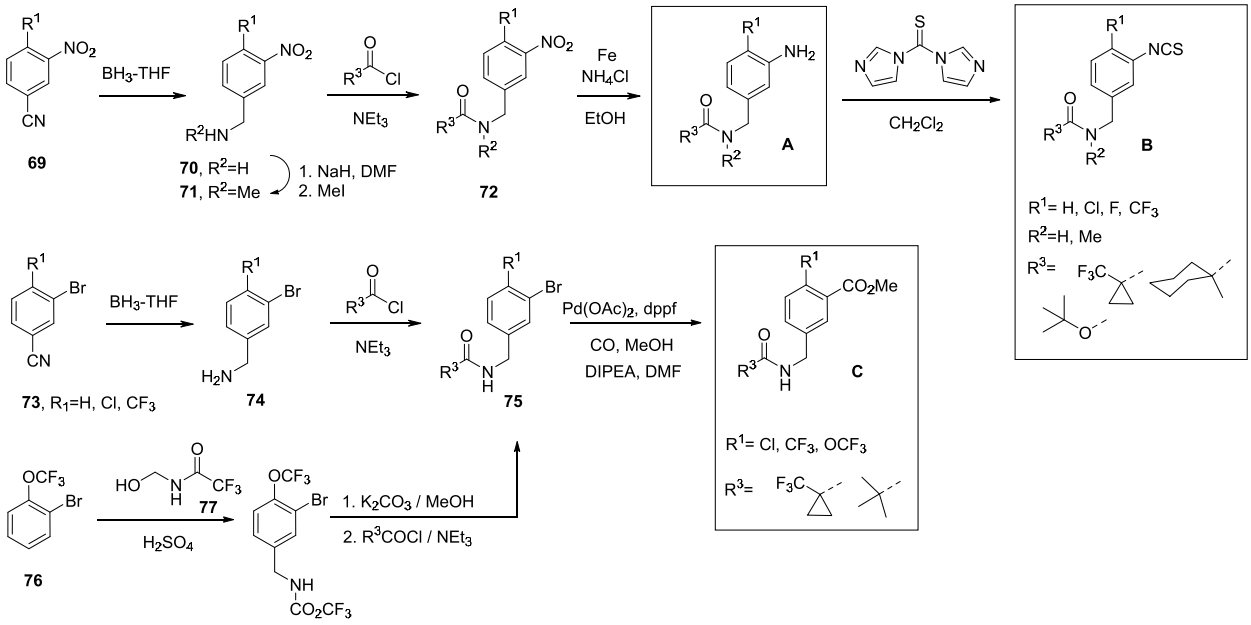
2.1.5. mPGES-1 inhibitoru sintēze

Jaunu mPGES-1 inhibitoru sintēzi balstījām uz būvbloku stratēģiju. Būvblokus izvēlējāmies tā, lai inhibitora molekulas optimizējamā struktūrelementa modifikāciju varētu veikt sintēzes noslēguma posmā. Tā kā inhibitoru struktūras modifikācijas neskāra centrālo benzilamīna struktūrelementu, bet bija vērstas galvenokārt uz aizvietotāju R^1, R^2,R^3 un R^4 variēšanu, inhibitoru sintēzei sākotnējā aktīvā savienojuma optimizācijas posmā izmantojām 3 pamatbūvbloku tipus: A, B un C (20. att.).



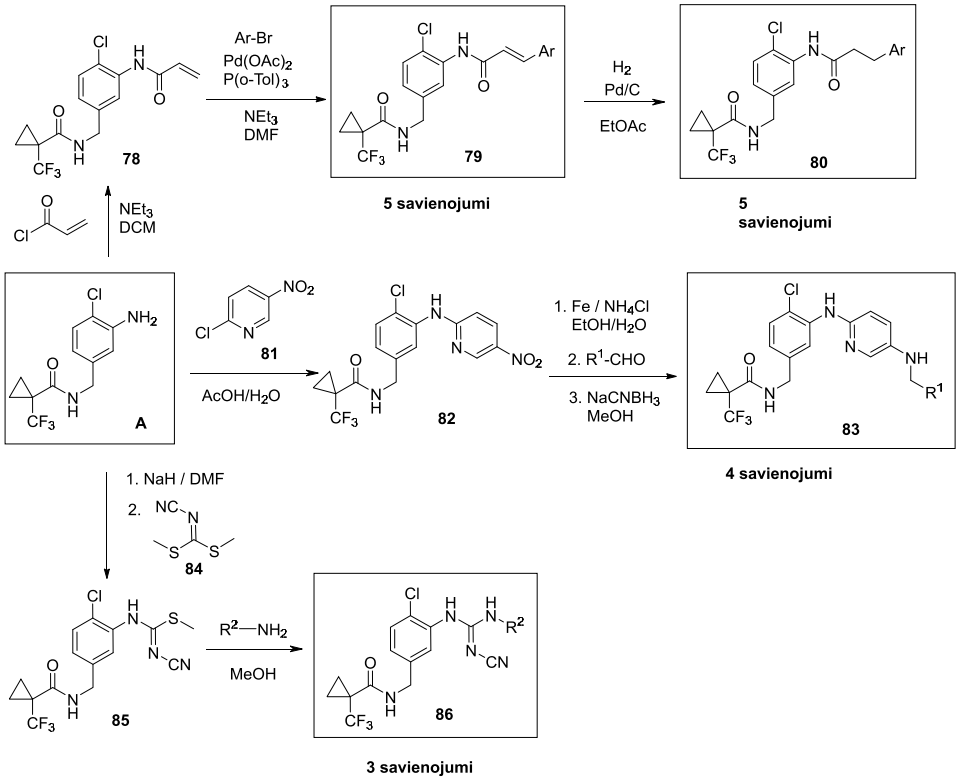
20. att. Pamatbūvbloku veidi aktīvās vielas **19** analogu sintēzei

Būvblokus A un B ieguvām no komerciāli pieejamiem 3-nitrobenzonitriliem **69**. Nitrilu reducējot ar borānu, ieguvām benzilamīnus **70**, kurus tālāk pārvērtām par *N*-metilatvasinājumiem **71**, deprotonējot ar NaH un alkilējot ar MeI. Amīnus **70**, **71** acilējām ar skābju hlorīdiem un nitrogrupu amīdos **72** reducējām ar dzelzi etanola un piesātināta NH_4Cl ūdens šķīduma maisījumā (21. att.). Iegūtos anilīnu būvblokus **A** tālāk izmantojām 17 inhibitoru sintēzei (22. att.). Savukārt anilīnu **A** reakcijā ar tiokarbonildiimidazolu ieguvām izotiocianātu būvblokus **B**, no kuriem pagatavojām 166 mPGES-1 inhibitorus (23. att.). Būvblokus **C** sintezējām pallādija katalizētajā metoksikarbonilēšanas reakcijā no brombenzoliem **73**, kurus ieguvām reducēšanas un sekojošajās *N*-acilēšanas reakcijās no ciānobenzoliem **74**, vai arī brombenzola **76** Manniha-tipa reakcijā ar amīdu **77** un sekojošu trifluoracetamīda šķelšanu/N-acilēšanu (21. att.). No būvblokiem **C** ieguvām 35 mPGES-1 inhibitorus (25. att.). Kopumā no 3 pamatbūvblokiem **A**, **B**, un **C** tika sintezēti 218 mPGES-1 inhibitori.



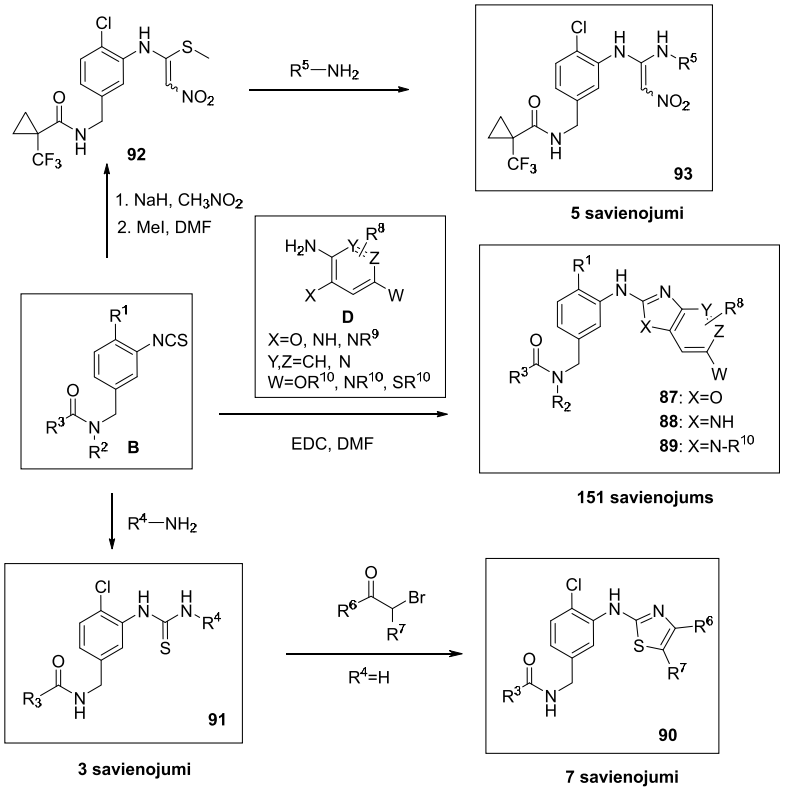
21. att. Pamatbūvbloku **A-C** iegūšana

Būvbloku **A** izmantojām *α,β*-nepiesātināto karbonskābes amīdu **79**, attiecīgo reducēto atvasinājumu **80**, diarilamīnu **83** un *N*-cianoguanidīnu **86** iegūšanai (22. att.). *α,β*-Nepiesātinātos amīdus **79** sintezējam būvbloka **A** reakcijā ar akroilhlorīdu un sekojošajā pallādija katalizētā Heka reakcijā ar arilbromīdiem. Pallādija katalizētā hidrogenēšanā no *α,β*-nepiesātinātajiem amīdiem **79** ieguvām amīdus **80**. Aminopiridīna atvasinājumi tika iegūti būvbloka **A** reakcijā ar 2-hlor-5-nitropiridīnu **81**, sekojošajā nitrogrupas reducēšanā un, visbeidzot, reducējošās aminēšanas reakcijā ar dažādiem aldehīdiem. Savukārt aizvietotus *N*-ciano-guanidīna atvasinājumus **86** sintezējām būvbloka **A** reakcijā ar *N*-ciano-*S,S*-dimetilditioimido-karbonātu **84** NaH klātbūtnē, *S*-metiltiourīnvielas starpsavienojumam **85** tālāk reaģējot ar dažādiem alifātiskajiem amīniem (22. att.).



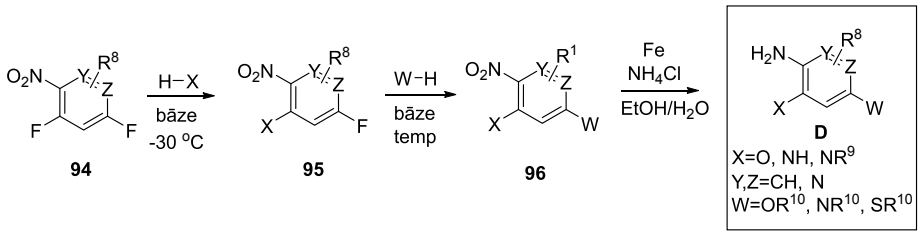
22. att. mPGES-1 inhibitoru iegūšanas shēma no būvbloka **A**

Būvbloks **B** tika izmantots tiourīnvielu **94** un to bioizostēru – diamino-nitroetēnu **93** sintēzei, 2-aminotiazolu **90** kā arī 2-aminobenzoksazolu **87** un 2-aminobenzimidazolu **88, 89** iegūšanai (23. att.). Tā, nitrometāna anjona pievienošanās izotiocianātam un sekojošajā *S*-metilēšanā tika iegūts 2-(nitrovinil)anilīns **92**, kura reakcijā ar dažādiem alifātiskajiem amīniem, veidojas mērķsavienojumus **93**. Būvbloka **B** reakcijā ar amīniem veidojās tiourīnvielas **91**, kuras reakcijā ar □-bromketoniem pārvērtām par aminotiazoliem **90**. Visbeidzot, būvbloka **B** reakcijā ar būvbloku **D** (aizvietotajiem *orto*-fenilēndiamīniem, *orto*-aminofenoliem, 2,3-diamino– un 3,4-diaminopiridīniem, sk. 5. att.) ieguvām attiecīgās tiourīnvielas, kuras neizdalot ciklizējām EDCI klātbūtnē par aizvietotiem 2-aminobenzoksazoliem **87** un 2-aminobenzimidazoliem **88, 89** (23. att.).



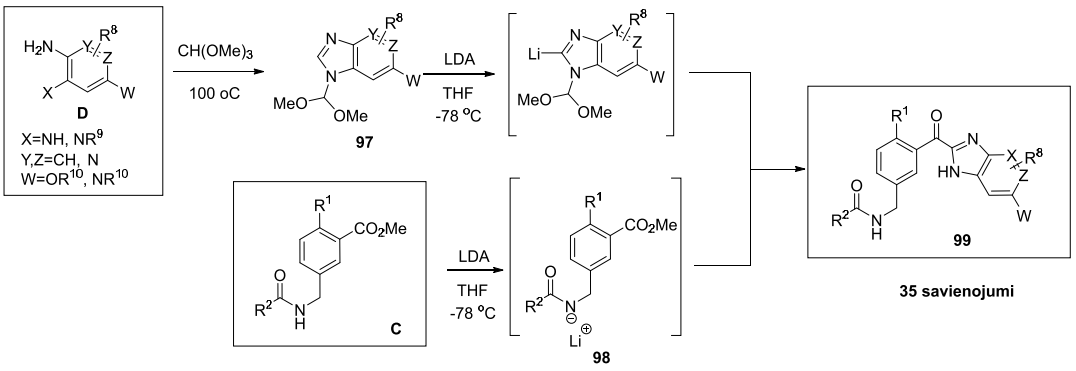
23. att. mPGES-1 inhibitoru iegūšanas shēma no būvbloka **B**

Būvbloku **D** sintezējām no aizvietotiem 2,4-difluor-nitrobenzoliem **94** (24. att). Nitrobenzola **94** *orto*-fluora atoma selektīvu aizvietošanu ar dažādiem amīniem vai alkoksīdiem veicām zemās temperatūrās (–30 °C). Savukārt otra fluora atoma aizvietošanai ar dažādiem nukleofiliem bija nepieciešama paaugstināta temperatūra. Nitrogrupu reducējām ar dzelzi amonija hlorīda škīdumā (24. att.).



24. att. Būvbloku **D** iegūšana.

Būvblokus **C** un **D** izmantojām ketogrupu saturošu mPGES-1 inhibitoru sintēzei. *Orto*-fenilēndiamīnus reakcijā ar trimetilortoformiātu pārvērtām par benzoksazoliem **97**, kuru 2. pozīcijā ar LDA ievadījām litiju un pievienojām esteriem **98** (25. att.).



25. att. mPGES-1 inhibitoru iegūšanas shēma no būvblokiem **C** un **D**.

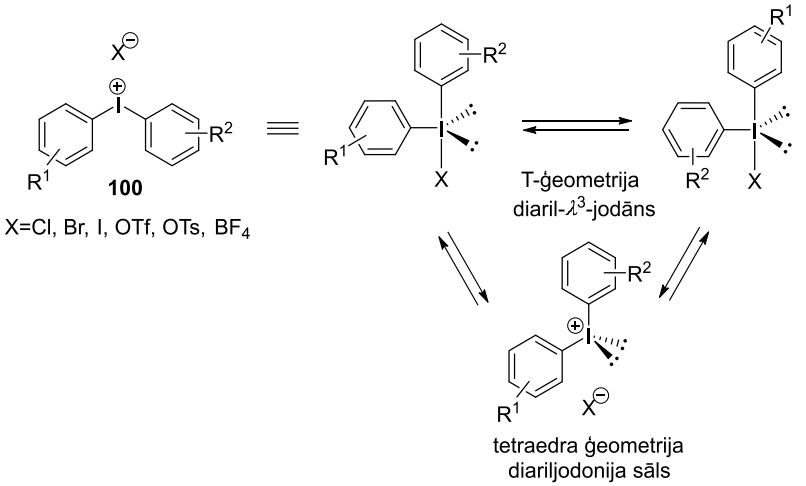
2.2. Sintēzes metožu izstrāde zāļvielu molekulu „vēlīnai modifikācijai"

Zāļvielu molekulu dizainā plašs pielietojums ir „vēlīnās modifikācijas" pieejai, kura paredz strukturālo daudzveidības ieviešanu pētāmajā bāzes struktūrā sintēzes beigu posmā. Pieeja ļauj ievērojami paātrināt struktūras-aktivitātes likumsakarību pētījumus un racionalizēt sintētisko darbu. Potenciālo zāļvielu molekulu „vēlīnām modifikācijām" konceptuāli vispiemērotākās ir sintēzes metodes, kuras ļauj ievadīt vēlamo aizvietotāju (potenciālo farmakoforu) optimizējamajā pamatstruktūrā tieši bez tās iepriekšējas funkcionalizēšanas. Piemēram, tradicionālā pieeja aromātisko un heteroaromātisko amīnu veidošanai paredz sākotnēju halogēna atoma vai analogas funkcionālās grupas (Cl, Br, I, OTf, OMs) ievadīšanu ciklā un sekojošu tās apmaiņu pret amīna grupu. Tieša, nepastarpināta aminogrupas ievadīšana aromātiskajā vai heteroaromātiskajā ciklā (C–H saišu funkcionalizācijas ceļā) ļautu ne tikai saīsināt sintēzes ceļu, bet arī risināt funkcionālo grupu savietojamības problēmu. Piemēram, tiešās C–H aminēšanas metodes visbiežāk neskar molekulā esošus halogēna atomus. Tai pat laikā būtisks tiešās C–H funkcionalizēšanas metodes trūkums ir zemā reģioselektivitāte, jo aromātiskajos vai heteroaromātiskajos savienojumos ir vairākas potenciāli funkcionalizējamas C–H saites. C–H Saišu funkcionalizēšanas reģioselektivitātes nodrošināšanai visbiežāk izmanto t.s. „virzošās grupas" – aizvietotājus, kuri nodrošina *orto*-vai *meta*-pozīcijās esošu C–H saišu aktivēšanu.[22,23] „Virzošās grupas" pēc aizvietotāja ievadīšanas visbiežāk jāaizvāc, kas daudzos gadījumos nav triviāls uzdevums. Promocijas darbā ir piedāvāta alternatīva C–H aktivēšanas pieeja, kurā C–H saišu funkcionalizēšanas reģioselektivitāti kontrolē substrāta reaģētspēja elektrofīlās aromātiskās aizvietošanas apstākļos. Attiecīgi C–H aktivēšana notiks elektrofilākajā aromātiskā vai heteroaromātiskā cikla pozīcijā, un reakcijai nav nepieciešama „virzošā grupa". Šāda pieeja bieži nodrošina no „virzītās" C–H funkcionalizēšanas atšķirīgu reģioselektivitāti, un tāpēc tā ir nozīmīga komplimentāra metode ar potenciāli plašu pielietojumu zāļvielu molekulu „vēlīnajai modifikācijai". Elektroniem bagātu aromātisko un heteroaromātisko ciklu C–H aktivēšanas metodoloģijas izstrādi nolēmām balstīt uz hipervalento joda(III)

savienojumu ķīmiju. Kā pētījumu mērķi izvēlējāmies medicīnas ķīmijai svarīgu C–H aminēšanas un C–H oksidēšanas metožu izstrādi.

2.2.1. Hipervalentā joda(III) ķīmijas pamatprincipi.

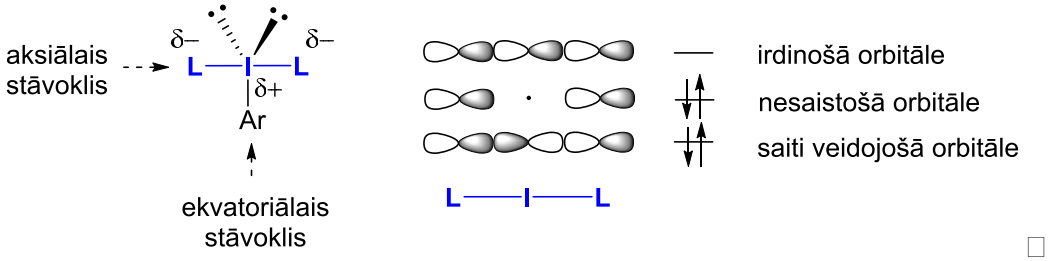
Hipervalentos joda savienojumus veido trīsvērtīgs jods un trīs ligandi. Ja divi no ligandiem ir aromātiskie savienojumi, tos sauc par diariljodonija sāļiem. Termins „jodonija sāļi" ir neprecīzs, jo „onija sāļiem", piemēram, amonija un sulfonija sāļiem raksturīga tetraedriska ģeometrija. Turpretī joda(III) savienojumiem raksturīga T–veida ģeometrija (pseidotrigonālā bipiramīda), kuru nosaka divas atšķirīgas ķīmiskās saites jodānos. Saite starp ekvatoriāli novietoto ligandu un joda(III) atomu ir kovalenta σ-saite, bet saite starp aksiālajos stāvokļos novietotajiem ligandiem un joda centru ir t.s. hipervalentā saite (26. att.). Uzskata, ka hipervalentajiem joda(III) savienojumiem T-veida ģeometrija saglabājas arī šķīdumos, un tādēļ joda(III) savienojumus pareizāk būtu saukt par λ^3-jodāniem un attiecīgi diariljodonija sāļus **100** par diaril-λ^3-jodāniem.



26. att. Diaril-λ^3-jodāni.

Hipervalento saiti veido 2 elektroni no joda 5*p* orbitāles un pa vienam elektronam no katra liganda. Līdz ar to hipervalentajai saitei raksturīga 4 elektronu trīs centru konfigurācija, un tā ir lineāra. Hipervalentās saites divas zemākās enerģijas orbitāles, saiti veidojošā un nesaistošā orbitāle, ir aizpildītas. Uz centrālā joda atoma ir gandrīz vienu vienību liels pozitīvs daļlādiņš ($\sigma_I \approx +1$),[24] bet uz aksiāli novietotajiem hipervalentās saites ligandiem ir negatīvs daļlādiņš. Šādu lādiņu sadalījumu saitē nosaka mezgla punkts (*node*) aizpildītās nesaistošās orbitāles centrā. Pozitīvais daļlādiņš uz joda atbildīgs par aril-λ^3-jodanilaizvietotāja izteikti elektrofīlo raksturu. Tā, fenil-λ^3-jodanilgrupa $Ph(BF_4)I^+$ induktīvi ir ļoti spēcīga elektronakceptora grupa ($\sigma_I = 1.34$). Tās aizvietotāja induktīvais efekts ir salīdzināms ar diazonija sāļiem $N_2^+–BF_4^-$ ($\sigma_I = 1.48$), un tas ir pat spēcīgāks nekā nitroaizvietotājam ($\sigma_I = 0.64$). Stipri polarizētā hipervalentā saite nosaka viselektronegatīvāko ligandu novietojumu aksiālajos stāvokļos (hipervalentās saites galos). Parādīts,

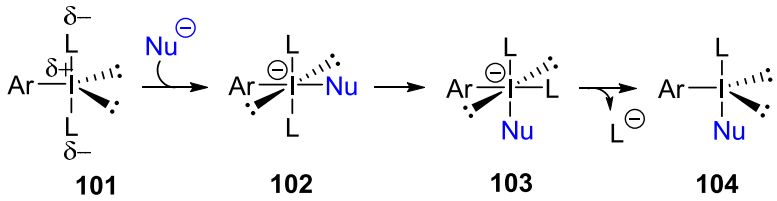
ka aksiālos stāvokļos esošu ligandu Hammeta aizvietotāju indukcijas konstantes tieši korelē ar λ^3-jodānu stabilitāti: jo augstāka ligandu elektronegativitāte, jo stabilāks ir λ^3-jodāns.[25]



27. att. Hipervalentā orbitāle λ^3–jodānos.

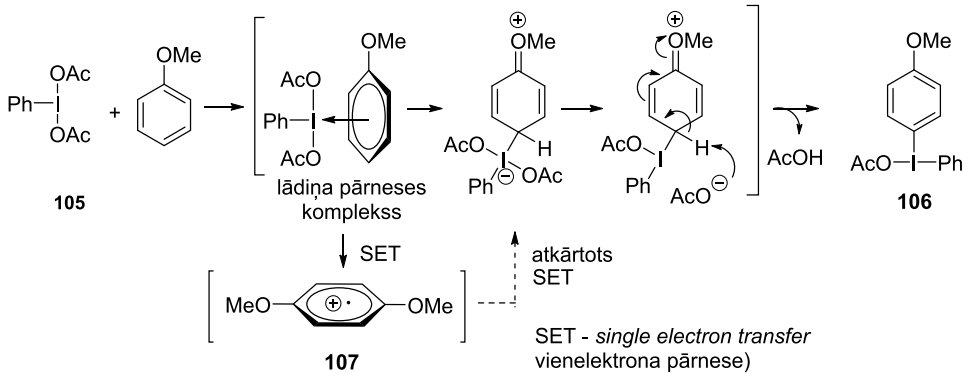
Hipervalento savienojumu elektroniskās struktūras attēlošanai bieži izmanto [N-X-L] apzīmējumu, kur N ir elektronu skaits, kas formāli pieder centrālajam atomam X, bet L ir centrālajam atomam piesaistīto ligandu skaits. Attiecīgi λ^3-jodāni ir [10-I-3] daļiņas, bet ariljodonija sāļi ir savienojumi ar [8-I-2] konfigurāciju.

λ^3-Jodāniem raksturīgas divas pamatreakcijas: ligandu apmaiņa, kura neietekmē joda(III) oksidēšanās pakāpi un reducējošā eliminēšanās, kuras rezultātā λ^3-jodāns reducējas līdz jodīdam. Pateicoties joda(III) jona elektrofīlajam raksturam, λ^3-jodāni reaģē ar dažādiem nukleofīliem. Nukleofīls uzbrūk C-I saites irdinošajai σ* orbitālei λ^3-jodānā **101**, un veidojas *trans*-tetrakoordinēts jodāts **102** [12-I-4] (28. att.). *Trans*-jodāts **102** izomerizējas par *cis*-jodātu **103**, un heteroatoma liganda L disociācijas rezultātā veidojas jauns hipervalentā joda savienojums **104**. Ligandu apmaiņa ir ātra un apgriezeniska. Jodāns **104** var stāties arī tālākajā ligandu apmaiņas reakcijā.



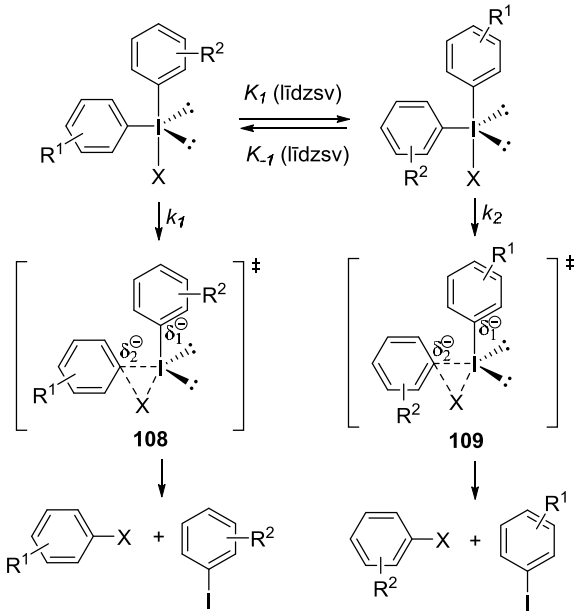
28. att. Ligandu apmaiņa λ^3–jodānos.

Par nukleofīlu reakcijā ar elektrofīlo aril-λ^3-jodānu **101** var kalpot arī elektroniem bagāts (hetero)aromātiskais cikls. Piemēram, diacetoksijodbenzols ($PhI(OAc)_2$) **105** reaģē ar anizolu, veidojot nesimetrisko diaril-λ^3-jodānu **106** (29. att.). Lai gan formāli jodāna **106** veidošanās notiek saskaņā ar elektrofīlās aromātiskās aizvietošanas S_EAr jeb Frīdela-Kraftsa (*Friedel-Crafts*) mehānismu, padziļināti pētījumi, izmantojot elektronu paramagnētiskās rezonanses metodi, liecina par sākotnēju katjonradikāļa **107** veidošanos viena elektrona pārnesē (*SET*) no elektroniem bagāta arēna uz elektrofīlo joda(III) centru (29. att.).[26]



29. att. Diaril-λ^3-jodānu veidošanās Frīdela-Kraftsa tipa reakcijā.

No sintētiskā viedokļa vissvarīgākā λ^3-jodānu, īpaši diaril-λ^3-jodānu, reakcija ir reducējošā eliminēšanās, kuras rezultātā starp diviem diaril-λ^3-jodāna ligandiem (nukleofīlo ligandu un arilligandu) veidojas saite, bet hipervalentais joda(III) centrs reducējas līdz joda(I) savienojumam. Reducējošās eliminēšanās virzītājspēks diaril-λ^3-jodānos ir okteta elektronu konfigurācijas joda(I) produktu veidošanās. Saskaņā ar vispārpieņemto mehānismu, elektronakceptorais nukleofīlais ligands X polarizē hipervalento saiti un izraisa tās heterolītisku šķelšanos. Vienlaicīgi notiek nukleofīlā liganda X uzbrukums ekvatoriāli novietotā arilliganda *ipso*-stāvoklim caur pārejas stāvokli **108** vai **109**,[27] veidojoties reducējošās eliminēšanas produktam un ariljodīdam (Ar-I) kā neitrālai aizejošajai grupai (30. att.).



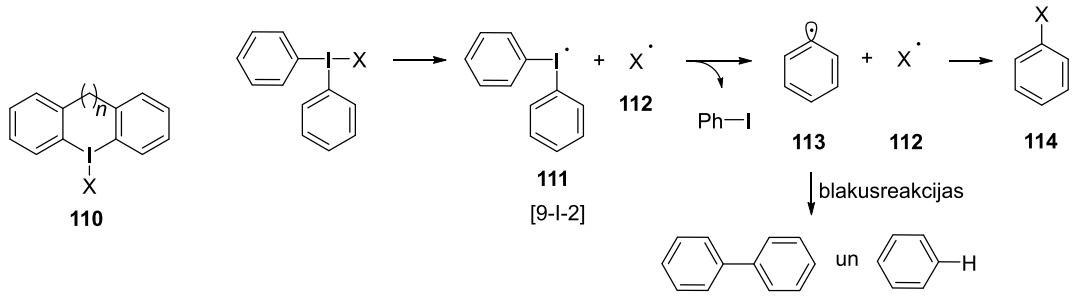
30. att. Reducējošā eliminēšanās diaril–λ^3–jodānos.

Nesimetrisko diaril-λ^3-jodānu gadījumā reducējošās eliminēšanās reakcijā teorētiski var veidoties divu produktu maisījums. Saskaņā ar *ab initio* DFT kvantu ķīmiskajiem aprēķiniem, reducējošās eliminēšanās selektivitāte atkarīga no daļlādiņu δ_1^- un δ_2^- lielumiem uz arilligandu *ipso*-oglekļa atomiem (30. att.).[24] Ar nukleofīlu reaģēs arilligands ar mazāku negatīvo daļlādiņu jeb

elektroniem nabadzīgākā aromātiskā sistēma.[28] Būtiski, ka reducējošās eliminēšanās notiek no līdzsvarā esošiem diaril-λ^3-jodānu izomēriem. Tā kā līdzsvara reakcijas aktivācijas barjera ir ievērojami zemāka par reducējošās eliminēšanās reakcijas aktivācijas barjeru ($K_1 >> k_1$ un k_2), reducējošās eliminēšanas selektivitāti *nesimetriskajos* diaril-λ^3-jodānos saskaņā ar Kurtina-Hammeta principu (*Curtin-Hammett principle*) nosaka reducējošās eliminēšanās aktivācijas barjeru atšķirības (k_1 pret k_2; sk. 30. att.).

Interesanti, ka reducējošās eliminēšanās selektivitātes elektroniskā kontrole nav spēkā gadījumos, kad viens no arilligandiem satur *orto*-aizvietotāju. Šādos nesimetriskajos diaril-λ^3-jodānos nukleofīlais ligands X veido saiti ar *orto*-aizvietoto ligandu neatkarīgi no daļlādiņu lielumiem uz arilligandu *ipso*-oglekļa atomiem. Šo parādību sauc par „*orto*-efektu" un visbiežāk to skaidro ar telpiskajiem faktoriem. Uzskata, ka stērisko efektu dēļ *orto*-aizvietotais arilligands vienmēr atradīsies termodinamiski izdevīgākajā ekvatoriālajā stāvoklī un tāpēc reaģēs ar nukleofīlo ligandu X.[29]

Būtiski, ka reducējošās eliminēšanās pārejas stāvoklī diaril-λ^3-jodāniem raksturīgā planārā T-veida ģeometrija tiek izjaukta. Novirze no planārās ģeometrijas enerģētiski ir īpaši neizdevīga gadījumos, kad divi no λ^3-jodānu ligandiem ir saistīti ar tiltiņu, piemēram, cikliskajā diaril-λ^3-jodānā **110** (sk. 31. att.). Uzskata, ka šādos gadījumos reducējošā eliminēšanās notiek ar radikāļu starpsavienojumu veidošanos.[30] Jāatzīmē, ka reducējošā eliminēšanās ar radikāļu iesaistīšanos tiek bieži postulēta arī neciklisko diaril-λ^3-jodānu gadījumā. Radikāļu mehānisms paredz sākotnēju hipervalentās saites homolītisku šķelšanu, veidojoties diariljoda radikālim **111** ar [9-I-2] elektronu konfigurāciju un heteroatoma radikālim **112**.[31] Radikālis **111** sabrūk par jodbenzolu un arilradikāli **113**, kurš veido produktu **114**. Radikālis **113** var iesaistīties arī blakusreakcijās, dimerizējoties vai rekombinējoties ar ūdeņraža atomu (31. att.).



31. att. Reducējošā eliminēšanās caur radikāļu mehānismu.

Diaril-λ^3-jodāni ir starp visefektīvākajiem elektrofīliem oksidējošās pievienošanās reakcijās pārejas metāliem. Augsto oksidējošās pievienošanās reaģētspēju galvenokārt nosaka labas aizejošās grupas – neitrālā jodbenzola veidošanās. Būtiski, ka *nesimetrisko* diaril-λ^3-jodānu oksidējošās pievienošanās reakcijā saiti ar pārejas metālu veido telpiski mazākais[32] vai arī elektroniem bagātākais no diviem arilligandiem.[33] Līdz ar to nesimetrisko diaril-λ^3-jodānu un pārejas metālu

reakcijas selektivitāte ir pretēja nesimetrisko diaril-λ^3-jodānu reducējošās eliminēšanās selektivitātei.

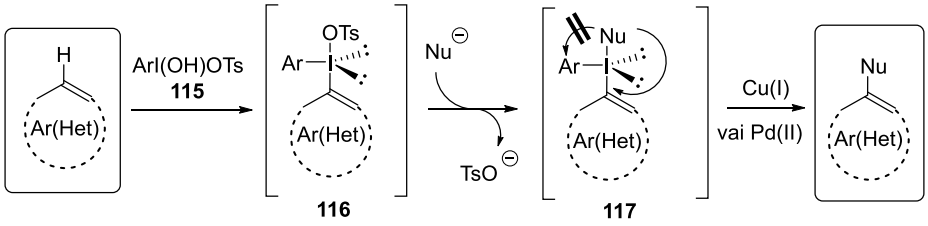
2.2.2. Uz hipervalentā joda(III) savienojumiem balstīta C–H saišu aktivēšanas koncepcija

Aromātisko un heteroaromātisko savienojumu C–H funkcionalizēšanas metodes izstrādes koncepcija balstās uz trīs secīgu viena reaktora reakciju virkni (32. att.):

1) elektroniem bagātu aromātisko vai heteroaromātisko savienojumu reakcija ar joda(III) reaģentu PhI(OH)OTs **115** un nesimetriska diaril-λ^3-jodāna **116** veidošanās;

2) diaril-λ^3-jodāna **116** tozilāta heteroatoma liganda *in situ* apmaiņa pret citu nukleofīlu heteroatoma ligandu;

3) produktu veidojošā reducējošā eliminēšanās no nukleofīlo ligandu saturoša nesimetriskā diaril-λ^3-jodāna **117**.



$Nu^{\ominus}$: HNR^1R^2 (1º un 2º alifātiskie un aromātiskie amīni), $^{\ominus}N_3$, $^{\ominus}OAc$

32. att. Uz hipervalentā joda(III) savienojumiem balstīta C–H aktivēšanas koncepcija.

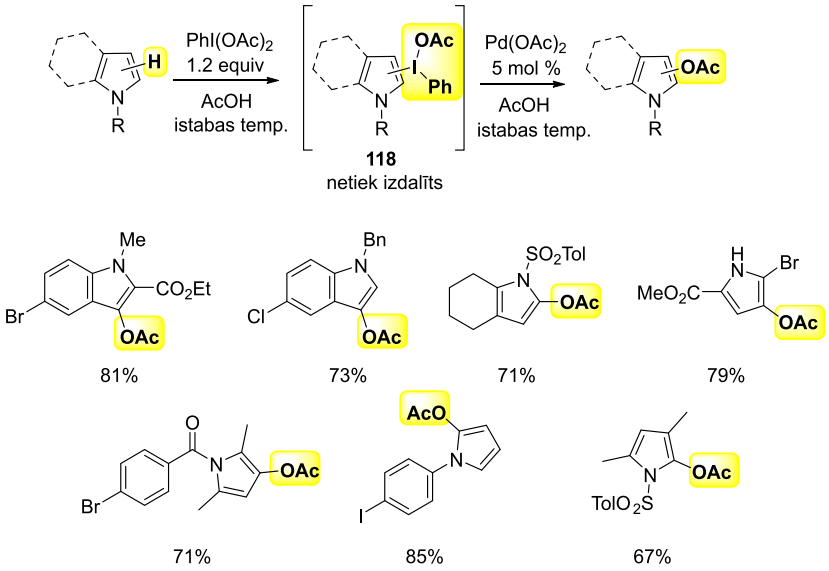
Diaril-λ^3-jodānu **116** veidošanās reakcijā starp PhI(OH)OTs **115** un elektroniem bagātu (hetero)aromātisko savienojumu (1. reakcija), kā arī heteroatoma ligandu apmaiņa diaril-λ^3-jodānos **116** (2. reakcija) ir plaši pētītas ķīmiskās norises (sk. 2.2.1. nodaļu). Arī *simetrisko* diaril-λ^3-jodānu reakcijas ar dažādiem nukleofīliem,[34] piemēram, ar amīniem, azoliem un amīdiem, ir plaši pētītas kā pārejas metālu katalizatoru (Pd(0)[35] un Cu(I)[36]) klātienē, tā arī bez katalizatoru pievienošanas.[37] Turpretī reducējošā eliminēšanās *nesimetriskajos* diaril-λ^3-jodānos **117** līdz šim nav atradusi praktisku pielietojumu selektivitātes problēmu dēļ: tā kā nesimetriskie diaril-λ^3-jodāni satur divus dažādus aromātiskos aizvietotājus, to reakcijās ar slāpekļa un skābekļa nukeofīliem bieži veidojas produktu maisījums.[36a,b] Turklāt elektroniem bagātu (hetero)aromātisko savienojumu saturošo *nesimetrisko* diaril-λ^3-jodānu **117** gadījumā sagaidāma nevēlama reducējošās eliminēšanas selektivitāte: nukleofīlais heteroatoma ligands vieglāk veidos saiti ar elektroniem nabadzīgāko arilligandu, nevis ar elektroniem bagātāko (hetero)aromātisko ligandu (sk. reducējošās eliminēšanas likumsakarību aprakstu 2.2.1. nodaļā).

Ņemot vērā *nesimetrisko* diaril-λ^3-jodānu un pārejas metālu reakcijas selektivitāti, mēs izvirzījām hipotēzi, ka pārejas metāla klātbūtne varētu mainīt „tradicionālo" nesimetrisko diaril-λ^3-jodānu reducējošās eliminēšanas selektivitāti. Līdz ar to koncepcijas novitāte balstās uz Pd(II) un

Cu(I) katalizatoru izmantošanu nukleofīla uzbrukuma selektivitātes kontrolei nesimetrisku diaril-λ^3-jodānu molekulās.

2.2.3. Elektroniem bagātu heteroaromātisko savienojumu C–H oksidēšanas metode

Elektroniem bagātu heteroaromātisko ciklu acetoksilēšanas reakcijas izstrādi balstījām uz viena reaktora divstadiju procesu: sākotnēju heteroaril(fenil)-λ^3-jodāna **118** veidošanos un tālāku produktu veidojošo reducējošo eliminēšanos Pd(II) katalizatora klātbūtnē (33. att.).[38]

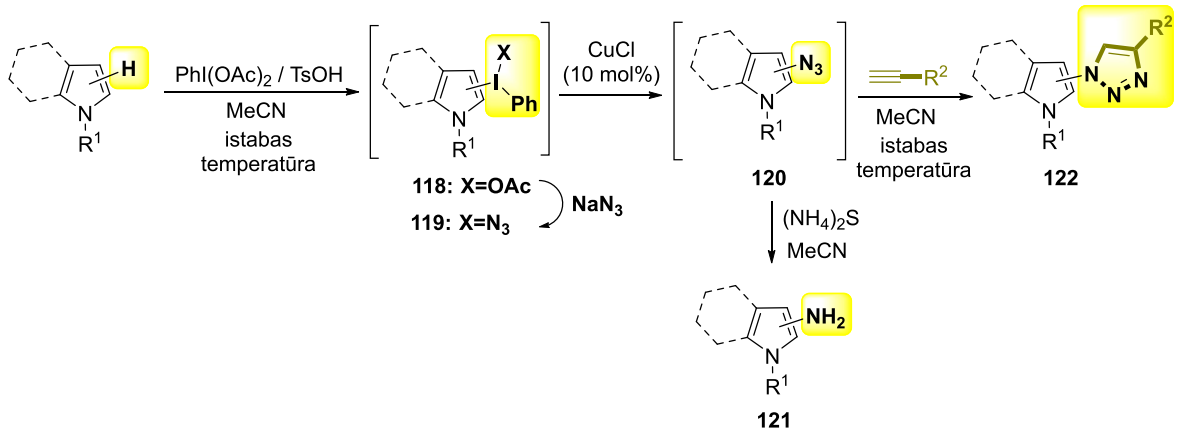


33. att. Elektroniem bagātu heteroaromātisko savienojumu C–H oksidēšanas metode

λ^3-Jodāna **118** starpsavienojumus iespējams izdalīt un attīrīt, tomēr no pielietojamā viedokļa ērtāk ir veikt viena reaktora divstadiju procesu. Pallādija(II) katalizators nodrošina vēlamo selektivitāti λ^3-jodāna **118** reducējošās eliminēšanās reakcijā. Acetoksilēšana notiek maigos apstākļos (istabas temperatūrā), un reakcijas apstākļi ir savietojami ar plašu funkcionālo grupu klāstu: broma un pat joda atomu heterociklos, kā arī ar *N*-alkil-, *N*-aril-, *N*-benzoil-, *N*-benzil-, *N*-tozil- un *N*-karbamoilaizsarggrupām. Tā kā λ^3-jodāns **118** reakcijas gaitā netiek izdalīts, izstrādātajā viena reaktora divstadiju procesā C-H saite tiek pārvērsta par C-O saiti, un tāpēc formāli to var uzskatīt par C-H oksidēšanas reakciju.

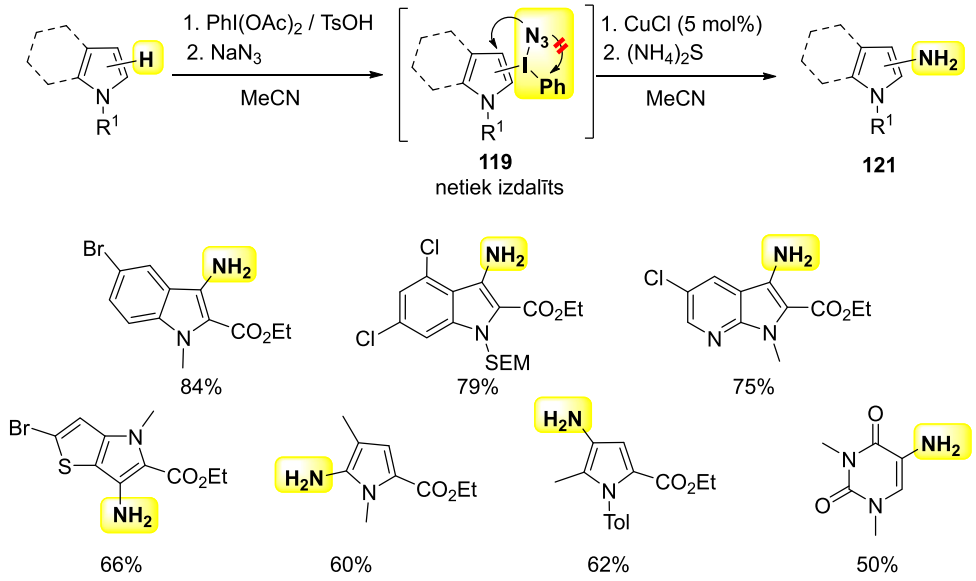
2.2.4. Elektroniem bagātu heteroaromātisko savienojumu C–H azidēšanas metode

Nukleofīlā acetāta liganda nomaiņa pret azīda ligandu nesimetriskajos λ^3-jodānos (**118** uz **119**) ļāva izstrādāt metodi elektroniem bagātu heteroaromātisko savienojumu C–H azidēšanai (34. att.).[39]



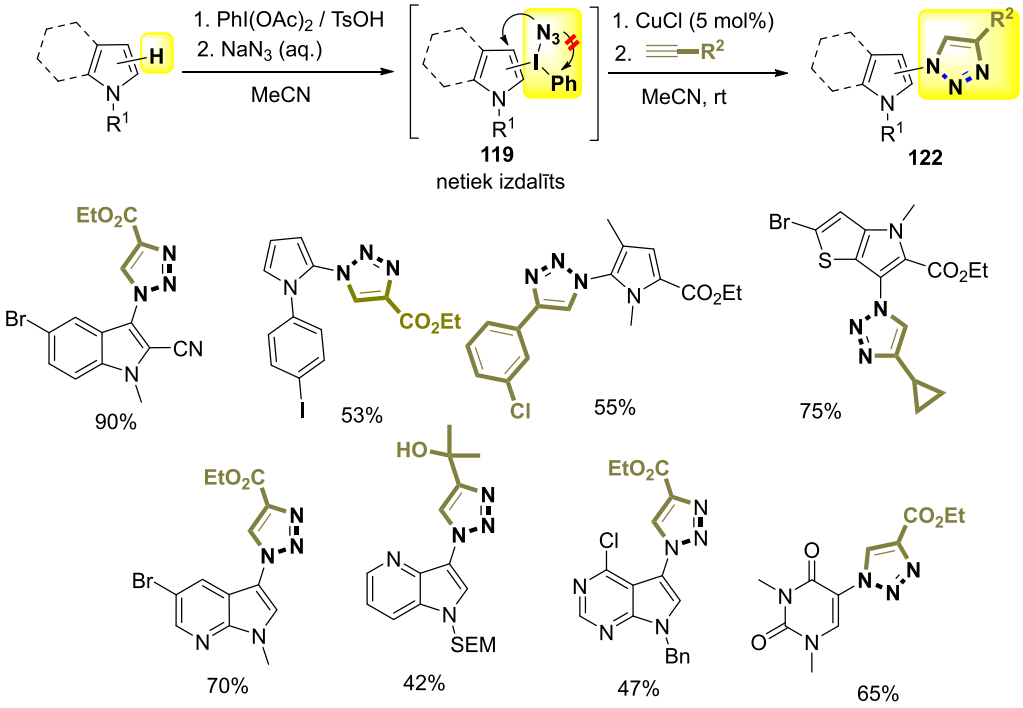
34. att. Elektroniem bagātu heteroaromātisko savienojumu C–H azidēšanas metode

Atslēgas pārvērtība viena reaktora 3 stadiju procesā ir azīdu saturošu nesimetrisko heteroaril(fenil)-λ^3-jodānu **119** reducējošā eliminēšanās, kuras reģioselektivitāti kontrolē Cu(I) kompleksi. Izveidojušies heteroarilazīdi **120** diemžēl ir nestabili, un tos ir ārkārtīgi grūti izdalīt un attīrīt. Heteroarilazīdus **120** tomēr ir iespējams iesaistīt tālākajās pārvērtībās, tos neizdalot no reakcijas maisījuma. Piemēram, heteroarilazīdi **120** viegli reducējas par atbilstošajiem aminoheterocikliem **121** (35. att.).



35. att. Heteroaromātisko amīnu iegūšana C–H azidēšanas-reducēšanas reakcijā

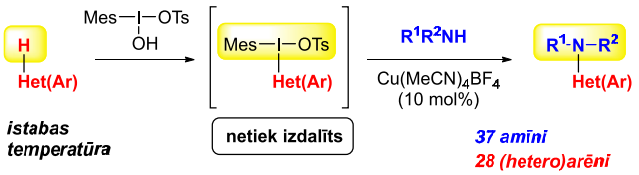
Heteroarilazīdi **120** stājas arī vara katalizētajā 1,3-dipolārās ciklopievienošanās reakcijā ar acetilēniem, veidojot 1,2,3-triazolus **122**. Līdz ar to vara(I) sāļi ne tikai katalizē azīdu saturošu heteroaril(fenil)-λ^3-jodānu **119** reducējošo eliminēšanos, bet arī veicina sekojošo azīdu **120** 1,3-dipolārās ciklopievienošanās reakciju (36. att.). Izstrādātā sintēzes metode ir piemērota plaša elektroniem bagātu heterociklu klāsta „vēlīnai modificēšanai".



36. att. Viena reaktora secīga heteroaromātisko C–H azidēšanas-1,3-dipolārās ciklopievienošanās reakcija

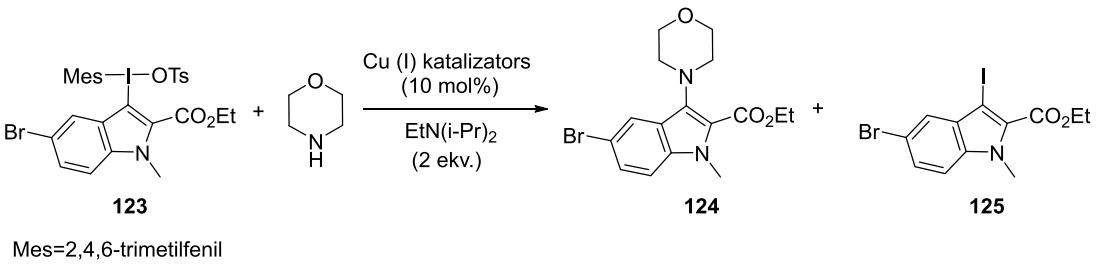
2.2.5. Elektroniem bagātu aromātisko un heteroaromātisko savienojumu C–H aminēšanas metode

Attīstot koncepciju par nesimetrisko diaril-λ^3-jodānu reducējošās eliminēšanas selektivitātes maiņu pārejas metālu klātienē, noskaidrojām, ka vara(I) sāļi nodrošina vēlamo selektivitāti arī amīnu reakcijā ar nesimetriskajiem heteroaril(fenil)-λ^3-jodāniem. Šis novērojums pavēra ceļu heteroaromātisko savienojumu C–H aminēšanas reakcijas izstrādei (37. att.).[40]



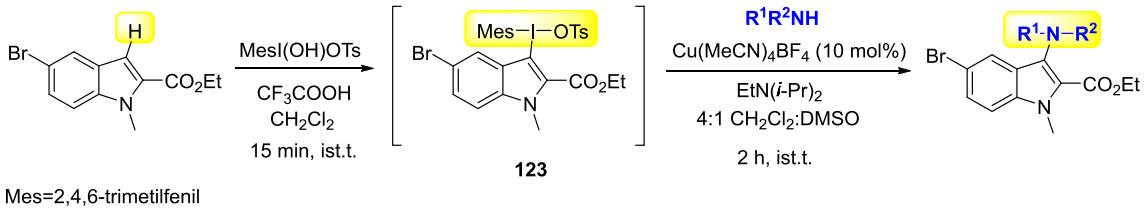
37. att. Heteroaromātisko savienojumu C–H aminēšanas reakcija

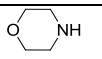
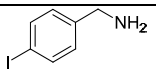
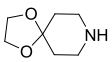
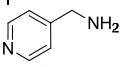
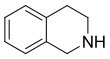
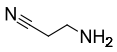
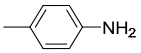
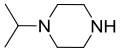
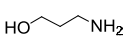
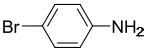
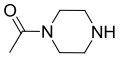
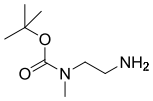
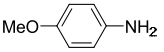
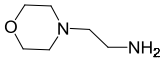
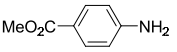
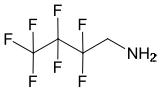
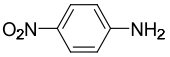
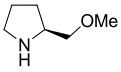
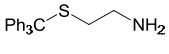
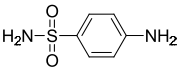
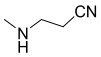
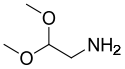
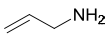
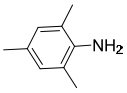
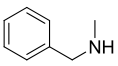
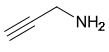
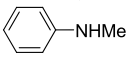
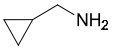
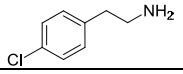
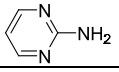
C-H Aminēšanas metodes izstrādei sākotnēji sintezējām, izdalījām un attīrījām meziltil(indolil)jodonija tozilātu **123**, kura uzbūvi viennozīmīgi pierādījām ar rentgenstruktūras analīzes metodi. λ^3-Jodāna **123** reakcijā ar morfolīnu bez pievienotā katalizatora veidojās tikai nevēlamais jodindols **124**. Savukārt Cu(I) katalizatora pievienošana pilnībā izmainīja reakcijas selektivitāti, un kā pamatprodukts tika izdalīts vēlamais indolilamīns **125** (38. att.). Pēc dažādu vara sāļu katalītiskās aktivitātes pārbaudes turpmākajiem pētījumiem izvēlējāmies salīdzinoši lētu un komerciāli pieejamu $Cu(MeCN)_4BF_4$.



38. att. C-H Aminēšanas apstākļu optimizācija.

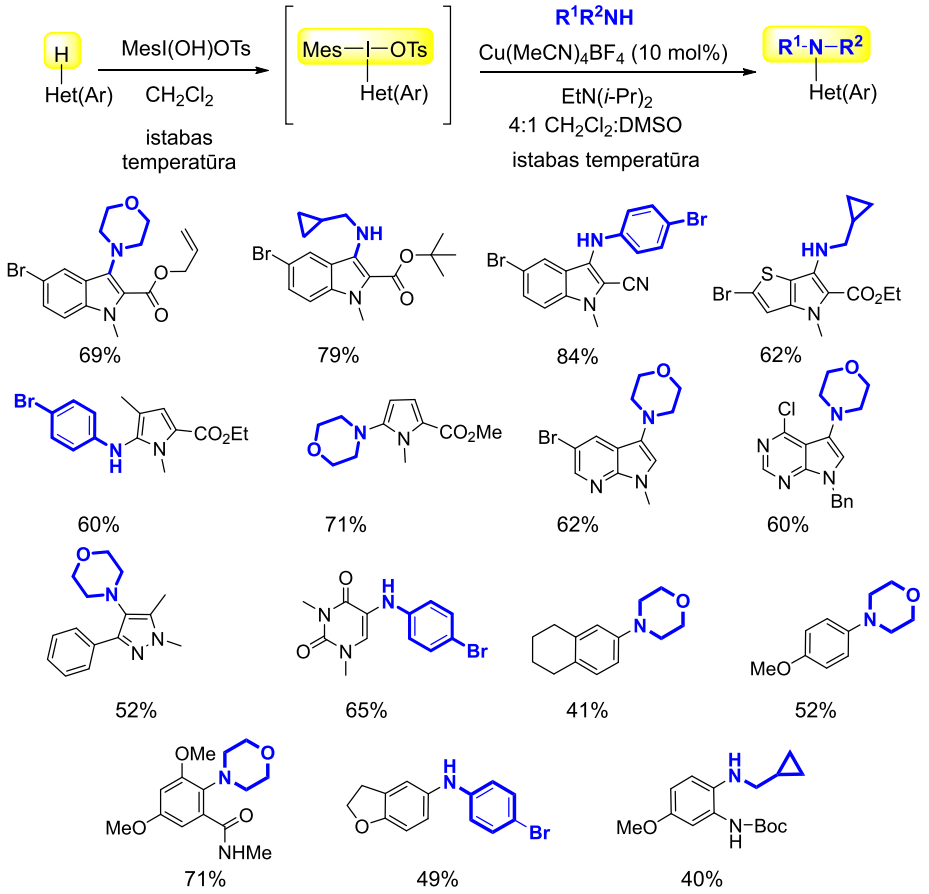
Tālākajā darbā atradām apstākļus, kuros λ^3-jodānu **123** bez izdalīšanas un attīrīšanas iespējams iesaistīt reakcijā ar morfolīnu. Atrastajos reakcijas apstākļos pārbaudījām amīnu klāstu, kuri piemēroti reakcijai ar λ^3-jodānu **123** (1. Tabula). Kā redzams, C-H aminēšanas metode ir savietojama ar ļoti plašu pirmējo un otrējo alifātisko kā arī aromātisko amīnu klāstu.



Nr.	R^1R^2NH	Izn. (%)	Nr.	R^1R^2NH	Izn. (%)	Nr.	R^1R^2NH	Izn. (%)
1		74	13		70	25		77
2		66	14		76	26		79
3		75	15		63	27		73
4		71	16		67	28		74
5		76	17		73	29		54
6		76	18		40	30		69
7		70	19		75	31		67
8		35[b]	20		73	32		62
9		65	21		80	33		79
10		67	22		80	34		76
11		65	23		71	35		77
12		71	24		83	36		65

1. Tabula. C-H aminēšanas reakcijā izmantojamo amīnu klāsts.

Pārbaudījām arī arēnu un heteroarēnu klāstu, kuri piemēroti izstrādātajai C-H aminēšanas metodei (39. att.). C-H Aminēšanas reakcijā stājas plašs elektroniem relatīvi bagātu heterociklu klāsts, tai skaitā indoli, piroli, pirolopiridini, tienopiroli, pirolopirimidīns, pirazoli un *N,N*-dimetiluracils. Jāuzsver, ka C-H aminēšanas apstākļos reaģē ne tikai heterocikli, bet arī elektroniem relatīvi bagātie aromātiskie savienojumi.



39. att. (Hetero)aromātisko savienojumu klāsts C-H aminēšanas reakcijā.

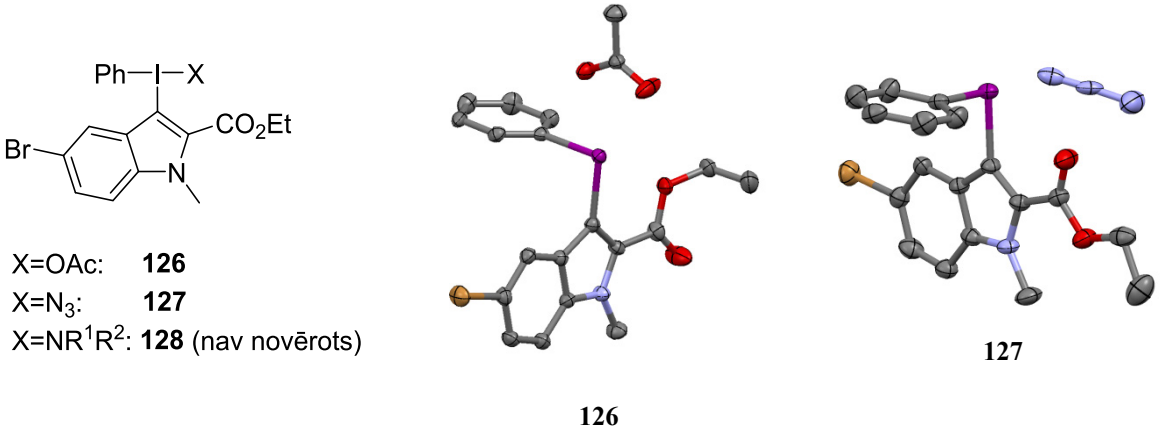
C–H Aminēšanas reakcijas apstākļi ir savietojami ar *O*-alil–, *O*-*terc*-butil– un *O*-alkil esteru funkcionālajām grupām, kā arī ar broma un hlora aizvietotājiem. Heterocikls vai aromātiskais savienojums var saturēt *N*–alkil-, *N*–aril-, *N*–benzoil-, *N*–benzilaizvietotāju, *N*–Boc kā arī *N*–SEM aizsarggrupas.

2.2.6. (Hetero)aromātisko savienojumu C-H funkcionalizācijas mehānisms

Aromātisko un heteroaromātisko savienojumu C–H funkcionalizēšanas metožu pirmā stadija ir nesimetrisko heteroaril(aril)-λ^3-jodānu veidošanās elektrofīlās aromātiskās aizvietošanas (Frīdela-Kraftsa) reakcijā. Šī stadija nosaka C–H funkcionalizēšanas reģioselektivitāti, jo nākamajā solī skābekļa vai slāpekļa nukleofīls aizvieto λ^3-jodāna funkcionālo grupu. Līdz ar to izstrādātajām C–H funkcionalizēšanas metodēm raksturīga elektrofīlās aromātiskās aizvietošanas reakcijām raksturīgā reģioselektivitāte. Tā, indolos un kondensētos pirolos C–H funkcionalizēšana notiek β-stāvoklī,

pirolos nukleofīls stājas α-stāvoklī, bet 2,5-diaizvietotajos pirolos – β-stāvoklī. Aromātiskajos savienojumos C–H funkcionalizēšanas reģioselektivitāti nosaka spēcīgākais elektrondonorais aizvietotājs, kurš λ^3-jodāna veidošanos un, līdz ar to, arī nukleofīla uzbrukumu virza *para* stāvoklī. Jāatzīmē, ka funkcionalizējamajam aromātiskajam vai heteroaromātiskajam savienojumam jābūt relatīvi elektroniem bagātam. C–H Aminēšanas metodes izstrādes gaitā noskaidrots, ka par toluolu elektroniem mazāk bagātie arēni ar λ^3-jodāniem nereģē. Būtiski, ka visos C–H funkcionalizēšanas piemēros veidojās tīri reģioizomēri, liecinot par reakcijas augsto reģioselektivitāti.

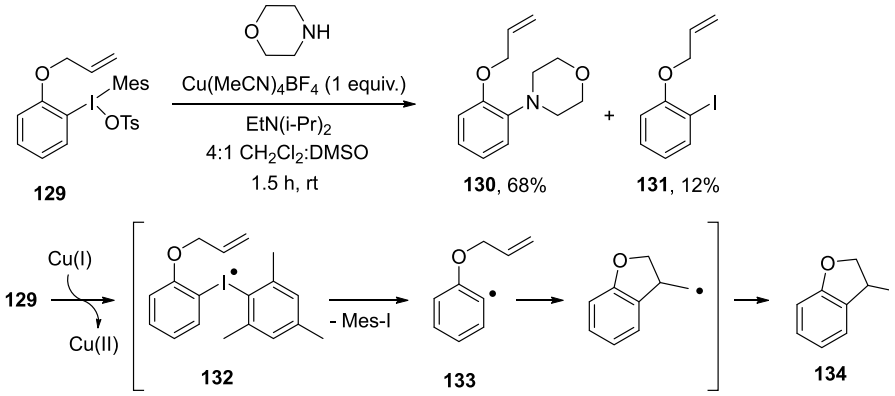
C–H Funkcionalizēšanas reakcijas noslēdzošā stadija ir produktu veidojošā Cu(I) vai Pd(II)-katalizētā nesimetrisko heteroaril(aril)-λ^3-jodānu reducējošā eliminēšanās. Lai gan heteroarēnu C-H acetoksilēšanas reakcijā par katalizatoru sākotnēji tika izmantoti Pd(II) sāļi, kontroles eksperimenti parādīja, ka Cu(I) sāļi tikpat efektīvi katalizē C–O saiti veidojošo reducējošo eliminēšanos. Diemžēl plašie Cu(I) katalizētās reducējošās eliminēšanas pētījumi nesniedz viennozīmīgu atbildi par reakcijas mehānismu. Piemēram, nukleofīlo pretjonu saturošie nesimetriskie heteroaril(aril)-λ^3-jodānu starpsavienojumi **126** un **127** ir izdalīti un raksturoti tikai acetoksilēšanas un azidēšanas reakciju gadījumā (40 att.), bet C–H aminēšanas gadījumā atbilstošo amīnu saturošu heteroaril(aril)-λ^3-jodānu **128** veidošanos reakcijas gaitā novērot neizdevās. Tai pat laikā jodānu **128** iesaistīšanos C–H aminēšanas katalītiskajā ciklā izslēgt nevar, jo amīnu saturoši λ^3-jodāni ir ārkārtīgi nestabili, un tie nav izdalīti.



40. att. Nesimetriskie heteroaril(aril)-λ^3-jodānu starpsavienojumi un to rentgenstruktūras attēli

C–H Aminēšanas mehānisma pētījumos noskaidrots, ka radikāļi visticamāk nav iesaistīti reakcijas katalītiskajā ciklā. Šāds atzinums izriet no *orto*-aliloksifenil-λ^3-jodāna **129** C–H aminēšanas eksperimenta rezultātiem (41. att.), kad no jodāna **129** tika iegūts vēlamais amīns **130** un jodīda blaskuprodukts **131**, bet dihidrobenzfurāna **134** veidošanās netika novērota. Heterocikls **134** veidotos tad, ja Cu(I)-katalizētā reducējošā eliminēšanās jodānā **129** norisinātos caur viena elektrona pārnesi no Cu(I) centra uz jodānu **129** un attiecīgā diariljoda radikāļa **132** veidošanos (sk.

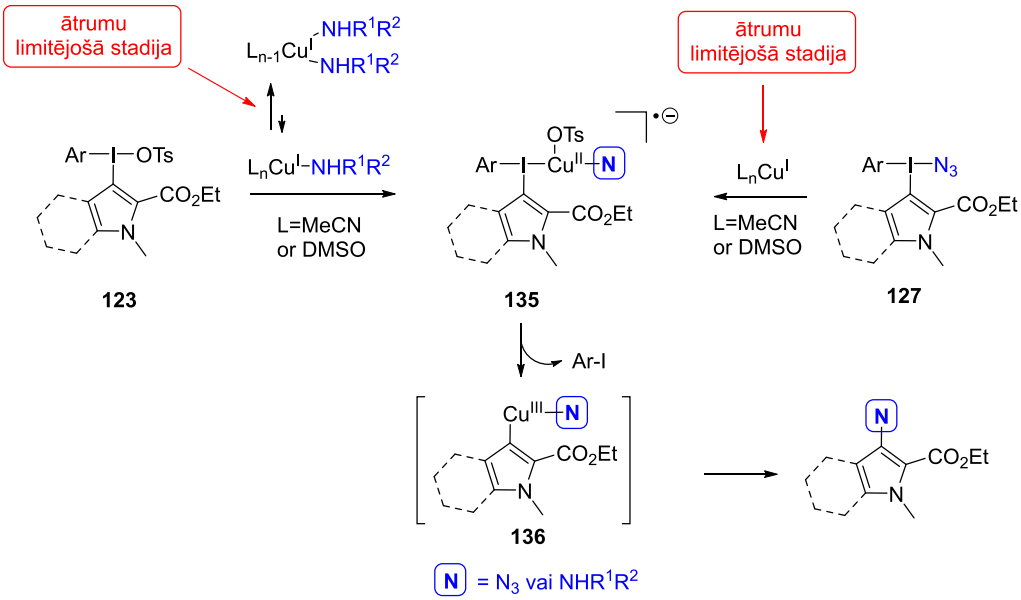
arī 2.2.1. nodaļu un 31. att.). Sekojošajā nestabilā radikāļa **132** fragmentācijā un fenilradikāļa **133** ciklizācijā veidotos dihidrobenzofurāns **134**.[41]



41. att. *Orto*-aliloksifenola C–H aminēšanas eksperiments.

Noskaidrots, ka Cu(I) sāļiem piemīt ievērojami augstāka katalītiskā aktivitāte nekā atbilstošajiem Cu(II) kompleksiem. Cu(I) Sāļu katalītiskais efekts acīmredzot nav saistīts ar to Lūisa skābju īpašībām, jo citas Lūisa skābes nekatalizēja nedz C–H azidēšanas reakciju (piemēram, $(Ph_3P)AuCl$, $Zn(OTf)_2$ un $Sc(OTf)_3$), nedz arī C–H aminēšanu ($Pd(OCOCF_3)_2$, $Ni(OTf)_2$ un $Sc(OTf)_3$). Vērtīgas atziņas par reakcijas mehānismu sniedza reakcijas ātruma mērījumi. Piemēram, noskaidrojām, ka C–H azidēšana ir pirmās kārtas reakcija attiecībā pret Cu(I) katalizatoru, bet nulltās kārtas attiecībā pret azīda anjonu. Rezultāti liecina, ka Cu(I) sāļi ir iesaistīti katalītiskā cikla reakcijas ātrumu limitējošajā stadijā, bet reducējošā eliminēšanās un heteroarilazīda produktu veidošanās ir iekšmolekulārs process. Turpretī C–H aminēšanas reakcijas ātruma pētījumi liecina, ka reakcija ir pirmās kārtas pret Cu(I) katalizatoru un pret amīnu (morfolīnu), bet nulltās kārtas attiecībā pret λ^3-jodānu **123**. Tātad, C–H aminēšanas katalītiskā cikla ātrumu limitējošajā stadijā iesaistīti tikai Cu(I) katalizators un amīns, bet visas tālākās λ^3-jodāna **123** pārvērtības ir ātrs process. Šī atziņa ievērojami apgrūtina reakcijas mehānisma pētījumus.

Reakcijas mehānisma pētījumi ļauj izvirzīt hipotētisku C–H funkcionalizēšanas mehānismu, kurš katalītiskā cikla noslēgumā paredz produktu veidojošo reducējošo eliminēšanos no Cu(III) kompleksa **136** (42. att.). Reakcijas mehānisma pirmā stadija ir viena elektrona pārnese no Cu(I) katalizatora uz λ^3-jodānu **123** vai **127**, veidojoties anjonradikālim **135**. Pieņemot, ka anjonradikālī **135** elektrons lokalizējas indola-joda(III) saites irdinošajā σ*–orbitālē un to pavājina, anjonradikālis **135** var sabrukt par Ar-I un indolilradikāli, kurš rekombinējas ar Cu(II)-amīna vai Cu(II)-azīda kompleksu un veido Cu(III) daļiņu **136**.[42]



42. att. Hipotētiskais C–H funkcionalizēšanas mehānisms

GALVENIE REZULTĀTI

I daļa. mPGES-1 inhibitoru sintēze

1. Struktūras-aktivitātes likumsakarību pētījumiem un farmakoforā modeļa izstrādei sintezēti 254 mPGES-1 inhibitori;

2. Izveidots mPGES-1 inhibitoru un mērķenzīma farmakoforais modelis, ar kura palīdzību veiksmīgi prognozēta inhibitorā aktivitāte virtuāli dizainētiem savienojumiem;

3. Darba rezultātā iegūti četri līdersavienojuma kandidāti tālākai izmantošanai *in vivo* pētījumos.

II daļa. C–H funkcionalizēšanas metožu izstrāde

1. Izstrādāta metode elektroniem bagātu heteroaromātisko savienojumu reģioselektīvai C–H acetoksilēšanai, izmanojot hipervalentos joda(III) savienojumus un Pd(II) katalizatorus;

2. Izstrādāta metode elektroniem bagātu aromātisko un heteroaromātisko savienojumu reģioselektīvai C–H azidēšanai un C–H aminēšanai istabas temperatūrā, izmanojot hipervalentos joda(III) savienojumus un Cu(I) sāļu katalīzi. Metode savietojama ar plašu amīnu klāstu.

SECINĀJUMI

I daļa. mPGES-1 inhibitoru sintēze

1. Ar otrās paaudzes farmakoforo modeli prognozētās mPGES-1 inhibējošās aktivitātes labi korelē ar eksperimentāli noteiktām vērtībām, tādējādi apstiprinot farmakoforā modeļa pareizību;

2. Saskaņā ar izstrādāto farmakoforo modeli, saistību ar mPGES-1 enzīmu nodrošina pieci farmakoforie struktūrelementi ligandā: otrējā amīda N-H protona ūdeņraža saite un hidrofobā tipa mijiedarbība ar liganda četriem lipofīlajiem fragmentiem;

3. Savienotājelements starp liganda centrālo gredzenu un benzimidazola fragmentu nav iesaistīts liganda–enzīma mijiedarbības nodrošināšanā.

II daļa. C–H funkcionalizēšanas metožu izstrāde

1. Pallādija(II) un vara(I) katalizatoru klātbūtnē reducējošā eliminēšanās nesimetriskajos diaril-λ^3-jodānos notiek ar pretēju selektivitāti nekā nekatalizēta procesa gadījumā: diaril-λ^3-jodānos heteroatoma ligands veidos saiti ar telpiski mazāk traucēto vai elektroniem bagātāko no diviem arilligandiem;

2. C–H Funkcionalizēšanas reģioselektivitāti aromātiskajos un heteroaromātiskajos savienojumos nosaka nesimetriskā λ^3-jodāna veidošanās elektrofīlās aromātiskās aizvietošanās (Frīdeļa-Kraftsa) reakcijā. Arēnos C–O un C–N saite veidosies *para* stāvoklī pret elektrondonoro aizvietotāju. Vairāku elektrondonoro aizvietotāju gadījumā λ^3-jodānu veidošanos un līdz ar to arī C–H funkcionalizēšanas reģioselektivitāti arēnos noteiks spēcīgākais no elektrondonorajiem aizvietotājiem. Heteroaromātiskie savienojumi reaģēs saskaņā ar tiem raksturīgo reaģētspēja Frīdeļa-Kraftsa reakcijas apstākļos.

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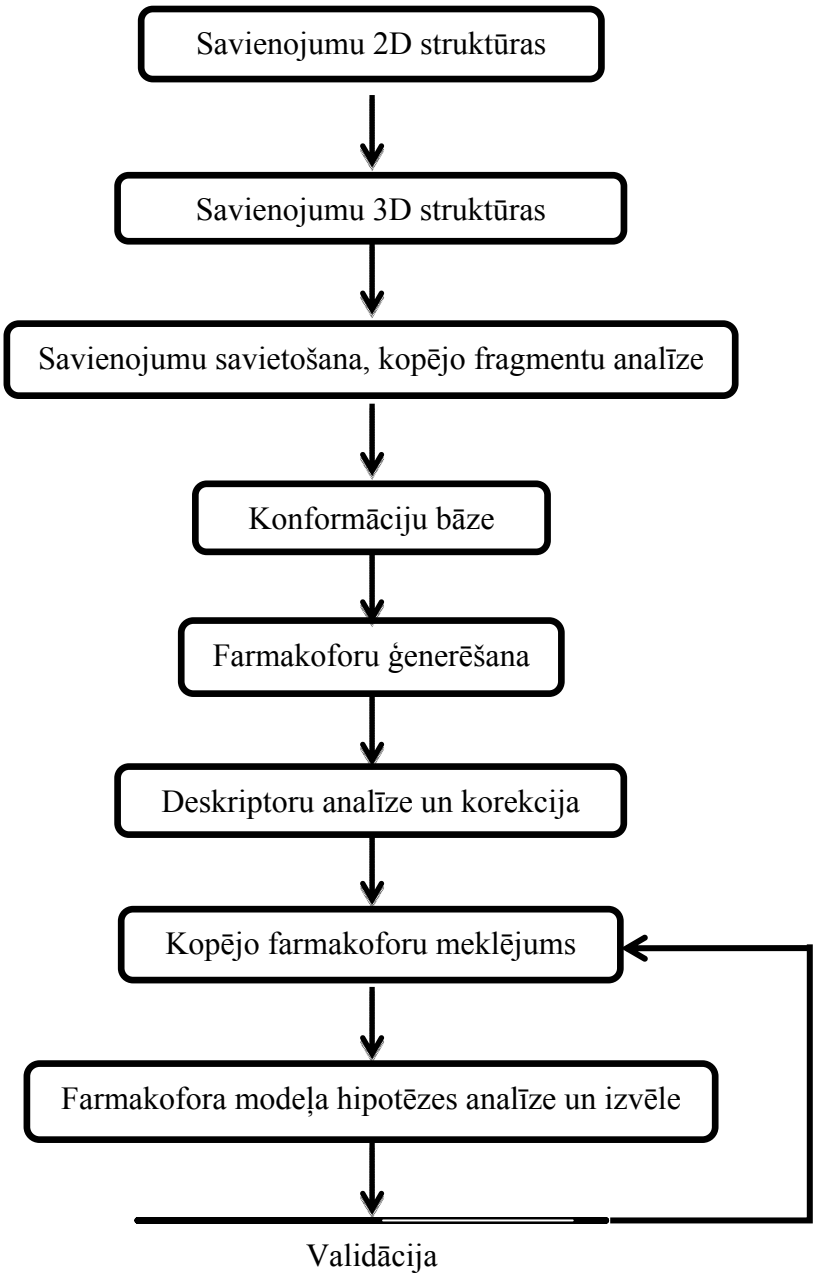
PIELIKUMS 1

Farmakoforā modeļa izveide

Farmakoforā modeļa izveide



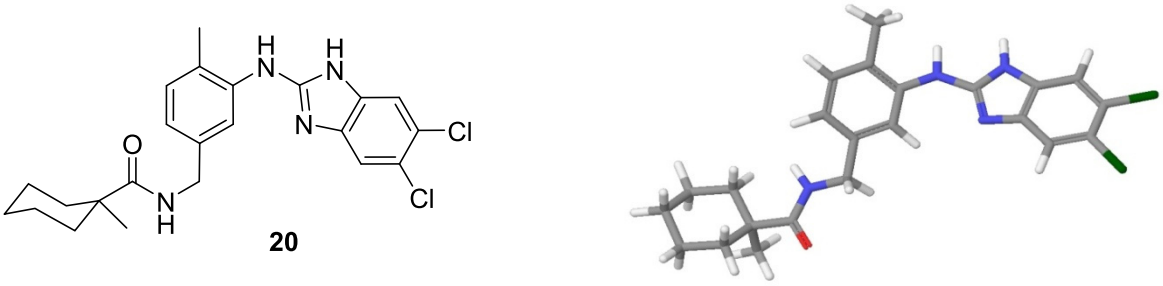
1. att. Farmakoforā modeļa izstrādes vispārīgs algoritms

Farmakofora modeļa izstrādei sagatavo darba un testa grupas. Šim nolūkam visas struktūras nejaušā kārtībā tiek sadalītas divās grupās: darba grupā un testa grupā (*training set*). Grupas var būt skaitliski gan vienādas, gan atšķirīgas. Darba grupu izmanto, lai izveidotu farmakoforo modeli, bet testa grupu – lai pārbaudītu izveidotā modeļa spēju prognozēt afinitāti. Testa un darba datubāzēs jābūt gan aktīviem, gan neaktīviem savienojumiem.

Ligandu darba un testa grupas veidojām no 120 sintezēto savienojumu klāsta, kurā 60 savienojumi bija neaktīvi (IC_{50}>10 μM), 35 savienojumiem piemita vidēja inhibējošā aktivitāte (IC_{50} robežās no 1 līdz 10 μM), bet 25 ligandi bija aktīvi, jo to inhibējošā aktivitāte bija zemāka par 1 μM. Farmakoforā modeļa darba datubāzes izveidei izvēlējāmies 15 visaktīvākās struktūras (IC_{50} robežās no 10 nM līdz 500 nM) un 15 visneaktīvākās (IC_{50} robežās no 5 μM līdz 60 μM).

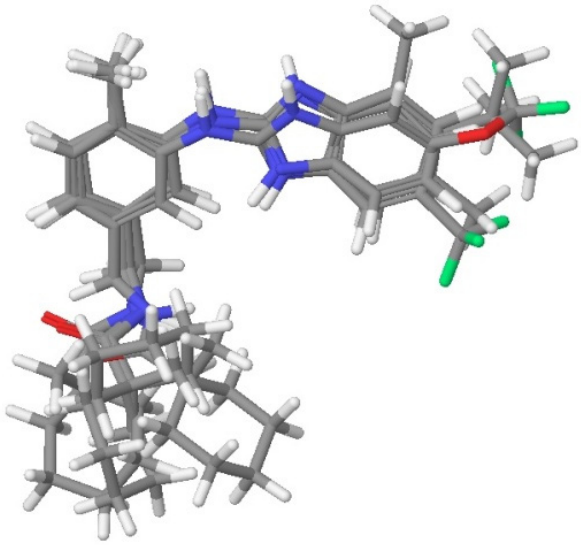
Farmakofora modeļa izveidošanu veicām saskaņā ar *Schrodinger Suite 2012* programmu paketē iekļautā moduļa *Phase* 3.4 lietošanas pamācību.

Pirmajā posmā ar *Schrodinger Suite 2012* programmu paketē iebūvēto *Maestro* 9.3 interfeisa palīdzību divdimensiju struktūras pārveidojām par trīsdimensiju struktūrām (2. att.). Pārveidošana notiek, balstoties uz atomu hibridizācijas leņķiem, un šajā posmā trīsdimensiju struktūra netiek optimizēta.



2. att. Divdimensiju struktūras pārveidošana par trīsdimensiju struktūru

Tālāk veicām struktūru savietošanu, izmantojot *Schrodinger Suite 2012* programmu paketē iebūvēto superpozīcijas funkciju (3. att.). Savienojumu savietošanas (superpozīcijas) mērķis ir katram analizējamajam savienojumam atrast tādu zemas enerģijas konformāciju, kura pēc iespējas vairāk līdzinātos izvēlētās bāzes struktūras **20** zemākās enerģijas konfromācijai. Superpozīcijas analīze ļāva atrast atšķirīgajām struktūrām kopīgus struktūrelementus.

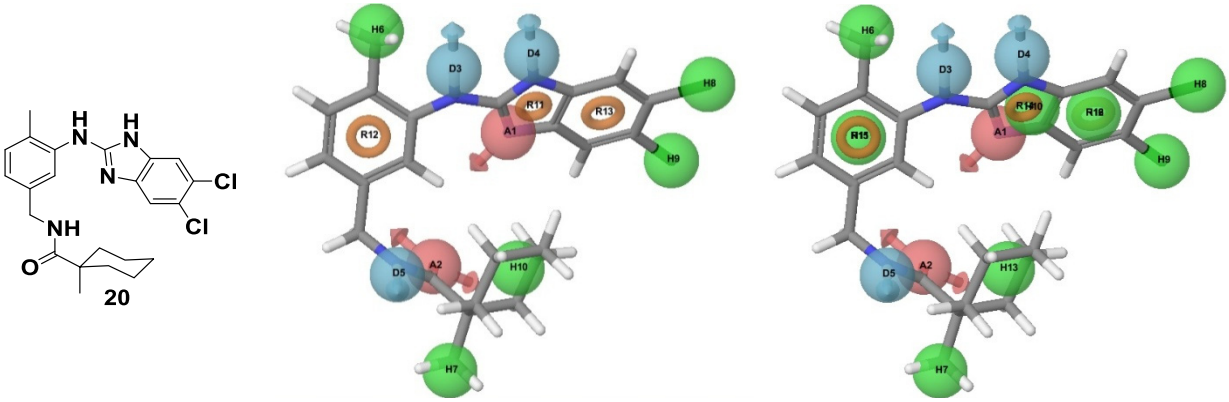


3. att. Ligandu savietošana (superpozīcija)

Vissvarīgākais solis ir savienojumu datubāzēs konformacionālā paplašināšana, tāpēc ka šajā solī ir nepieciešams atrast ne tikai lielu skaitu savienojumu konformāciju, bet arī molekulas konformāciju kopu, kas varētu būt pietiekami līdzīga bioaktīvajai konformācijai. Konformacionālā paplašināšana ļauj atrast molekulā visas iespējamās strukturālās īpašības, kas apraksta liganda farmakoforu. Ja ir zināma liganda bioloģiski aktīvā konformācija, tad farmakoforu veidošanas process ir ātrs un vienkāršs. Gadījumos, kad tā nav zināma, modelis tiek veidots, izmantojot eksperimentāli noteiktās aktivitātes un konformāciju kopas kombināciju. Rezultātā bioloģiski aktīvā konformācija tiek meklēta farmakoforu veidošanas procesā.

Konformāciju paplašināšanu (konformāciju kopu aprēķinus) veicām ar apakšprogrammu *ConfGen* 2.4, izmantojot standarta parametrus. Katram no 120 izvēlētajiem savienojumiem aprēķinājām konformāciju kopas, un ieguvām paplašinātu ligandu darba grupu, kurā katram ligandam atbilda aptuveni 100 minimizētas enerģijas konformāciju. Paplašināto ligandu darba grupu tālāk izmantojām farmakoforā modeļa veidošanā.

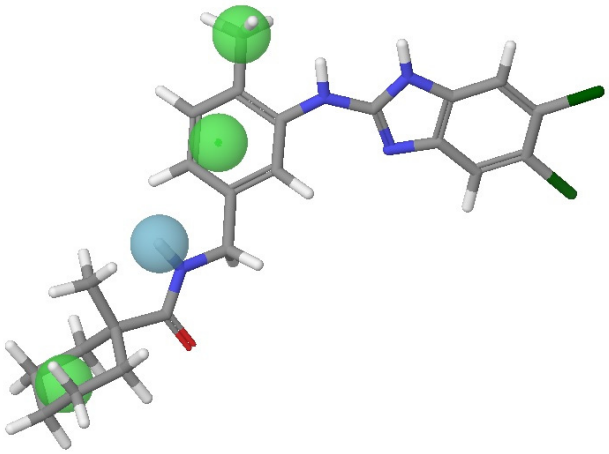
Nākamā solī ar *Phase* apakšprogrammas palīdzību katram savienojumam atradām farmakoforus (4. att.; **A**). Katram farmakoforam parasti cenšas atrast pēc iespējas vairāk dažādu deskriptoru, lai ar matemātiskās analīzes palīdzību atrastu visām analizējamajām zāļvielu molekulām pēc iespējas vairāk kopīgo deskriptoru. Piemēram, benzola ciklu raksturo aromātiskā π-sistēmas esamība, kas ir deskriptors. Tai pat laikā zināms, ka benzola gredzenam piemīt arī hidrofobas īpašības. Tādēļ benzola gredzenu raksturošanai kā papildus deskriptoru pievienojām hidrofobās virsmas īpašību (4. att.; **B**).



4. att. Liganda farmakofori un to deskriptori (zaļā krāsa–hidrofobitāte, sarkanā–protonu akceptors, zilā–protonu donors, oranžā-aromātiskā π-sistēma)

Pēc farmakofora punktu ģenerēšanas seko statistiskie aprēķini un kopīgo farmakoforā deskriptoru meklējumi. To rezultātā *Phase* modulis piedāvā vairākas farmakoforu modeļu hipotēzes. Veicot farmakofora modeļa hipotēzes analīzi ir nepieciešams izvēlēties vispiemērotāko modeļa hipotēzi: ar lielāku savienojumā fragmentu sakritību (pēc rādiusa, pēc vektora, pēc īpašības) ar kopējiem modeļā farmakoforiem, un mazāko vidējo kvadrātisko novirzi.

Modelis, kurš tika izvēlēts no 240 hipotēzēm, reprezentē dominējošās farmakoforās īpatnības: viens ūdeņraža saites donors (D) un trīs hidrofobas (H) mijiedarbības (5. att.).



5. att. Pirmais farmakofora modelis (DHHH)

Būtisks solis farmakofora modeļa izstrādes gaitā ir farmakoforā modeļa validācija. Šajā solī izveidotā savienojumu konformāciju datubāze (100 konformācijas katram no 120 savienojumiem) tiek ievietota farmakoforajā modelī, lai pārbaudītu katras konformācijas atbilstību modelim. Datubāzes skanēšanas rezultātā katrai molekulai atstājām tikai vienu, modelim vislabāk atbilstošo konformāciju. Gadījumā, ja kādam savienojumam neviena konformācija nebija saderīga ar modeli, datubāzē attiecīgais savienojums neiekļuva.

Pēc būtības, šīs farmakofora modelis strādā un spēj atlasīt visaktīvākos savienojumus no neaktīviem. Atrastais modelis 120 sintezēto savienojumu klāstā identificēja visus 25 aktīvos

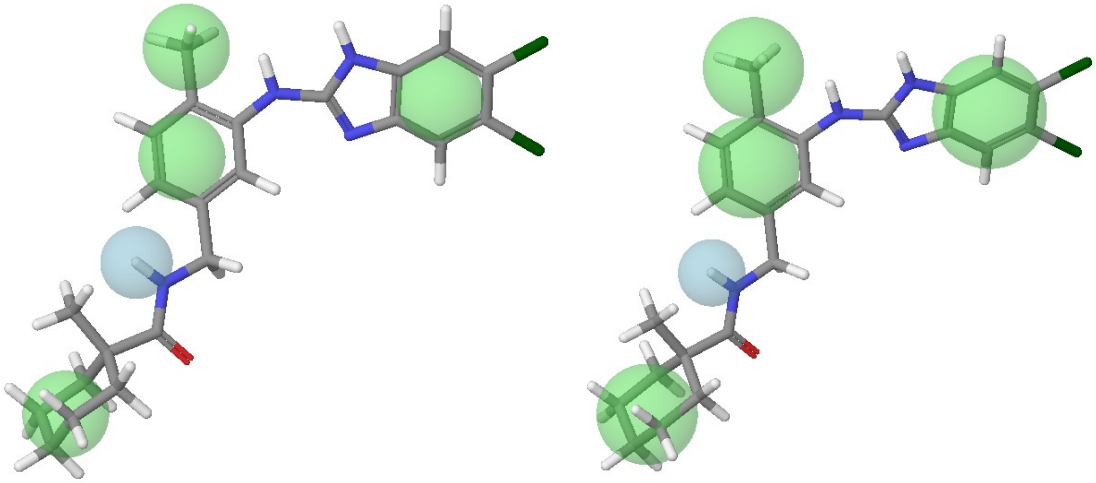
savienojumus, tos atlasot no neaktīvajiem un vidēji aktīvajiem. Tomēr modelis nepareizi atlasīja 17 vidējās aktivitātes savienojumus un 5 neaktīvos savienojumus.

Izveidotā farmakofora modeļa precizitātes uzlabošanai nolēmām ieviest papildus farmakoforus, kas izslēgs mazaktīvus savienojumus un mazāk ietekmēs aktīvus savienojumus. Modeļa pilnveidošana ļautu precīzāk atlasīt neaktīvus un vidēji aktīvus savienojumus.

Pirmās paaudzes farmakoforā modeļa optimizācijai tika izmantoti visi papildus sintezētie mPGES-1 inhibitori, kopskaitā vairāk nekā 180 savienojumu.

Farmakofora modeļa uzlabošanai sagatavojām jaunas darba un testa datubāzes izmantojot visus papildus sintezētus mPGES-1 inhibitorus un atkartojām visu procesu vēlreiz.

Pirmās paaudzes modelī izveidotus farmakoforus atstāja nemainīgus, bet modeļa efektivitātes palielināšanai pievienoja piekto farmakoforu ar hidrofobu mijiedarbību. Pēc kopējo farmakoforā deskriptoru aprēķināšanas tika iegūtas 35 farmakoforā modeļa hipotēzes. No tām par otrās paaudzes farmakoforo modeli tika izvēlēta hipotēze ar 5 farmakoforiem: vienu ūdeņraža saites donoru un četrām hidrofobām mijiedarbībām (6. att.).



6. att. Farmakofora modelis 2 (DHHHH)

Otrās paaudzes modelis spēja ievērojami precīzāk atlasīt aktīvākus savienojumus no neaktīviem, tomēr 4 mazaktīvi un 1 neaktīvs savienojums tika prognozēti kļūdaini. Farmakoforā modeļa tālākai uzlabošanai izvēlējāmies nesarežģīt modeli ar papildus farmakoforiem, bet izmainīt esošo farmakoforu sfēru rādiusus. Pārbaudot dažādus farmakoforu sfēru rādiusus atradām, ka lipofilu (hidrofobo) farmakoforu rādiusu palielināšana par 0.3 Å (no 1.2Å uz 1.5Å) un neliela attālumu izmainīšana starp farmakoforiem ļāva izveidot modeli, kurš veiksmīgi un gandrīz kvantitatīvi spēj atlasīt aktīvus savienojumus no neaktīvajiem un vidēji aktīvajiem (6. att.).

PIELIKUMS 2

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(75) Inventors/Applicants *(for US only)*: **PFAU, Roland** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **ARNDT, Kirsten** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **DOODS, Henri** [NL/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **KLINDER, Klaus** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **KUELZER, Raimund** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **LUBRIKS, Dimitrijs** [UA/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV). **MACK, Juergen** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **PELCMAN, Benjamin** [SE/SE]; Orexo AB, Box 303, S-75105 Uppsala (SE). **PRIEPKE, Henning** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **ROENN, Robert** [SE/SE]; Orexo AB, Box 303, S-75105 Uppsala (SE). **STENKAMP, Dirk** [DE/DE]; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **SUNA, Edgars** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV).

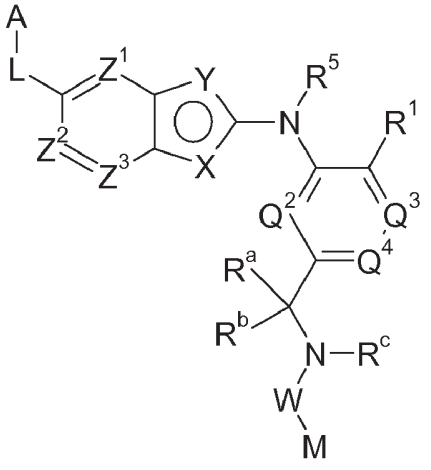
(74) Agents: **HAMMANN, ET.AL., Heinz** et al.; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

[Continued on next page]

(54) Title: 3H-IMIDAZO [4, 5 -C] PYRIDINE- 6 -CARBOXAMIDES AS ANTI- INFLAMMATORY AGENTS



(I)

(57) Abstract: The present invention relates to compounds of general formula (I) in which A, L, M, Q^2, Q^3, Q^4, R^1, R^5, R^a, R^b, R^c, W, X, Y, Z^1, Z^2, Z^3 are defined in the description, the salts thereof, particularly the physiologically acceptable salts thereof. The compounds are of potential utility in the treatment and/or prevention of inflammatory diseases and associated conditions, in particular, in the treatment and/or prevention of pain. The invention also relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to their preparation.

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(19) **United States**

(12) **Patent Application Publication**

PFAU et al.

(10) **Pub. No.: US 2010/0256188 A1**

(43) **Pub. Date: Oct. 7, 2010**

(54) **NEW COMPOUNDS**

(75) Inventors: **Roland PFAU**, Biberach (DE); **Kirsten ARNDT**, Ravensburg (DE); **Henri DOODS**, Warthausen (DE); **Klaus KLINDER**, Oggelshausen (DE); **Raimund KUELZER**, Mittelbiberach (DE); **Dimitrijs LUBRIKS**, Riga (LV); **Juergen MACK**, Biberach (DE); **Benjamin PELCMAN**, Uppsala (SE); **Henning PRIEPKE**, Warthausen (DE); **Robert ROENN**, Uppsala (SE); **Dirk STENKAMP**, Biberach (DE); **Edgars SUNA**, Riga (LV)

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(73) Assignee: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, Ingelheim am Rhein (DE)

(21) Appl. No.: **12/717,407**

(22) Filed: **Mar. 4, 2010**

(30) **Foreign Application Priority Data**

Mar. 5, 2009 (EP) 09154414.8
Dec. 17, 2009 (EP) 09179618.5

Publication Classification

(51) **Int. Cl.**

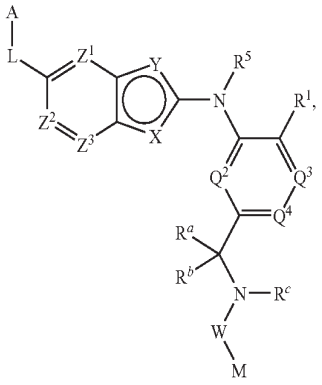
A61K 31/454	(2006.01)
C07D 235/30	(2006.01)
A61K 31/4184	(2006.01)
A61P 29/00	(2006.01)
C07D 401/12	(2006.01)
A61K 31/4439	(2006.01)

(52) **U.S. Cl.** **514/322**; 548/307.4; 514/395; 546/199; 546/273.4; 514/338

(57) **ABSTRACT**

The present invention relates to compounds of general formula I

I



in which A, L, M, Q^2, Q^3, Q^4, R^1, R^5, R^a, R^b, R^c, W, X, Y, Z^1, Z^2, Z^3 are defined in the description, the salts thereof, particularly the physiologically acceptable salts thereof.

The compounds are of potential utility in the treatment and/or prevention of inflammatory diseases and associated conditions, in particular, in the treatment and/or prevention of pain.

The invention also relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to their preparation.

PIELIKUMS 3

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 February 2012 (23.02.2012)

PCT

(10) International Publication Number
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(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 29/00* (2006.01)
A61K 31/437 (2006.01)

(21) International Application Number:
PCT/EP2011/064257

(22) International Filing Date:
19 August 2011 (19.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10173502.5 20 August 2010 (20.08.2010) EP

(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Straße 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PRIEPKE, Henning** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **DOODS, Henri** [NL/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **KUELZER, Raimund** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PFAU, Roland** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **STENKAMP, Dirk** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PELCMAN, Benjamin** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **ROENN, Robert** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **LUBRIKS, Dimitrijs** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV). **SUNA, Edgars** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV).

(74) Agents: **HAMMANN, ET.AL., Heinz** et al.; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

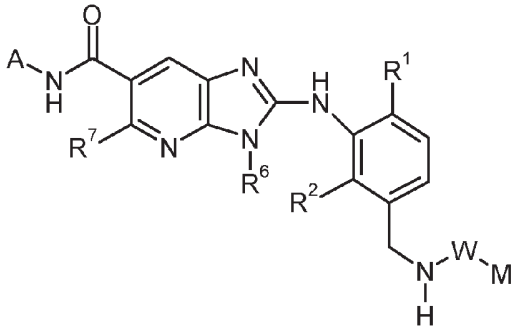
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: 2-(ARYLAMINO)-3H-IMIDAZO[4,5-B]PYRIDINE-6-CARBOXAMIDE DERIVATIVES AND THEIR USE AS MPGES-1 INHIBITORS



(I)

(57) Abstract: This invention relates to compounds of formula (I) their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, M, W, R^1, R^2, R^6, R^7 have meanings given in the description.

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US 20120208839A1

(19) United States

(12) Patent Application Publication

(10) Pub. No.: US 2012/0208839 A1

(43) Pub. Date: Aug. 16, 2012

PRIEPKE et al.

(54) NEW COMPOUNDS

(75) Inventors: **Henning PRIEPKE**, Warthausen (DE); **Henri DOODS**, Warthausen (DE); **Raimund KUELZER**, Mittelbiberach (DE); **Roland PFAU**, Biberach (DE); **Dirk STENKAMP**, Biberach (DE); **Benjamin PELCMAN**, Stockholm (SE); **Robert ROENN**, Uppsala (SE); **Dimitrijs LUBRIKS**, Riga (LV); **Edgars SUNA**, Riga (LV)

(73) Assignee: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, Ingelheim am Rhein (DE)

(21) Appl. No.: **13/211,471**

(22) Filed: **Aug. 17, 2011**

(30) **Foreign Application Priority Data**

Aug. 20, 2010 (EP) 10 173 502.5

Publication Classification

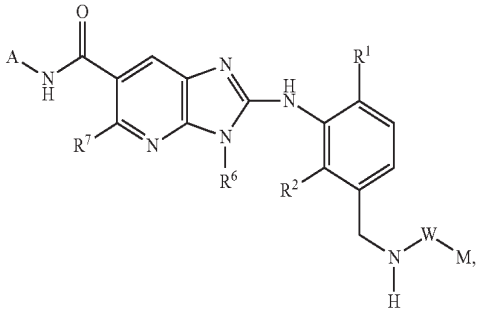
(51) **Int. Cl.**

A61K 31/437 (2006.01)
A61P 29/00 (2006.01)
C07D 471/04 (2006.01)

(52) **U.S. Cl.** **514/303**; 546/118

(57) **ABSTRACT**

This invention relates to compounds of formula I



I

their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, M, W, R^1, R^2, R^6, R^7 have meanings given in the description.

PIELIKUMS 4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2012 (14.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/076672 A1

(51) International Patent Classification:
C07D 235/30 (2006.01) *C07D 405/12* (2006.01)
C07D 401/04 (2006.01) *C07D 409/14* (2006.01)
C07D 401/12 (2006.01) *C07D 413/12* (2006.01)
C07D 401/14 (2006.01) *C07D 417/12* (2006.01)
C07D 403/04 (2006.01) *A61K 31/4184* (2006.01)
C07D 403/12 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/EP2011/072256

(22) International Filing Date:
9 December 2011 (09.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10194456.9 10 December 2010 (10.12.2010) EP

(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Straße 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PRIEPKE, Henning** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **KUELZER, Raimund** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **MACK, Juergen** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PFAU, Roland** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **STENKAMP, Dirk** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PELCMAN, Benjamin** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **ROENN, Robert** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **LUBRIKS, Dimitrijs** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV). **SUNA, Edgars** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV).

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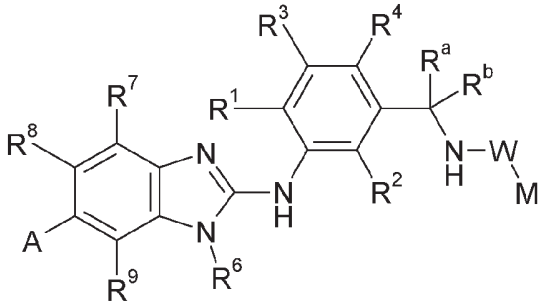
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: 2 -AMINOBENZ IMIDAZOLE DERIVATIVES USEFUL IN THE TREATMENT OF INFLAMMATION



(I)

(57) Abstract: This invention relates to compounds of formula (I), their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the 10 treatment and/or prevention of inflammatory diseases and associated conditions. A, M, W, R^1, R^2, R^3, R^4, R^6, R^2,R^7, R^8, R^9, R^a, R^b have meanings given in the description.

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US 20120309738A1

(19) United States

(12) Patent Application Publication

(10) Pub. No.: US 2012/0309738 A1

(43) Pub. Date: Dec. 6, 2012

Priepke et al.

(54) **NOVEL COMPOUNDS**

(75) Inventors: **Henning Priepke**, Warthausen (DE); **Raimund Kuelzer**, Mittelbiberach (DE); **Juergen Mack**, Biberach an der Riss (DE); **Roland Pfau**, Biberach an der Riss (DE); **Dirk Stenkamp**, Biberach an der Riss (DE); **Benjamin Pelcman**, Stockholm (SE); **Robert Roenn**, Uppsala (SE); **Dimitrijs Lubriks**, Riga (LV); **Edgars Suna**, Riga (LV)

(73) Assignee: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, Ingelheim am Rhein (DE)

(21) Appl. No.: **13/314,565**

(22) Filed: **Dec. 8, 2011**

(30) **Foreign Application Priority Data**

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Publication Classification

(51) **Int. Cl.**

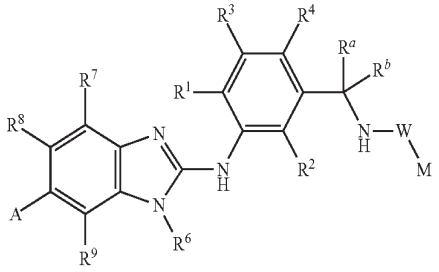
A61K 31/497	(2006.01)
A61K 31/454	(2006.01)
C07D 403/10	(2006.01)
A61K 31/4184	(2006.01)
C07D 413/10	(2006.01)
A61K 31/5377	(2006.01)
A61K 31/496	(2006.01)
A61K 31/4709	(2006.01)
C07D 409/14	(2006.01)
C07D 405/14	(2006.01)
C07D 417/14	(2006.01)
A61K 31/427	(2006.01)
C07D 403/14	(2006.01)
C07D 235/30	(2006.01)
C07D 401/14	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/422	(2006.01)
C07D 413/14	(2006.01)
A61K 31/4545	(2006.01)
A61P 29/00	(2006.01)
C07D 401/10	(2006.01)

(52) **U.S. Cl.** **514/210.18**; 546/199; 514/322; 548/306.1; 514/395; 544/139; 514/234.5; 544/370; 514/254.06; 546/169; 514/314; 548/181; 514/365; 548/307.4; 546/273.4; 514/338; 548/236; 514/374; 544/405; 514/255.05; 548/248; 546/194; 514/318; 548/300.7; 514/378

(57) **ABSTRACT**

This invention relates to compounds of formula I

I



their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), to pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, M, W, R^1, R^2, R^3, R^4, R^6, R^2, R^7, R^8, R^9, R^a, R^b have meanings given in the description.

PIELIKUMS 5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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WIPO | PCT

(10) International Publication Number
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(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 29/00* (2006.01)
A61K 31/4188 (2006.01)

(21) International Application Number:
PCT/EP2011/072258

(22) International Filing Date:
9 December 2011 (09.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10194459.3 10 December 2010 (10.12.2010) EP

(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PRIEPKE, Henning** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **DOODS, Henri** [NL/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **KUELZER, Raimund** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PFAU, Roland** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **STENKAMP, Dirk** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **PELCMAN, Benjamin** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **ROENN, Robert** [SE/SE]; Orexo AB, Box 303, S-751 05 Uppsala (SE). **LUBRIKS, Dimitrijs** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV). **SUNA, Edgars** [LV/LV]; Latvian Institute of Organic Synthesis, 21 Aizkraukles Str., LV-1006 Riga (LV).

(74) Agents: **HAMMANN, ET.AL., Heinz** et al.; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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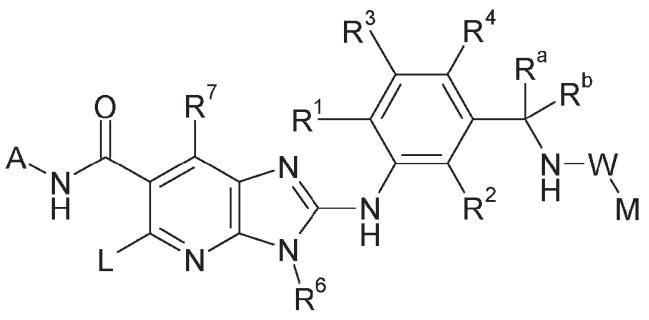
WO 2012/076674 A1

(54) Title: IMIDAZO(4,5-B)PYRIDINE-6-CARBOXAMIDES AS ANTI-INFLAMMATORY AGENTS



(I)

(57) Abstract: This invention relates to compounds of formula I their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, L, M, W, R^1, R^2, R^3, R^4, R^6, R^7, R^a, R^b have meanings given in the description.

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(54) **NOVEL COMPOUNDS**

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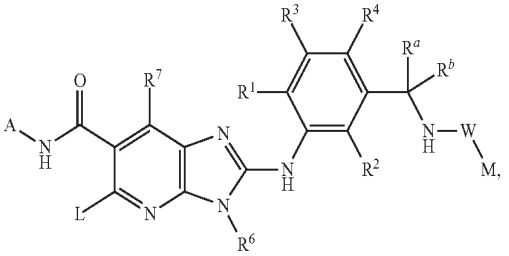
(52) **U.S. Cl.** **514/234.2**; 546/118; 514/303; 544/127

(57) **ABSTRACT**

This invention relates to compounds of formula I

I



their use as inhibitors of the microsomal prostaglandin E_2 synthase-1 (mPGES-1), pharmaceutical compositions containing them, and their use as medicaments for the treatment and/or prevention of inflammatory diseases and associated conditions. A, L, M, W, R^1, R^2, R^3, R^4, R^6, R^7, R^a, R^b have meanings given in the description.

PIELIKUMS 6

Lubriks, D.; Sokolovs, I.; Suna, E. Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles. *Org. Lett*. **2011**, *13*, 4324–4327

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Iodonium Salts Are Key Intermediates in Pd-Catalyzed Acetoxylation of Pyrroles

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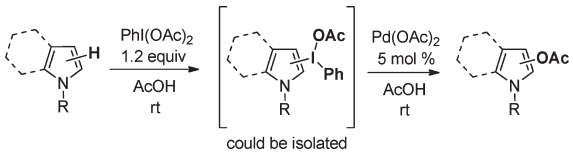
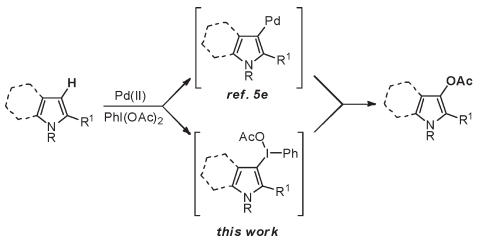
ABSTRACT



A mild, room-temperature Pd-catalyzed acetoxylation of pyrroles with phenyliodonium acetate is described. The acetoxylation was found to proceed via the initial formation of pyrrolyl(phenyl)iodonium acetates, which were converted to acetoxypyrroles in the presence of $Pd(OAc)_2$. The acetoxylation could also be carried out as a one-pot sequential procedure without the isolation of the intermediate iodonium salts.

Transition metal catalyzed selective C−H oxidation is an efficient methodology for the construction of C−O bonds.[1] The regioselectivity of the C−H activation/oxidation in aromatic systems usually is controlled by suitable *ortho*-directing groups.[2] Intriguingly, in contrast to the many examples of C−O bond formation in benzene rings,[3] the direct acetoxylation of heterocycles is much less explored.[4] Thus, there are only a few reports on direct acetoxylation of heterocycles, and the scope of substrates is limited to indoles[5] and uracil.[6] It should be noted that the regioselectivity of C−O bond formation in heterocycles typically is controlled by the inherent reactivity of a given heterocyclic system and, consequently, there is no need for the *ortho*-directing group.

Direct acetoxylation examples frequently employ $Pd(OAc)_2$ as a catalyst and $PhI(OAc)_2$ as a terminal oxidant in acetic acid, conditions that have been developed by Crabtree.[7] Mechanistic studies evidence that the Pd-catalyzed direct acetoxylation involves palladation of an aryl C−H bond with Pd(II) species as the first step,[8] which is followed by oxidation to dinuclear Pd(III) complexes[9] and, finally, product forming reductive elimination. By analogy, carbopalladation via C−H activation was considered to be the initial step also in Pd-catalyzed acetoxylation of indoles (eq 1).[5e]



(1)

The present report on a selective oxidation of substituted pyrroles[10] expands the scope of heterocycles for the

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(2) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.

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(6) Lee, H. S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2010**, *31*, 238.

(7) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35.

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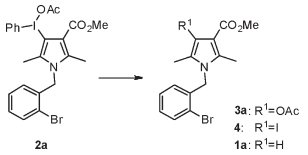
Pd-catalyzed acetoxylation reaction. Also, we provide evidence that the acetoxylation of electron-rich heterocycles such as pyrroles and indoles under Crabtree conditions most likely occurs via the initial formation of heteroaryliodonium acetates (eq 1).[11] The latter are transformed into an acetoxylated product in the presence of a Pd catalyst.

Initially, Crabtree acetoxylation conditions were examined for synthesis of acetoxypyrroles and the progress of the reaction was followed by NMR methods. Thus, stirring the pyrrole **1a** with $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (2 equiv) in AcOH-d_4 showed complete conversion within 2 h at ambient temperature.[12] Two sets of signals in a 3.5:1 ratio were observed in the ^1H NMR spectrum of the reaction mixture. The minor set of signals corresponded to acetoxypyrrole **3a**, whereas the major set of signals was assigned to a structure of pyrrolyliodonium acetate **2a** based on ^1H NMR, ^{13}C NMR, MS data and X-ray crystallographic analysis of purified **2a**.

The iodonium acetate **2a** was stable in AcOH-d_4 solution at rt (entry 1, Table 1). However, in the presence of 5 mol % $Pd(OAc)_2$ in AcOH-d_4, **2a** was converted into the target acetoxypyrrole **3a** (90% yield) within 18 h (entry 2). Acetonitrile was equally efficient to AcOH, affording **3a** in 91% yield (entry 3). Additional experiments were performed to investigate the reactivity of iodonium salt **2a**. Heating of **2a** without the Pd catalyst yielded a mixture of products **3a**, **4**, and the starting **1a** (entry 4). Interestingly, only unreacted **2a** was observed after prolonged heating in $(CF_3)_2CHOH$, a solvent of choice for oxidative nucleophilic acetoxylation of alkylphenyl ethers (entry 5).[13] $PtCl_2$ was inferior to $Pd(OAc)_2$ as a catalyst[5e] (entry 6), whereas $PtCl_4$ did not catalyze the conversion of **2a** (entry 7). Likewise, $BF_3{\bullet}OEt_2$[14] in DCM (entry 8) and $Cu(OTf)_2$ in DCM[15] were not efficient as catalysts (entries 8, 9), whereas addition of TMS-OTf[16] resulted in the formation of an inseparable mixture of products (entry 10).

Table 1. Reactivity of Arylpyrrolyliodonium Acetate **2a**



entry	catalyst (mol %)	solvent	t (°C)	time (h)	products (yield, %)
1	–	AcOH	rt	18	**2a**
2	$Pd(OAc)_2$(5)	AcOH	rt	18	**3a**(90%)
3	$Pd(OAc)_2$(5)	MeCN	60	18	**3a**(91%)
4	–	AcOH	100	24	**3a**(45%) + **4**(20%) + **1a**(27%)
5	–	HFIP	100	18	**2a**
6	$PtCl_2$(5)	AcOH	80	48	**3a**:**1a** = 3:2
7	$PtCl_4$(5)	AcOH	80	48	**2a**
8	$BF_3{\bullet}OEt_2$(400)	CH_2Cl_2	rt	3	**2a**
9	$Cu(OTf)_2$(10)	CH_2Cl_2	35	24	**2a**
10	TMS-OTf(200)	HFIP	rt	2	products mixture

A series of pyrrolyliodonium acetates **2b**–**k** was subsequently prepared in the reaction of pyrroles **1b**–**k** with 1.2 equiv of $PhI(OAc)_2$ in AcOH at ambient temperature (63–79% yields; see Table 2). The iodonium acetates **2b**–**k** were sufficiently stable to be isolated and characterized,[17] and they can be stored in the freezer for several months. To the best of our knowledge, pyrrolyl-3-iodonium acetates have not been previously prepared in a direct electrophilic substitution of pyrrole.[18]

The yields of iodonium salts **2a**–**k** were found to be sensitive to the electronic properties of substituents on the pyrrole ring.[19] Iodonium acetates were formed from *N*-unsubstituted pyrroles **2h,k** (entries 8,11, Table 2). The regioselectivity of pyrrolyliodonium salt formation apparently is a result of the combined directing effects of pyrrole substituents.[20] Nevertheless, there is a strong preference for the formation of iodonium salts at the α-position (entries 2, 3, 9, 10),[21] and β-pyrrolyliodonium salts could be obtained only for 2,5-disubstuted heterocycles **1a,e**–**h,k** (entries 1, 5–8, 11, Table 2).

In the presence of 5 mol % $Pd(OAc)_2$ in AcOH solution at ambient temperature iodonium salts **2a**–**k**

(8) It has been shown that cyclopalladation is the rate-limiting step of the acetoxylation reaction: Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584.

(9) (a) Powers, D.; Ritter, T. *Top. Organomet. Chem.* **2011**, *35*, 129. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.

(10) (a) The 3-hydroxypyrrole subunit is incorporated into Obatoclax, an experimental drug candidate for the treatment of various types of cancer: *Drugs Future*, **2007**, *32*, 228. Substituted 3-hydroxypyrroles have also been employed: (b) as anti-tumor agents: Cholody, W. M.; Petukhova, V.; O'Brien, S.; Ohler, N.; Pikul, S. WO 011675 *A1*, 2005; *Chem. Abstr.* **2005**, *142*, 197868. (c) in the design of DNA-binding ligands: Wellenzohn, B.; Loferer, M. J.; Trieb, M.; Rauch, C.; Winger, R. H.; Mayer, E.; Liedl, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 1088.

(11) Consequently, the acetoxylation with $PhI(OAc)_2$ does not involve a C–H activation step by a Pd catalyst. The role of transition metal catalysts has recently been reinvestigated also in other $PhI(OAc)_2$ mediated reactions; see: (a) Kang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. (b) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996.

(12) The use of $Pd(OAc)_2$ together with other oxidants such as $PhCO_3tBu$ (2 equiv, 65 °C, Ac_2O, 21 h), *m*-CPBA (2 equiv, 100 °C, AcOH, 2 h), $K_2S_2O_8$ (2 equiv, 100 °C, AcOH, 2 h), and Oxone (2 equiv, 100 °C, AcOH, 2 h) did not afford the acetoxylated pyrrole **3a**.

(13) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

(14) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109.

(15) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(16) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto., K.; Fujioka, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 3334.

(17) The majority of solid aryliodonium acetates **2b**–**k** are hygroscopic and decompose at temperatures above 25 °C. However, they are stable in acetic acid solutions.

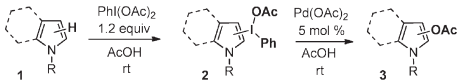
(18) Single report on preparation of pyrrolyl-3-iodonium triflates from 3-trimethylsilylpyrrole: Liu, J.-H.; Chan, H.-W.; Xue, F.; Wang, Q.-G.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1999**, *64*, 1630.

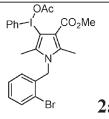
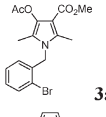
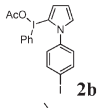
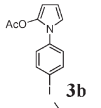
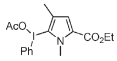
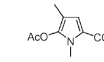
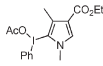
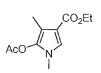
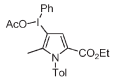
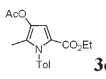
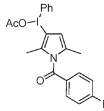
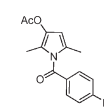
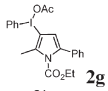
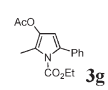
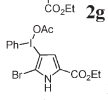
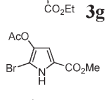
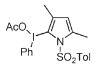
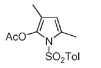
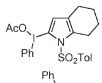
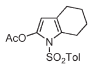
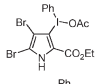
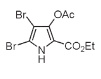
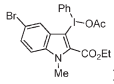
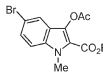
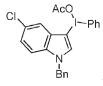
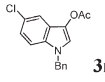
(19) Correlation between yields of phenyliodonium salts and Hammett σ constants of substituents has been reported: Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775. See also the Supporting Information, p S26.

(20) For substituent effect on regioselectivity of S_EAr reactions of pyrroles, see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons: Chichester, 2010; pp 289–323.

(21) For other examples, see: (a) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775. (b) Reference 16. (c) Martin-Santamaria, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, 649.

Table 2. Acetoxylation of Pyrroles **1a**–**k** and Indoles **1l**–**m** via Isolation of Intermediate Iodonium Salts **2a**–**m**



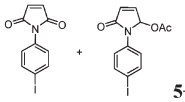
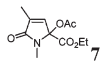
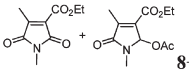
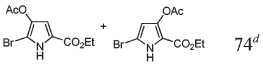
entry	iodonium salt	time (h)	yield (%)	product	time (h)	yield[a] (%)
1	 **2a**	6	78	 **3a**	18	90
2	 **2b**	3	77	 **3b**	1	85
3	 **2c**	6	72	 **3c**	3	79
4	 **2d**	3	79	 **3d**	3	78
5	 **2e**	6	65	 **3e**	18	79
6	 **2f**	3	79	 **3f**	18	71
7	 **2g**	18	63	 **3g**	18	73
8	 **2h**	18	73	 **3h**	18	79
9	 **2i**	3	71	 **3i**	18	67
10	 **2j**	18	71	 **3j**	18	71
11	 **2k**	18	79	 **3k**	1	74[b]
12	 **2l**	18	79	 **3l**	1	81[b]
13	 **2m**	6	66	 **3m**	3	73

[a] Yields for the conversion from **2** to **3**. [b] Heating at 100 °C.

were readily converted into the target acetoxypyrroles **3a**–**k** (see Table 2). A simple workup and purification by chromatography afforded pure **3a**–**k** (Table 2). The Pd-catalyzed acetoxylation conditions are compatible with the presence of bromine (entries 8, 11) and even iodine (entry 2). *N*-Alkyl, *N*-aryl, *N*-benzoyl, *N*-benzyl, *N*-tosyl, and *N*-carbamoyl are tolerated at the pyrrole nitrogen (Table 2).

We have found that the acetoxypyrroles **3a**–**k** could also be synthesized in a sequential one-pot approach without

Table 3. One-Pot Sequential Procedure vs Crabtree Conditions

entry	pyrrole	One-pot[a] product	yield (%)	Crabtree conditions[b] product	yield (%)
1	**1a**	**3a**	92	**3a**	85
2	**1b**	**3b**	56	 **5+6**	27 (**5**)[c] 41 (**6**)[c]
3	**1c**	**3c**	80	 **7**	75[c]
4	**1d**	**3d**	77	 **8+9**	34 (**8**)[c] 51 (**9**)[c]
5	**1e**	**3e**	86	**3e**	76
6	**1f**	**3f**	60	**3f**	65
7	**1g**	**3g**	50	-	-
8	**1h**	**3h**	74	 **3h**:**10**=4:1	74[d]
9	**1i**	**3i**	42	-	-
10	**1j**	**3j**	41	-	-
11	**1k**	**3k**	69	**3k**	41[e,e]
12	**1l**	**3l**	86	**3l**	77[f]
13	**1m**	**3m**	70	**3m**	51

[a] Pyrrole **1** (1 equiv) and $PhI(OAc)_2$ (1.2 equiv) were stirred in AcOH at rt for 3–18 h (see Table 2 for time; the formation of **2** was monitored by ^1H NMR), then $Pd(OAc)_2$ (0.05 equiv) was added, and stirring at rt was continued for 1–18 h (see Table 2). [b] Pyrrole **1** (1 equiv), $PhI(OAc)_2$ (1.3 equiv), and $Pd(OAc)_2$ (0.05 equiv) were heated in AcOH at 100 °C for 1 h. [c] 2.3 equiv of $PhI(OAc)_2$. [d] Yield of a 4:1 mixture of **3h** and **10**. [e] Heating at 100 °C for 3 h. [f] Reference 5e.

isolation of the intermediate iodonium salts **2a**–**k** (see Table 3). Accordingly, $Pd(OAc)_2$ was added to the reaction mixture after the corresponding iodonium acetate has been formed.[22] In general, the sequential one-pot approach afforded higher yields of **3a**–**k** compared to the two-step reaction. Importantly, the original Crabtree[7] conditions are inferior to the sequential one-pot approach. Thus, not only the yields are substantially lower (Table 3, entries 1, 5, 8, 11, 12) but also the formation of overoxidation products is more pronounced. For example, acetoxylation of pyrroles **1b**–**d** under Crabtree conditions (entries 2–4, Table 3) afforded mixtures of pyrrole-2,5-diones **5,8** and 5-functionalized pyrrolidin-2-ones **6,7,9**. γ-Lactams such as **6,7,9** have been found in a wide range of biologically active natural products.[23]

The initial formation of salts **2a**–**k** in the Pd-catalyzed acetoxylation reaction prompted us to hypothesize that the previously reported acetoxylation of indoles under similar conditions ($Pd(OAc)_2$ and $PhI(OAc)_2$)[5e] may also proceed via the intermediate indolyliodonium acetates. Indeed, treatment of indoles **1l,m** with $PhI(OAc)_2$ in AcOH afforded C3-iodonium salts **2l,m** which were stable in AcOH-d_4 solution and could be isolated.[24]

(22) The formation of iodonium acetates **2a**–**k** was controlled by ^1H NMR. The addition of $Pd(OAc)_2$ early on resulted in the formation of overoxidation products.

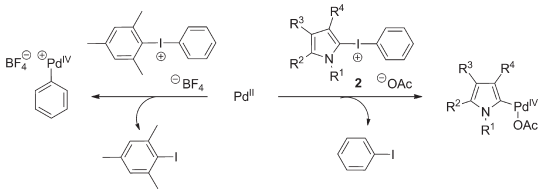
(23) For a review, see: Nay, B.; Riache, N.; Evanno, L. *Nat. Prod. Rep.* **2009**, *26*, 1044.

(24) The structures of **2a** and **2l** were confirmed by X-ray analysis; see the Supporting Information, pp S29 and S30.

Furthermore, salts **2l,m** were smoothly converted into acetoxyindoles **3l,m** in the presence of $Pd(OAc)_2$ (5 mol %) (see Table 2, entries 12, 13). The sequential one-pot approach afforded higher yields of **3l** compared to the Crabtree conditions (86% vs 77%, Table 3, entry 12).

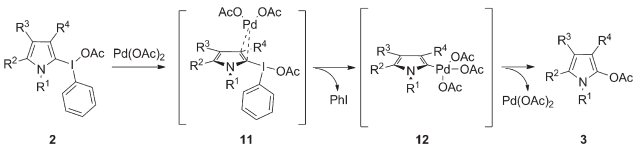
The Pd-catalyzed formation of C−O bonds from iodonium acetates **2a**−**m** showed high regioselectivity for the sterically more bulky heterocycle ring, and *O*-acetylphenol formation was not observed. Assuming that acetoxylation occurs via the initial transfer of pyrroles and indoles from the iodonium salts **2** to Pd, the observed regioselectivity is striking, because the less hindered aryl group usually is transferred from nonsymmetrical diaryliodonium salts (such as [Ar-I-Mes]BF_4) to Pd (Scheme 1).[25]

Scheme 1. Regioselectivity in the Reaction of Nonsymmetrical Iodonium Salts with Palladium



Apparently, electronic preferences rather than steric factors control the acetoxylation regioselectivity of salts **2**. Thus, it has been demonstrated that in Pd(II)-catalyzed reactions the more electron-rich Ar moiety is selectively transferred from unsymmetrical diaryliodonium salts [Ar-I-Ar′]BF_4 to a Pd catalyst.[26,27] The high regioselectivity of the pyrrole and indole ring transfer to a Pd catalyst, presumably, is ensured by η^2-coordination of an iodonium substituted double bond of the more electron-rich pyrrolyliodonium moiety to the Pd(II) species (complex **11**, Scheme 2).[28] Subsequent oxidative addition would generate a transient pyrrolyl−Pd(IV) complex **12**, which undergoes C−O bond forming reductive elimination.

Scheme 2. Proposed Mechanism for Acetoxylation of Pyrroles



The acetoxylation of pyrroles presumably involve a Pd(II)/Pd(IV) or Pd(II)/Pd(III) catalytic cycle. However, the Pd(0)/Pd(II) catalytic cycle cannot be ruled out, as evidenced by the "mercury drop" test.[29] Thus, addition of a large excess (> 300 equiv) of metallic Hg to a mixture of iodonium acetate **2a** and $Pd(OAc)_2$ (5 mol %) in AcOH resulted in complete inhibition of the acetoxylation (< 5% of acetoxypyrrole **3a** was formed).[30] Additional work is ongoing to elucidate the mechanism of the Pd-catalyzed conversion of **2** to **3**.

In summary, a series of stable pyrrolyl(aryl)iodonium and indolyl(aryl)iodonium acetates **2a**−**m** have been prepared and characterized. The formation of intermediate iodonium salts of pyrroles **2a**−**k** and indoles **2m,l** under the acetoxylation conditions as well as their Pd-catalyzed conversion to oxidized heterocycles **3a**−**l** indicate that iodonium salts **2a**−**l** are actual intermediates in the acetoxylation reaction. Consequently, we propose that the formation of iodonium salts **2** is the first step in the catalytic cycle for the acetoxylation of pyrroles and indoles. Such a mechanism differs from the closely related Pd-catalyzed C2-arylation of pyrroles and indoles with diaryliodonium salts, which proceeds via the initial carbopalladation of the pyrrole ring.[31] Further studies to expand the scope of heterocycles in the Pd-catalyzed regioselective acetoxylation reaction via iodonium acetates are ongoing in our laboratory.

Acknowledgment. This work was supported by the European Regional Development Fund (No. 2DP/2.1.1.1.0/10/APIA/VIAA/066).

Supporting Information Available. Experimental procedures, products characterization, copies of ^1H and ^{13}C NMR spectra, and X-ray crystallographic data for iodonium salts **2a,l** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

(25) The presence of a bulky mesityl group in iodonium salts [Mes-I-Ar]X ensured the selective transfer of the smaller Ar group in Pd-catalyzed arylations: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. For the analogous use of a nontransferrable 2,4,6-tri-isopropylphenyl group, see:Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(26) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924 and references cited therein.

(27) Decomposition of [Mes-I-Ph]OAc under Crabtree acetoxylation conditions ($Pd(OAc)_2$, AcOH, 100 °C, 18 h) was moderately selective for the formation of Mes-OAc (ratio Mes-OAc/Mes-I = 3.4:1).

(28) (a) Related η^2-coordination of 2-tributylstannylfurane to Pd(II) followed by tin-to-palladium transmetallation of the furyl group has been observed: Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016. (b) For related stable η^2-arylgold(I) complexes, see: Herrero-Gómez, E.; Nieto-Oberhuber, C.; Salomé, L.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(29) (a) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855. (b) Foley, P.; DiCosimo, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 6713.

(30) The formation of palladium black has always been observed in the late stages of the acetoxylation.

(31) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

Catalytic Acetoxylation of Pyrroles

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CONTENTS

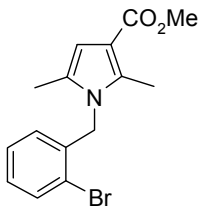
General.

All reactions were carried out under an argon atmosphere. Progress of reactions was monitored by thin-layer chromatography on Merck Kieselgel $60F_{254}$. Flash column chromatography was performed using Biotage SP1 Flash Purification System and Biotage KP-Sil 25+M or Biotage KP-Sil 12+M silica cartridges.

^{1}H NMR spectra were recorded on Varian Inova 400 MHz NMR spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Melting points were uncorrected. Elemental analyses were performed using Carlo-Erba CHNS-0 EA1108 instrument. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

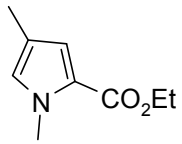
All reagents were obtained commercially and used as received.

Experimental Procedures for Synthesis of Starting Pyrroles and Indoles 1a–o.

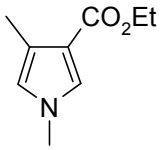


Methyl 1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (1a). NaH (60% in mineral oil, 240 mg, 6.0 mmol, 1.2 equiv) was washed under an argon atmosphere with anhydrous Et_2O (2x5 mL) to remove the mineral oil, suspended in anhydrous DMF (6 mL) and cooled to 1-2 ^{o}C in an ice-bath. A solution of methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate (766 mg, 5.0 mmol, 1 equiv) in anhydrous DMF (6 mL) was added dropwise. When gas evolution ceased, the ice-bath was removed. After stirring at ambient temperature for 1 h, a solution of 2-bromobenzylbromide (1.50 g, 6.0 mmol, 1.2 equiv) in anhydrous DMF (10 mL) was added. After stirring for 12 h at room temperature the solvent was evaporated and the residue was partitioned between water (50 mL) and EtOAc. Aqueous layer was extracted with EtOAc (2x30 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow oil (1.48 g, 92% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.31. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 95-96 ^{o}C. IR (film, cm^{-1}) 1695 (C=O), 1221 (C-O), 733 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.58 (1H, dd, *J*=7.7, 1.4 Hz), 7.18 (1H, td, *J*=7.5, 1.4 Hz), 7.13 (1H, td, *J*=7.7, 1.9 Hz), 6.36 (1H, d, *J*=1.0 Hz), 6.25-6.21 (1H, m), 5.02 (2H, s), 3.80 (3H, s), 2.41 (3H, s), 2.09 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm)

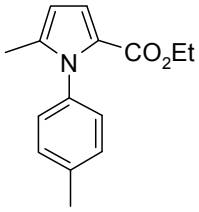
δ 166.2, 136.2, 135.8, 132.8, 129.1, 128.2, 128.2, 126.7, 121.6, 111.3, 108.1, 50.9, 47.5, 12.1, 11.3. Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; N, 4.35 Found: C, 55.98; H, 4.96; N, 4.14.



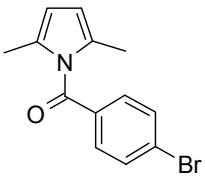
Ethyl 1,4-dimethyl-1*H*-pyrrole-2-carboxylate (1c). The same procedure was used as for **1a**. Accordingly, ethyl 4-methyl-1*H*-pyrrole-2-carboxylate (500 mg, 3.26 mmol) was converted into pyrrole **1c.** Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow oil (472 mg, 87% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.59. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.68 (1H, d, *J*=2.0 Hz), 6.51–6.44 (1H, m), 4.18 (2H, q, *J*=7.1 Hz), 3.78 (3H, s), 1.98 (3H, s), 1.26 (3H, t, *J*=7.1 Hz).



Ethyl 1,4-dimethyl-1*H*-pyrrole-3-carboxylate (1d). The same procedure was used as for **1a**. Accordingly, ethyl 4-methyl-1*H*-pyrrole-3-carboxylate (500 mg, 3.26 mmol) was converted into pyrrole **1d**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow oil (514 mg, 94% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.37. IR (film, cm^{-1}) 1704 (C=O), 1251 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.17 (1H, d, *J*=2.5 Hz), 6.33 (1H, dd, *J*=2.5, 1.0 Hz), 4.23 (2H, q, *J*=7.1 Hz), 3.58 (3H, s), 2.24 (3H, d, *J*=1.0 Hz), 1.32 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 165.5, 127.7, 121.9, 121.5, 114.4, 59.3, 36.4, 14.6, 11.8. HRMS-ESI (m/z) calcd for $C_9H_{14}NO_2$ $[M+H]^+$ 168.1053, found 168.1025.

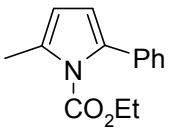


Ethyl 5-methyl-1-(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (1e). An oven-dried screw-cap pressure tube was charged with CuI (0.15 mmol, 29 mg, 0.05 equiv), ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (460 mg, 3.00 mmol, 1 equiv), K_3PO_4 (1.34 g, 6.30 mmol, 2.1 equiv). 4-Iodotoluene (785 mg, 3.60 mmol, 1.2 equiv), *N*,*N*'-dimethylethylen-1,2-diamine (65 µL, 0.60 mmol, 2 equiv) and toluene (5 mL) were then added successively under a stream of argon. After stirring at 110 °C for 48 h and cooling to room temperature, the reaction was diluted with EtOAc and filtered through a Celite pad (20 mL of Celite). Celite pad was washed with EtOAc (25 mL), combined filtrates were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow oil (470 mg, 92% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.37. IR (film, cm^{-1}) 1704 (C=O), 1169 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28–7.25 (2H, m), 7.14–7.07 (2H, m), 7.03 (1H, d, *J*=3.8 Hz), 6.05 (1H, dd, *J*=3.8, 1.0 Hz), 4.13 (2H, q, *J*=7.1 Hz), 2.44 (3H, s), 2.04 (3H, s), 1.20 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 160.6, 138, 137.7, 136.8, 129.5, 127.6, 123.7, 117.7, 108.0, 77.2, 59.6, 21.4, 14.4, 13.1. HRMS-ESI (m/z) calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1320, found 244.1338.

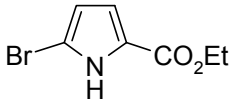


1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrole (1f). KHMDS (11.6 mL, 1M solution in THF, 1.1 equiv) was added dropwise to a cooled solution (-78 °C) of 2,5-dimethyl-1*H*-pyrrole (1.00 g, 10.51 mmol, 1 equiv) in anhydrous THF (15 mL) under argon atmosphere. After stirring at -78 °C for 1 h, the solution of 4-bromo-benzoyl chloride (2.54 g, 11.56 mmol, 1.1 equiv) in anhydrous THF (10 mL) was added dropwise. After stirring for 1 h at -78 °C, the reaction was warmed to room temperature and left to stir for more 12 h. Aqueous saturated 1N NH_4Cl (50 mL) was added and product was extracted with MeO*t*Bu (3x25 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a brown solid (1.9 g, 65% yield); analytical

TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.59. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 48-49 °C. IR (film, cm^{-1}) 1699 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64–7.60 (2H, m), 7.58–7.54 (2H, m), 5.88 (2H, s), 2.07 (6H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.3, 134.6, 132.2, 131.7, 130.4, 128.5, 110.6, 77.2, 14.9. Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04 Found: C, 56.15; H, 4.29; N, 4.89.



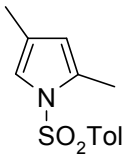
Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (1g). NaH (60% in mineral oil, 516 mg, 12.9 mmol, 1.2 equiv) was washed under an argon atmosphere with anhydrous Et_2O (2x5 mL) to remove the mineral oil, suspended in anhydrous DMF (5 mL) and cooled to 1-2 °C in an ice-bath. A solution of methyl 2-methyl-5-phenyl-1*H*-pyrrole (1.69 g, 10.75 mmol, 1 equiv) in anhydrous DMF (5 mL) was added dropwise. When gas evolution ceased, the ice bath was removed. After stirring at ambient temperature for 1 h, a solution of ethyl chloroformate (1.4 g, 12.9 mmol, 1.2 equiv) in anhydrous DMF (3 mL) was added. After stirring for 12 h the solvent was evaporated and the residue was partitioned between H_2O (50 mL) and EtOAc (100 mL). Aqeous layer was extracted with EtOAc (2x100 mL), combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a colourless oil (1.55 g, 63% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.48. IR (film, cm^{-1}) 1739 (C=O), 1215 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36–7.26 (5H, m), 6.12 (1H, d, *J*=3.2 Hz), 5.99 (1H, dd, *J*=3.2, 1.0 Hz), 4.15 (2H, q, *J*=7.1 Hz), 2.47 (3H, d, *J*=1.0 Hz), 1.01 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 152, 135.2, 133.3, 128.4, 127.8, 126.9, 112.9, 111, 77.2, 63.1, 15.5, 13.6. HRMS-ESI (m/z) calcd for $C_{14}H_{16}NO_2$ $[M+H]^+$ 230.1259, found 230.1293.



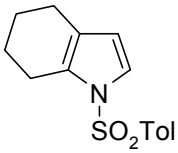
Ethyl 5-bromo-1*H*-pyrrole-2-carboxylate (1h). Ethyl 1*H*-pyrrole-2-carboxylate (1 g, 7.19 mmol) was converted into pyrrole **1h** (650 mg, 41%) in accordance with literature procedure.[1] Purification of the crude product by column chromatography (30x150 mm) using isocratic elution 12% EtOAc/light petroleum ether afforded product as a yellow solid (650 mg, 41% yield); analytical

([1]) Furukawa, A.; Fukuzaki, T.; Onishi, Y.; Kobayashi, H.; Honda, T.; Matsui, Y.; Konishi, M.; Matsufuji, T.; Ueda, K. EP 2239253 A1, 2010; *Chem. Abstr.* **2010**, *151*, 245651.

TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.36. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.65–9.34 (1H, br s), 6.83 (1H, dd, *J*=3.8, 2.6 Hz), 6.21 (1H, dd, *J*=3.8, 2.6 Hz), 4.34 (2H, q, *J*=7.1 Hz), 1.36 (3H, t, *J*=7.1 Hz).

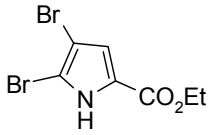


2,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole (1i). The same procedure was used as for **1f**. Accordingly, 2,4-dimethyl-1*H*-pyrrole (730 mg, 7.67 mmol) was converted into pyrrole **1i**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a brown solid (1.72 g, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.41. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 85-86 °C (lit.[2] mp 85 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.67–7.59 (2H, m), 7.28–7.24 (2H, m), 7.01–6.92 (1H, m), 5.81–5.73 (1H, m), 2.38 (3H, s), 2.24 (3H, s), 1.97 (3H, d, *J*=1.0 Hz).

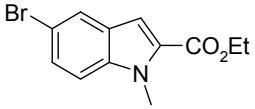


1-[(4-Methylphenyl)sulfonyl]-4,5,6,7-tetrahydro-1*H*-indole (1j). The same procedure was used as for **1f**. Accordingly, 4,5,6,7-tetrahydro-1*H*-indole (500 mg, 4.13 mmol) was converted into pyrrole **1j**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a brown solid (1.01 g, 89% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.41. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 100–101 °C. IR (film, cm^{-1}) 1168 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.68–7.64 (2H, m), 7.30–7.26 (2H, m), 7.15 (1H, d, *J*=3.3 Hz), 6.05 (1H, d, *J*=3.3 Hz), 2.66 (2H, t, *J*=6.1 Hz), 2.40 (3H, s), 2.38 (2H, t, *J*=6.1 Hz), 1.74–1.68 (2H, m), 1.65-1.59 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 144.6, 136.8, 130.1, 129.3, 126.9, 123.6, 120.7, 112.4, 77.2, 23.3, 23.2, 23.1, 22.7, 21.7. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09 Found: C, 65.47; H, 6.16; N, 4.99.

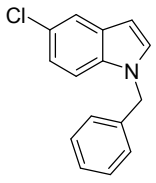
([2]) Voshchula, V. N.; Dulenko, V. I. *Chem. Het. Comp.* **1987**, *23*, 819.



Ethyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (1k). Ethyl 1*H*-pyrrole-2-carboxylate (2 g, 14.4 mmol) was converted to pyrrole **1k** (2.9 g, 68%) in accordance to literature procedure.[3] Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 10% EtOAc/light petroleum ether to 40% EtOAc/light petroleum ether afforded product as a yellow solid (2.9 g, 68% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.41. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 124-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.05-9.78 (1H, br s), 6.89 (1H, d, *J*=3.0 Hz), 4.36 (2H, q, *J*=7.1 Hz), 1.36 (3H, t, *J*=7.1 Hz).



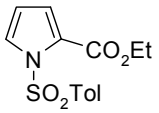
Ethyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (1l). Ethyl 5-bromo-1*H*-indole-2-carboxylate (2 g, 14.4 mmol) was converted to indole **1l** (1.96 g, 93%) in accordance to literature procedure.[4] Purification of the crude product by column chromatography (Biotage Si 40+M) using gradient elution from 10% EtOAc/light petroleum ether to 40% EtOAc/light petroleum ether afforded product as a white solid (1.96 g, 93% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.55. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, dd, *J* = 1.8, 0.8 Hz), 7.41 (1H, dd, *J* = 8.9, 1.8 Hz), 7.27-7.24 (1H, m, overlapped with $CHCl_3$), 7.21 (1H, d, *J* = 0.8 Hz), 4.38 (2H, q, *J* = 7.1 Hz), 4.06 (3H, s), 1.41 (3H, t, *J* = 7.1 Hz).



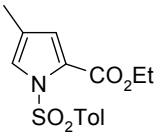
1-Benzyl-5-chloro-1*H*-indole (1m). The same procedure was used as for **1a**. Accordingly, 5-chloro-1*H*-indole (500 mg, 3.26 mmol) was converted to indole **1m**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow solid (748 mg, 95% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.46. Pure material

([3]) Hurley, P.; Ding, H.; Andrew, G.; Harran, P. G.; Li, Q.; Akella, R. *J. Org. Chem.* **2009**, *74*, 5909.
([4]) Stefany, D.; Harris, K. J.; Gillespy, T. A.; Gardner, C. J.; Aguiar, J., C. WO 121280 A1, 2007; *Chem. Abstr.* **2007**, *147*, 469370.

was obtained by crystallization from EtOAc/light petroleum ether: mp 63–64 °C (lit.[5] mp 61–62.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (1H, d, *J*=2.0 Hz), 7.35-7.28 (3H, m), 7.19 (1H, d, *J*=8.7 Hz), 7.16 (1H, d, *J*=3.2 Hz), 7.13 (1H, dd, *J*=8.7, 2.0 Hz), 7.11–7.08 (2H, m), 6.51 (1H, d, *J*=3.2 Hz), 5.31 (2H, s).



Ethyl 1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (1n). The same procedure was used as for **1g**. Accordingly, ethyl 1*H*-pyrrole-2-carboxylate (500 mg, 3.59 mmol) was converted to pyrrole **1n**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a yellow oil (970 mg, 92% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.33. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.91–7.82 (2H, m), 7.70 (1H, dd, *J*=3.2, 1.9 Hz), 7.33–7.29 (2H, m), 7.04 (1H, dd, *J*=3.7, 1.9 Hz), 6.29 (1H, dd, *J*=3.7, 3.2 Hz), 4.19 (2H, q, *J*=7.1 Hz), 2.42 (3H, s), 1.25 (3H, t, *J*=7.1 Hz).

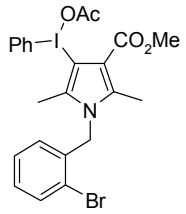


Ethyl 4-methyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole-2-carboxylate (1o). The same procedure was used as for **1g**. Accordingly, ethyl 4-methyl-1*H*-pyrrole-2-carboxylate (500 mg, 3.26 mmol) was converted to pyrrole **1o**. Purification of the crude product by column chromatography (Biotage Si 25+M) using gradient elution from 5% EtOAc/light petroleum ether to 30% EtOAc/light petroleum ether afforded product as a brown solid (450 mg, 83% yield); analytical TLC on silica gel, 1:10 EtOAc/light petroleum ether, Rf=0.26. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 93–94 °C. IR (film, cm^{-1}) 1726 (C=O), 1228 (C-O), 1178 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88–7.83 (2H, m), 7.47–7.43 (1H, m), 7.32–7.28 (2H, m), 6.88 (1H, d, *J*=2.0 Hz), 4.17 (2H, q, *J*=7.1 Hz), 2.41 (3H, s), 2.08 (3H, s), 1.24 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 158.9, 144.8, 136.3, 129.5, 128.1, 126.7, 125.1, 124.9, 120.9, 77.2, 60.7, 21.8, 14.3, 11.6. Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.58; N, 4.56 Found: C, 58.56; H, 5.45; N, 4.43.

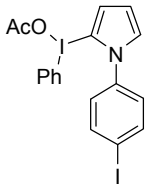
[5] Trost, B. M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074.

General Procedure for Synthesis of Iodonium Salts 2a–m.

An oven-dried flask was cooled under stream of argon, charged with $PhI(OAc)_2$ (1.2 equiv) and pyrroles **1a-k** or indoles **1l-m** (1 equiv) and closed with septa. Glacial acetic acid (4 mL/1.0 mmol of pyrrole) was added via syringe and the reaction was stirred at room temperature for 3-18 h (see Table 2 for appropriate time) whereupon it was dry-absorbed on silica gel (concentrated *in vacuo* at room temperature in the presence of silica gel). The residue was purified by column chromatography on silica gel.

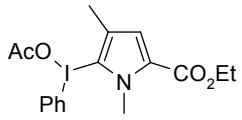


Methyl 4-[(acetyloxy)(phenyl)-λ^3-iodanyl]-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (2a). Following the general procedure, pyrrole **1a** (700 mg, 2.18 mmol) was converted into iodonium salt **2a**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (995 mg, 78% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.75. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 147-148 ^oC (dec.). IR (film, cm^{-1}) 1699 (C=O), 1558 (AcO^-), 1219 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95–7.86 (2H, m), 7.65–7.58 (1H, m), 7.49–7.39 (1H, m), 7.38–7.29 (2H, m), 7.23–7.16 (2H, m), 6.11–6.03 (1H, m), 5.12 (2H, s), 3.83 (3H, s), 2.44 (3H, s), 2.36 (3H, s), 1.97 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 178.9, 163.3, 138.9, 136.6, 134.5, 133.2, 133.1, 131.1, 130.5, 129.7, 128.4, 126, 121.7, 121.2, 112.6, 93.4, 51.4, 48.9, 24.7, 13, 11.9. Anal. Calcd for $C_{23}H_{23}BrINO_4$: C, 47.28; H, 3.97; N, 2.40 Found: C, 47.34; H, 3.89; N, 2.22.

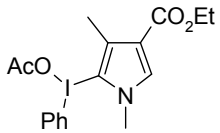


2-[(Acetyloxy)(phenyl)-λ^3-iodanyl]-1-(4-iodophenyl)-1*H*-pyrrole (2b). Following the general procedure, pyrrole **1b** (800 mg, 2.97 mmol) was converted into iodonium salt **2b**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (1.15 g, 77% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.64. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 101-102 ^oC (dec.). IR (film, cm^{-1}) 1699 (C=O), 1543 (AcO^-); ^1H

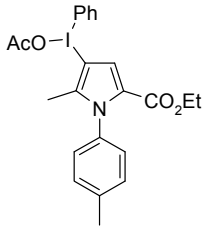
NMR (400 MHz, $CDCl_3$, ppm) δ 7.69–7.64 (2H, m), 7.54 (2H, dd, *J*=8.4, 1.0 Hz), 7.42–7.36 (1H, m), 7.27–7.24 (2H, m), 6.96 (1H, dd, *J*=3.8, 1.6 Hz), 6.92 (1H, dd, *J*=3.0, 1.6 Hz), 6.78–6.72 (2H, m), 6.39 (1H, dd, *J*=3.8, 3.0 Hz), 1.88 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 178.8, 139, 138.8, 133, 131.2, 130.7, 128.1, 128.1, 124.4, 122, 112.6, 103.3, 94.2, 24. HRMS-ESI (m/z) calcd for $C_{16}H_{12}I_2N$ $[M\text{-}OAc]^+$ 471.9086, found 471.9059.



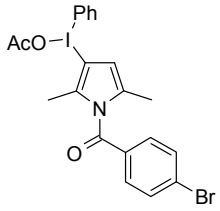
Ethyl 5-[(acetyloxy)(phenyl)-λ^3-iodanyl]-1,4-dimethyl-1*H*-pyrrole-2-carboxylate (2c). Following the general procedure, pyrrole **1c** (426 mg, 2.55 mmol) was converted into iodonium salt **2c**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (780 mg, 72% yield); analytical TLC on silica gel, 20:80:5 $MeOH/CH_2Cl_2/AcOH$, Rf=0.60. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 133-134 °C. IR (film, cm^{-1}) 1705 (C=O), 1550 (AcO^-), 1242 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81–7.74 (2H, m), 7.48–7.42 (1H, m), 7.38–7.31 (2H, m), 6.89 (1H, s), 4.26 (2H, q, *J*=7.1 Hz), 3.96 (3H, s), 2.26 (3H, s), 1.88 (3H, s), 1.32 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 179.2, 160.4, 132.8, 131.7, 130.9, 128.8, 127.8, 121.1, 118.2, 113.7, 60.8, 37, 14.4, 13.8. HRMS-ESI (m/z) calcd for $C_{15}H_{17}INO_2$ $[M\text{-}OAc]^+$ 370.0281, found 370.0304.



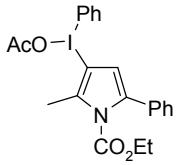
Ethyl 5-[(acetyloxy)(phenyl)-λ^3-iodanyl]-1,4-dimethyl-1*H*-pyrrole-3-carboxylate (2d). Following the general procedure, pyrrole **1d** (490 mg, 2.93 mmol) was converted into iodonium salt **2d**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a yellow solid (990 mg, 79% yield); analytical TLC on silica gel, 20:80:5 $MeOH/CH_2Cl_2/AcOH$, Rf=0.50. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 112-113 °C (dec.). IR (film, cm^{-1}) 1705 (C=O), 1535 (AcO^-), 1238 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79–7.74 (2H, m), 7.45–7.41 (1H, m), 7.45 (1H, s), 7.36–7.31 (2H, m), 4.24 (2H, q, *J*=7.1 Hz), 3.66 (3H, s), 2.48 (3H, s), 1.84 (3H, s), 1.31 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 177, 161.7, 130.5, 130.4, 129.6, 128.8, 119.2, 114, 104.5, 58, 36.1, 22.2, 12.5, 11.8. Anal. Calcd for $C_{17}H_{20}INO_4$: C, 47.57; H, 4.70; N, 3.26 Found: C, 47.20; H, 4.85; N, 3.39.



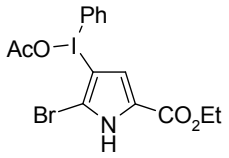
Ethyl 4-[(acetyloxy)(phenyl)-λ^3-iodanyl]-5-methyl-1-(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (2e). Following the general procedure, pyrrole **1e** (400 mg, 1.64 mmol) was converted into iodonium salt **2e**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (554 mg, 65% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.64. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 137-138 ^oC. IR (film, cm^{-1}) 1715 (C=O), 1514 (AcO^-), 1169 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.94–7.86 (2H, m), 7.49–7.44 (1H, m), 7.40–7.33 (2H, m), 7.31 (1H, s), 7.26–7.22 (2H, m), 7.05–6.99 (2H, m), 4.09 (2H, q, *J*=7.1 Hz), 2.41 (3H, s), 2.16 (3H, s), 1.89 (3H, s), 1.16 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 179, 159.3, 141.8, 139.3, 135.6, 133.2, 131.4, 130.7, 129.9, 127.2, 126.5, 122.3, 120.5, 92.2, 60.5, 24.6, 21.4, 14.2, 13.3. HRMS-ESI (m/z) calcd for $C_{21}H_{21}INO_2$ $[M\text{-}OAc]^+$ 446.0641, found 446.0617.



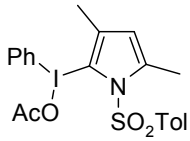
3-[(Acetyloxy)(phenyl)-λ^3-iodanyl]-1-[(4-bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrole (2f). Following the general procedure, pyrrole **1f** (700 mg, 2.52 mmol) was converted into iodonium salt **2f**. Purification of the crude product by column chromatography (25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a brown powder (1.08 g, 79% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.62. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 105-106 ^oC (dec.). IR (film, cm^{-1}) 1705 (C=O), 1568 (AcO^-); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93–7.77 (2H, m), 7.71–7.58 (2H, m), 7.57–7.41 (3H, m), 7.40–7.29 (2H, m), 6.22 (1H, s), 2.26 (3H, s), 2.03 (3H, s), 1.90 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.3, 135.6, 133.2, 132.8, 132.8, 132.2, 131.9, 131.4, 130.9, 130.6, 119.4, 114, 93.7, 77.2, 14.6, 14.2. Anal. Calcd for $C_{21}H_{19}BrINO_3$: C, 46.69; H, 3.55; N, 2.59 Found: C, 46.31; H, 3.27; N, 2.72.



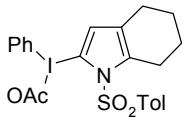
Ethyl 3-[(acetyloxy)(phenyl)-λ^3-iodanyl]-2-methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (2g). Following the general procedure, pyrrole **1g** (700 mg, 3.05 mmol) was converted into iodonium salt **2g**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a hygroscopic powder (950 mg, 63% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.60. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 95-96 ^oC (dec.). IR (film, cm^{-1}) 1751 (C=O), 1558 (AcO^-), 1292 (C-O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19–8.05 (1H, m), 7.73–7.46 (4H, m), 7.42–7.24 (5H, m), 6.92–6.70 (1H, m), 4.22 (2H, q, *J*=7.1 Hz), 2.78 (3H, s), 2.09 (3H, s), 0.97 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 150.1, 139.7, 137.8, 134.3, 132.3, 132, 131.9, 128.1, 128, 127.9, 115.2, 88.7, 64.7, 19.5, 14.3, 12.4. HRMS-ESI (m/z) calcd for $C_{20}H_{19}INO_2$ $[M\text{-}OAc]^+$ 432.0401, found 432.0409.



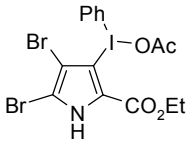
Ethyl 4-[(acetyloxy)(phenyl)-λ^3-iodanyl]-5-bromo-1*H*-pyrrole-2-carboxylate (2h). Following the general procedure, pyrrole **1h** (310 mg, 1.42 mmol) was converted into iodonium salt **2h**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a yellow solid (501 mg, 73% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.44. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 143-144 ^oC (dec.). IR (film, cm^{-1}) 1684 (C=O), 1456 (AcO^-), 1172 (C-O); ^1H NMR (400 MHz, AcOH-d_4, ppm) δ 11.6 (1H, s, overlapped with acetic acid), 8.13–8.04 (2H, m), 7.65–7.59 (1H, m), 7.52–7.44 (3H, m), 4.32 (2H, q, *J*=7.1 Hz), 2.02 (3H, s, overlapped with acetic acid), 1.32 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, AcOH-d_4, ppm) δ 159.5, 134.4, 132.1, 131.8, 127.3, 121.7, 116.4, 115.5, 89.3, 61.7, 19.5, 13.3. Anal. Calcd for $C_{15}H_{15}BrINO_4$: C, 37.53; H, 3.15; N, 2.92 Found: C, 37.15; H, 3.12; N, 2.93. HRMS-ESI (m/z) calcd for $C_{13}H_{12}BrINO_2$ $[M\text{-}OAc]^+$ 419.9067, found 419.9096.



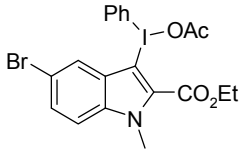
5-[(Acetyloxy)(phenyl)-λ^3-iodanyl]-2,4-dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrole (2i). Following the general procedure, pyrrole **1i** (500 mg, 2.01 mmol) was converted into iodonium salt **2i**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (730 mg, 71% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.69. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 141-142 ^oC (dec.). IR (film, cm^{-1}) 1558 (AcO^-), 1175 (SO_2); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88–7.82 (2H, m), 7.49–7.44 (2H, m), 7.42–7.37 (1H, m), 7.30–7.25 (2H, m), 7.22–7.18 (2H, m), 5.97 (1H, s), 2.38 (3H, s), 2.32 (3H, s), 2.17 (3H, s), 1.89 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 179.1, 145.7, 138.8, 136.6, 135.8, 133.4, 131.1, 130.7, 130.4, 127, 123.3, 116.9, 103.9, 24.3, 21.7, 15.8, 14.6. Anal. Calcd for $C_{21}H_{22}INO_4S$: C, 49.32; H, 4.34; N, 2.74 Found: C, 49.35; H, 4.22; N, 2.59.



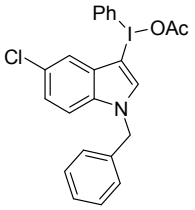
2-**[(Acetyloxy)(phenyl)-λ^3-iodanyl]-1-[(4-methylphenyl)sulfonyl]-4,5,6,7-tetrahydro-1*H*-indole (2j).** Following the general procedure, pyrrole **1j** (519 mg, 1.88 mmol) was converted into iodonium salt **2j**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a yellow powder (715 mg, 71% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.70. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 95-96 ^oC (dec.). IR (film, cm^{-1}) 1558 (AcO^-), 1175 (SO_2); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.04–7.95 (2H, m), 7.54–7.43 (3H, m), 7.38–7.30 (2H, m), 7.23–7.20 (2H, m), 6.16 (1H, s), 2.67 (2H, t, *J*=5.6 Hz), 2.35 (3H, s), 2.25 (2H, t, *J*=5.6 Hz), 1.85 (3H, s), 1.67–1.59 (2H, m), 1.57–1.48 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 178.6, 145.7, 136.2, 135.6, 134.6, 131.2, 131.1, 130.4, 127.1, 126.3, 125.7, 121.9, 24.4, 23.9, 23, 22.9, 22.2, 21.8. Anal. Calcd for $C_{23}H_{24}INO_4S$: C, 51.40; H, 4.50; N, 2.61 Found: C, 51.07; H, 4.31; N, 2.54.



Ethyl 3-[(acetyloxy)(phenyl)-λ^3-iodanyl]-4,5-dibromo-1*H*-pyrrole-2-carboxylate (2k). Following the general procedure, pyrrole **1k** (500 mg, 1.68 mmol) was converted into iodonium salt **2k**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a yellow powder (720 mg, 79% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.52. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 175-176 ^oC. IR (film, cm^{-1}) 1682 (C=O), 1458 (AcO^-), 1182 (C-O); ^1H NMR (400 MHz, AcOH-d_4, ppm) δ 11.59 (1H, s, overlapped with acetic acid), 8.17–8.07 (2H, m), 7.65–7.58 (1H, m), 7.51–7.42 (2H, m), 4.44 (2H, q, *J*=7.1 Hz), 2.02 (3H, s, overlapped with acetic acid), 1.39 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, AcOH-d_4, ppm) δ 157.4, 134.9, 132.3, 131.7, 126.8, 117, 108.6, 107.6, 94.2, 62.4, 19.5, 13.3. Anal. Calcd for $C_{15}H_{14}Br_2INO_4$: C, 32.23; H, 2.52; N, 2.51 Found: C, 31.87; H, 2.49; N, 2.55.



Ethyl 3-[(acetyloxy)(phenyl)-λ^3-iodanyl]-1,5-dimethyl-1*H*-indole-2-carboxylate (2l). Following the general procedure, pyrrole **1k** (700 mg, 2.48 mmol) was converted into iodonium salt **2k**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a white solid (1.1 g, 79% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.64. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 166-167 ^oC. IR (film, cm^{-1}) 1705 (C=O), 1558 (AcO^-), 1246 (C-O); ^1H NMR (400 MHz, AcOH-d_4, ppm) δ 8.21–8.15 (2H, m), 7.92 (1H, d, *J*=1.7 Hz), 7.68–7.58 (3H, m), 7.53–7.46 (2H, m), 4.65 (2H, q, *J*=7.1 Hz), 4.22 (3H, s), 2.10 (3H, s), 1.54 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, AcOH-d_4, ppm) δ 160.4, 138.9, 135.7, 133.2, 133.1, 132.8, 131.1, 130.2, 124.5, 118.1, 117.3, 115, 82.9, 64.2, 34.3, 20.7, 14.5. Anal. Calcd for $C_{20}H_{19}BrINO_4$: C, 44.14; H, 3.52; N, 2.57 Found: C, 44.11; H, 3.22; N, 2.41.



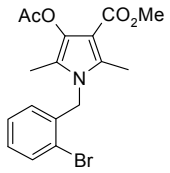
3-[(Acetyloxy)(phenyl)-λ^3-iodanyl]-1-benzyl-5-chloro-1*H*-indole (2m). Following the general procedure, pyrrole **1k** (700 mg, 2.90 mmol) was converted into iodonium salt **2k**. Purification of the crude product by column chromatography (column size 25x150 mm) using isocratic elution 20:80:5 (MeOH/DCM/AcOH) afforded product as a off-white powder (950 mg, 66% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.60. Pure material was obtained by crystallization from AcOH/diethyl ether: mp 121-122 ^oC (dec.). IR (film, cm^{-1}) 1560 (AcO^-); ^1H NMR (400 MHz, AcOH-d_4, ppm) δ 8.52–8.32 (1H, m), 8.20–7.94 (2H, m), 7.67 (1H, s), 7.60–7.52 (1H, m), 7.51–7.38 (3H, m), 7.37–7.09 (6H, m), 5.52 (2H, s), 2.05 (3H, s). ^{13}C NMR (100.6 MHz, AcOH-d_4, ppm) δ 139.8, 135.8, 135.1, 133.8, 131.9, 131.7, 129.4, 128.8, 128.6, 128.2, 127.1, 124.5, 118.7, 115.8, 113, 73.4, 51, 19.5. Anal. Calcd for $C_{23}H_{19}ClINO_2$: C, 54.84; H, 3.80; N, 2.78 Found: C, 54.49; H, 3.93; N, 2.46.

General Procedure A for Pd-Catalyzed Conversion of Iodonium Salts 2a–m to Acetoxylated Heterocycles 3a–m.

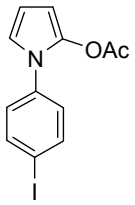
An oven-dried flask was cooled under stream of argon, charged with $Pd(OAc)_2$ (0.05 equiv) and iodonium salt **2a-m** (1 equiv) and closed with septa. Glacial acetic acid (10 mL/1 mmol of salt **2a–m**) was introduced via syringe and the reaction mixture was stirred for appropriate time and temperature (see Table 2). Water (25 mL) was added and product was extracted with EtOAc (3x25 mL). Combined organic extracts were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel.

General Procedure B for One-pot Sequential Synthesis of Acetoxylated Heterocycles 3a–m.

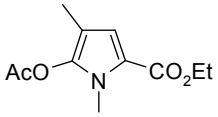
A solution of heterocycles **1a–m** (1 equiv) and $PhI(OAc)_2$ (1.2 equiv) in glacial AcOH (5.0 mL/1.0 mmol of heterocycle **1a–m**) was stirred at room temperature under argon atmosphere and the progress of the reaction was followed by ^1H-NMR or TLC. After full conversion of the starting **1a–m** was observed (see Table 2 for appropriate time), $Pd(OAc)_2$ (0.05 equiv) was added and stirring at ambient temperature was continued for appropriate time (see Table 2), whereupon water (25 mL) was added and product was extracted with EtOAc (3x25 mL). Combined organic extracts were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel.



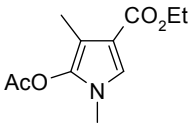
Methyl 4-(acetyloxy)-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3a). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3a** as a yellow solid (General Procedure A: 34 mg, 90% yield; General Procedure B: 174 mg, 92% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.22. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 111-112 °C. IR (film, cm^{-1}) 1761 (C=O), 1703 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.58 (1H, dd, *J*=7.8, 1.3 Hz), 7.21 (1H, dt, *J*=7.6, 1.3 Hz), 7.14 (1H, dt, *J*=7.6, 1.6 Hz), 6.34–6.29 (1H, m), 5.01 (2H, s), 3.78 (3H, s), 2.39 (3H, s), 2.31 (3H, s), 1.95 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.3, 164.6, 135.7, 133.7, 132.8, 129.3, 128.4, 126.7, 121.55, 118.5, 104.7, 50.9, 47.5, 20.8, 11.35, 8.23. Anal. Calcd for $C_{17}H_{18}BrNO_4$: C, 53.70; H, 4.77; N, 3.68 Found: C, 53.77; H, 4.57; N, 3.54.



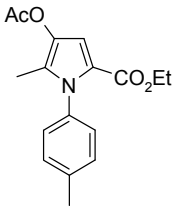
1-(4-Iodophenyl)-1*H*-pyrrol-2-yl acetate (3b). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3b** as a brown solid (General Procedure A: 53 mg, 85% yield; General Procedure B: 92 mg, 56% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.60. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 97-98 °C. IR (film, cm^{-1}) 1786 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.77–7.72 (2H, m), 7.11–7.07 (2H, m), 6.59 (1H, dd, *J*=3.5, 2.0 Hz), 6.22 (1H, dd, *J*=3.5, 3.5 Hz), 5.98 (1H, dd, *J*=3.5, 2.0 Hz), 2.15 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.2, 138.5, 137.9, 135.5, 126.3, 116.2, 107.9, 97.5, 91.8, 20.7. Anal. Calcd for $C_{12}H_{10}INO_2$: C, 44.06; H, 3.08; N, 4.28 Found: C, 43.95; H, 2.90; N, 4.11.



Ethyl 5-(acetyloxy)-1,4-dimethyl-1*H*-pyrrole-2-carboxylate (3c). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3c** as a yellow solid (General Procedure A: 84 mg, 79% yield; General Procedure B: 90 mg, 80% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.51. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 81-82 ^{o}C. IR (film, cm^{-1}) 1728 (C=O), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.76 (1H, s), 4.25 (2H, q, *J*=7.1 Hz), 3.66 (3H, s), 2.35 (3H, s), 1.90 (3H, s), 1.32 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.1, 161.2, 138.5, 117.1, 116.7, 106.3, 59.8, 31.1, 20.3, 14.6, 9.6. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22 Found: C, 58.70; H, 6.76; N, 6.05.

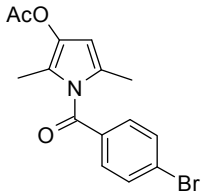


Ethyl 5-(acetyloxy)-1,4-dimethyl-1*H*-pyrrole-3-carboxylate (3d). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3d** as a brown oil (General Procedure A: 88 mg, 78% yield; General Procedure B: 77 mg, 77% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.28. IR (film, cm^{-1}) 1778 (C=O), 1708 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.04 (1H, s), 4.24 (2H, q, *J*=7.1 Hz), 3.39 (3H, s), 2.33 (3H, s), 2.07 (3H, s), 1.30 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.7, 165, 133.9, 121.9, 112, 106.8, 59.3, 32.5, 20, 14.4, 9. HRMS-ESI (m/z) calcd for $C_{11}H_{16}NO_4$ $[M+H]^+$ 226.1083, found 226.1079.

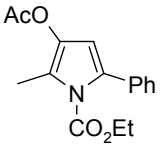


Ethyl 4-(acetyloxy)-5-methyl-1-(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (3e). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3e** as a yellow oil (General Procedure A: 95 mg, 79% yield; General Procedure B: 130 mg, 86% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.48. IR (film, cm^{-1}) 1759 (C=O), 1706 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26–7.22 (2H, m), 7.12–7.08 (2H, m), 6.93 (1H, s), 4.08 (2H, q, *J*=7.1 Hz), 2.41 (3H, s),

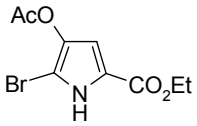
2.28 (3H, s), 1.89 (3H, s), 1.17 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.3, 160.3, 138.3, 136.1, 133.9, 129.6, 127.7, 127.1, 120, 110, 59.8, 21.4, 20.9, 14.3, 9.6. HRMS-ESI (m/z) calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1365, found 302.1392.



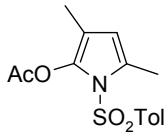
1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrol-3-yl acetate (3f). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3f** as a yellow oil (General Procedure A: 110 mg, 71% yield; General Procedure B: 101 mg, 60% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.56. IR (film, cm^{-1}) 1755 (C=O), 1697 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.57-7.54 (2H, m), 7.52-7.49 (2H, m), 5.88 (1H, s), 2.19 (3H, s), 2.02 (3H, s), 1.82 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.5, 169.2, 136.3, 134.3, 132.3, 131.7, 128.7, 128.3, 118.2, 106, 20.9, 15, 11.1. HRMS-ESI (m/z) calcd for $C_{15}H_{15}BrNO_3$ $[M+H]^+$ 336.0247, found 336.0235.



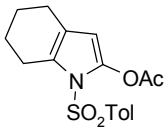
Ethyl 3-(acetyloxy)-2-methyl-5-phenyl-1*H*-pyrrole-1-carboxylate (3g). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3g** as a colorless oil (General Procedure A: 133 mg, 73% yield; General Procedure B: 72 mg, 50% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 71-72 °C. IR (film, cm^{-1}) 1748 (C=O), 1601 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29–7.21 (5H, m), 6.09 (1H, s), 4.08 (2H, q, *J*=7.1 Hz), 2.28 (3H, s), 2.23 (3H, s), 0.94 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.2, 151.5, 136.1, 134.4, 132.5, 129.3, 128.6, 127.8, 127.2, 121.2, 108.1, 63.3, 20.9, 13.6, 11.3. Anal. Calcd for C16H17NO4: C, 66.89; H, 5.96; N, 4.88 Found: C, 66.57; H, 5.92; N, 4.68. HRMS-ESI (m/z) calcd for $C_{14}H_{15}NO_3$ $[M-Ac]^+$ 246.1144, found 246.1130.



Ethyl 4-(acetyloxy)-5-bromo-1*H*-pyrrole-2-carboxylate (3h). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3h** as a yellow solid (General Procedure A: 55 mg, 79% yield; General Procedure B: 100 mg, 74% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.36. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 128-129 ^{o}C. IR (film, cm^{-1}) 3258 (NH), 1761 (C=O), 1692 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.94–9.80 (1H, br s), 6.81 (1H, d, *J*=3.0 Hz), 4.34 (2H, q, *J*=7.1 Hz), 2.29 (3H, s), 1.35 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.4, 160.6, 135.9, 121.1, 108.9, 96.6, 61.2, 20.8, 14.5. Anal. Calcd for $C_9H_{10}BrNO_4$: C, 39.15; H, 3.65; N, 5.07 Found: C, 39.39; H, 3.45; N, 4.90.

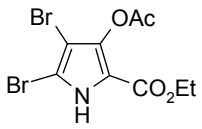


2,4-Dimethyl-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-5-yl acetate (3i). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3i** as a yellow powder (General Procedure A: 80 mg, 67% yield; General Procedure B: 65 mg, 42% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.52. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 85-86 ^{o}C. IR (film, cm^{-1}) 1792 (C=O), 1194 (SO_2), 1177 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74–7.69 (2H, m), 7.31–7.27 (2H, m), 5.73 (1H, s), 2.41 (3H, s), 2.33 (3H, s), 2.30 (3H, s), 1.78 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.1, 144.9, 137, 132.7, 130, 127.1, 126.8, 112.8, 109.6, 21.8, 20.6, 15.2, 9.3. Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.62; H, 5.58; N, 4.56 Found: C, 58.51; H, 5.40; N, 4.49.

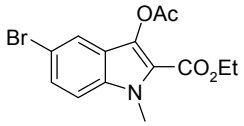


1-[(4-Methylphenyl)sulfonyl]-4,5,6,7-tetrahydro-1*H*-indol-2-yl acetate (3j). **C**olumn chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3j** as a white powder (General Procedure A: 110 mg, 71% yield; General Procedure B: 68 mg, 41% yield); analytical TLC on silica gel, 1:3 EtOAc/light

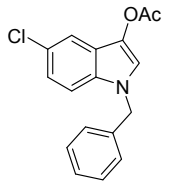
petroleum ether, Rf=0.48. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 116-117 °C. IR (film, cm^{-1}) 1792 (C=O), 1192 (SO_2), 1180 (SO_2); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74–7.69 (2H, m), 7.31–7.28 (2H, m), 5.61 (1H, s), 2.73–2.69 (2H, m), 2.42 (3H, s), 2.37–2.32 (2H, m), 2.32 (3H, s), 1.77–1.71 (2H, m), 1.67–1.62 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.2, 144.9, 137, 136, 130, 126.9, 126, 120.3, 101.7, 23.9, 23.2, 23.1, 22.5, 21.8, 20.7. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20 Found: C, 61.27; H, 5.60; N, 4.12.



Ethyl 3-(acetyloxy)-4,5-dibromo-1*H*-pyrrole-2-carboxylate (3k). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3k** as a yellow powder (General Procedure A: 65 mg, 74% yield; General Procedure B: 122 mg, 69% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.36. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 151-152 °C. IR (film, cm^{-1}) 3194 (NH), 1773 (C=O), 1678 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.82–9.68 (1H, br s), 4.32 (2H, q, *J*=7.1 Hz), 2.34 (3H, s), 1.34 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168, 159, 139, 114.8, 105.9, 96.1, 61.4, 20.5, 14.4. Anal. Calcd for $C_9H_9Br_2NO_4$: C, 30.45; H, 2.56; N, 3.95 Found: C, 30.66; H, 2.37; N, 3.82.

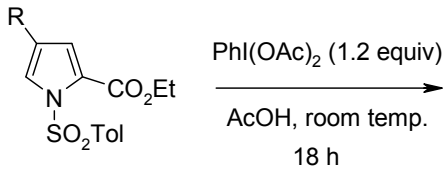


Ethyl ethyl 3-(acetyloxy)-1,5-dimethyl-1*H*-indole-2-carboxylate (3l). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3l** as a yellow powder (General Procedure A: 115 mg, 81% yield; General Procedure B: 146 mg, 86% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.46. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 139-140 °C. IR (film, cm^{-1}) 1769 (C=O), 1701 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.66 (1H, d, *J*=1.8 Hz), 7.42 (1H, dd, *J*=8.9, 1.8 Hz), 7.24 (1H, d, *J*=8.9 Hz), 4.36 (2H, q, *J*=7.1 Hz), 4.01 (3H, s), 2.39 (3H, s), 1.39 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.2, 160.9, 135.1, 133.2, 129.1, 121.6, 121.1, 118.9, 114.1, 112.1, 61, 32.2, 20.8, 14.4. Anal. Calcd for $C_{14}H_{14}BrNO_4$: C, 49.43; H, 4.15; N, 4.12 Found: C, 49.49; H, 4.04; N, 3.98.



1-Benzyl-5-chloro-1*H*-indol-3-yl acetate (3m). Column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **3l** as a green powder (General Procedure A: 88 mg, 73% yield; General Procedure B: 105 mg, 70% yield); analytical TLC on silica gel, 1:3 EtOAc/light petroleum ether, Rf=0.56. Pure material was obtained by crystallization from diethyl ether/light petroleum ether: mp 83-84 ^{o}C (dec.). IR (film, cm^{-1}) 1749 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.57–7.53 (1H, m), 7.36 (1H, s), 7.34–7.26 (3H, m), 7.18–7.13 (2H, m), 7.13–7.09 (2H, m), 5.24 (2H, s), 2.35 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 168.5, 136.9, 131.8, 129.2, 129, 128, 126.9, 125.6, 123.1, 121.5, 118.8, 117.4, 111.1, 50.5, 21.1. Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67 Found: C, 67.96; H, 4.68; N, 4.56.

Unsuccessful attempts to synthesize iodonium salts 2n,o.



1n: R=H
1o: R=Me

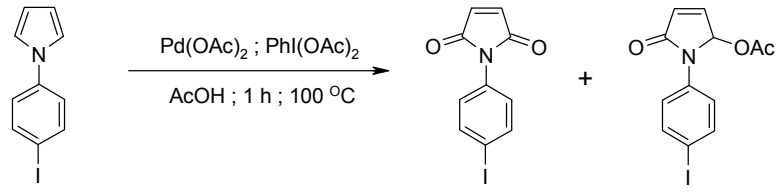
Following the General Procedure B, a solution of pyrroles **1n–o** (1 equiv) and $PhI(OAc)_2$ (1.2 equiv) in glacial AcOH (5.0 mL/1.0 mmol of pyrrole **1n–o**) was stirred at room temperature under argon atmosphere and the progress of the reaction was followed by ^{1}H-NMR.

No conversion of the starting **1n–o** was observed by ^{1}H-NMR after 18 hours.

General Procedure C for Direct Acetoxylation of Heterocycles 1a–m (Crabtree conditions).

An oven-dried flask was cooled under stream of argon, charged with $Pd(OAc)_2$ (0.05 equiv), $PhI(OAc)_2$ (1.3 equiv for **1a,e,f,l,m** or 2.3 equiv for **1b–d,h,k**) and heterocycles **1a–m** (1 equiv) and closed with septa. Glacial acetic acid (4 mL/1 mmol of heterocycle **1a–m**) was introduced via syringe and the reaction mixture was stirred for 1 h at 100 °C. Water (25 mL) was added and product was extracted with EtOAc (3x25 mL). Combined organic extracts were washed with aqueous saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel.

Direct Acetoxylation of Pyrrole 1b.



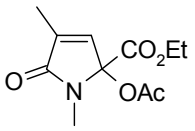
1b **5** **6**

Following the General Procedure C, pyrrole **1b** (135 mg, 0.50 mmol) was converted into 1-(4-iodophenyl)-1*H*-pyrrole-2,5-dione (**5**) and 1-(4-iodophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl acetate (**6**). Products were separated by column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether.

Product 5 was obtained as a yellow solid (40 mg, 27% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.19. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 149-151 °C (lit.[6] mp 145-147 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81-7.77 (2H, m), 7.15-7.11 (2H, m), 6.85 (2H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.2, 138.4, 134.5, 131.2, 127.7, 93.13. GC–MS m/z (% relative intensity, ion): 299 (100, M+), 255 (7), 229 (8), 203 (2), 172(4) 144 (4), 116 (19), 90 (14).

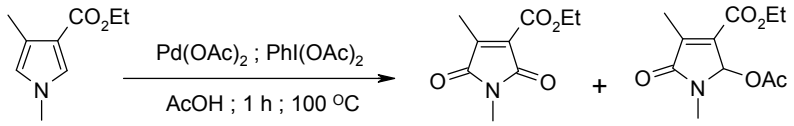
Product 6 was obtained as a yellow solid (70 mg, 41% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.13. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 137-138 °C. IR (film, cm^{-1}) 1719 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.72–7.67 (2H, m), 7.29–7.26 (2H, m), 7.10 (1H, dd, *J*=6.0, 1.9 Hz), 7.06 (1H, d, *J*=1.9 Hz), 6.36 (1H, d, *J*=6.0 Hz), 2.07 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.3, 168.4, 142, 138.3, 135.8, 130.3, 123.3, 89.7, 82.4, 20.9. GC–MS m/z (% relative intensity, ion): 343 (88, M+), 301 (100), 284 (65), 230 (34), 219 (41), 145 (11), 129 (62), 102 (23). Anal. Calcd for $C_{12}H_{10}INO_3$: C, 42.01; H, 2.94; N, 4.08 Found: C, 41.73; H, 2.96; N, 4.00.

([6]) Matuszak, N.; Muccioli, G. G.; Labar, G.; Lambert, D. M. *J. Med. Chem.* **2009**, *52*, 7410.



Ethyl 2-(acetyloxy)-1,4-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (7). Following the General Procedure C, pyrrole **1c** (84 mg, 0.50 mmol) was converted into **7**. Purification of the crude product by column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether afforded **7** as a yellow oil (90 mg, 75% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.20. IR (film, cm^{-1}) 1750 (C=O), 1715 (C=O), 1230 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.95 (1H, q, *J*=1.8 Hz), 4.27–4.18 (2H, m), 2.91 (3H, s), 2.13 (3H, s), 1.93 (3H, d, *J*=1.8 Hz), 1.25 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 171, 170.3, 165.3, 138.1, 135.7, 90.8, 62.8, 25.8, 20.8, 14.1, 11.1. GC–MS m/z (% relative intensity, ion): 241 (1, M+), 199 (67), 182 (33), 154 (100), 136 (37), 126 (81), 110 (95). HRMS-ESI (m/z) calcd for $C_{11}H_{16}NO_5$ $[M+H]^+$ 242.1039, found 242.1028.

Direct Acetoxylation of Pyrrole 1d.



1d **8** **9**

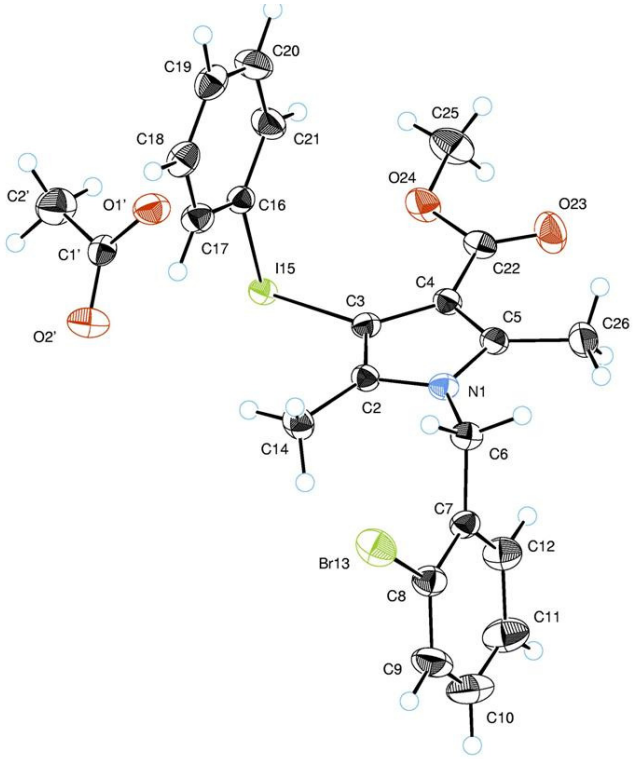
Following the General Procedure C, pyrrole **1d** (135 mg, 0.50 mmol) was converted into ethyl 1,4-dimethyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**8**) and ethyl 2-(acetyloxy)-1,4-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**9**). Products were separated by column chromatography (Biotage Si 12+M) using gradient elution from 5% EtOAc/light petroleum ether to 35% EtOAc/light petroleum ether.

Product 8 was isolated as a yellow oil (34 mg, 34% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.29. IR (film, cm^{-1}) 1789 (C=O), 1734 (C=O), 1707 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.38 (2H, q, *J*=7.1 Hz), 3.04 (3H, s), 2.33 (3H, s), 1.38 (3H, t, *J*=7.1 Hz). GC–MS m/z (% relative intensity, ion): 197 (28, M+), 169 (14), 152 (100), 125 (30), 111 (5). HRMS-ESI (m/z) calcd for $C_9H_{12}NO_4$ $[M+H]^+$ 198.0773, found 198.0766.

Product 9 was isolated as a yellow oil (62 mg, 51% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.18. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 69-70 °C. IR (film, cm^{-1}) 1749 (C=O), 1719 (C=O), 1211 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.75 (1H, q, *J*=1.4 Hz), 4.32 (1H, dq, *J*=11.0, 7.1 Hz), 4.23

(1H, dq, *J*=11.0, 7.1 Hz), 2.93 (3H, s), 2.25 (3H, d, *J*=1.4 Hz), 2.13 (3H, s), 1.31 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.3, 169.2, 162, 147.3, 135.8, 80.6, 61.2, 27.1, 20.8, 14.2, 11.1. GC–MS m/z (% relative intensity, ion): 241 (1, M+), 199 (50), 183 (33), 154 (80), 136 (31), 126 (62), 110 (100). Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81 Found: C, 54.39; H, 6.14; N, 5.60.

The X-ray structure, crystal data and structure refinement for **2a**



Crystal data

$C_{21}H_{20}BrINO_2 \cdot C_2H_3O_2$	$Z = 2$
$M_r = 584.25$	$F(000) = 576$
Triclinic, $P\overline{1}$	$D_x = 1.761$ Mg m^{-3}
$a = 8.7653$ (2) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 11.1641$ (2) Å	Cell parameters from 10598 reflections
$c = 12.7663$ (3) Å	$\theta = 0.9$–$27.5°$
$\alpha = 70.5552$ (12)°	$\mu = 3.30$ mm^{-1}
$\beta = 70.5023$ (10)°	$T = 173$ K
$\gamma = 89.8715$ (14)°	Prism, colourless
$V = 1102.10$ (4) Å^3	0.17 × 0.15 × 0.14 mm

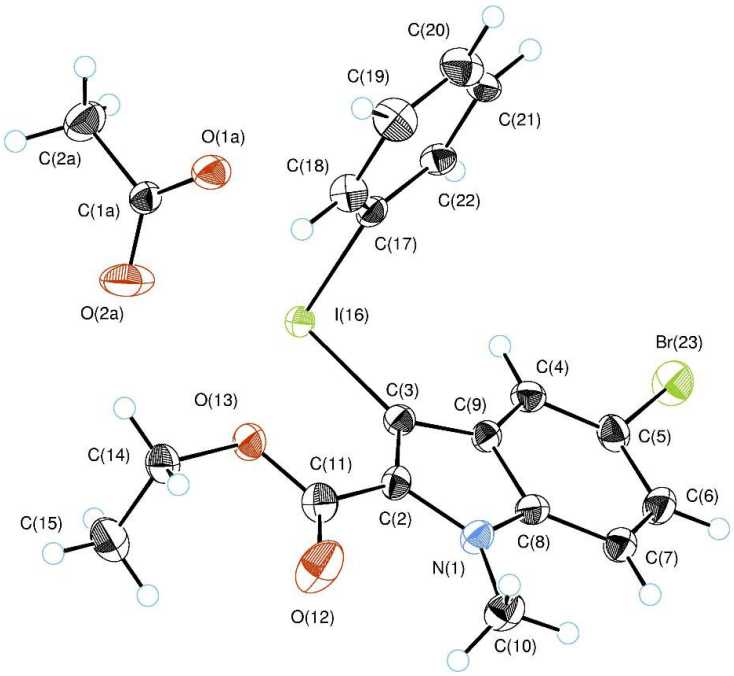
Data collection

Bruker-Nonius KappaCCD diffractometer	$R_{int} = 0.021$
Radiation source: fine-focus sealed tube	$\theta_{max} = 28.5°$, $\theta_{min} = 2.1°$
φ and ω scan	$h = -11 \rightarrow 11$
7641 measured reflections	$k = -14 \rightarrow 14$
5347 independent reflections	$l = -16 \rightarrow 15$
4707 reflections with $I > 3.00\ \sigma(I)$	

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.026$	Hydrogen site location: geom, diff
$wR(F^2) = 0.082$	H-atom parameters constrained
	Weighting scheme based on measured s.u.'s $w = 1 / (s^2(F_o^2) + 0.10000 * F_o^2)$
$S = 1.18$	$(\Delta/\sigma)_{max} = 0.018$
4706 reflections	$\Delta\rho_{max} = 0.88$ e Å^{-3}
271 parameters	$\Delta\rho_{min} = -0.98$ e Å^{-3}
0 restraints	
23 constraints	

The X-ray structure, crystal data and structure refinement for **2l**



Crystal data

$C_{18}H_{16}BrINO_2 \cdot C_2H_3O_2$	$Z = 2$
$M_r = 544.18$	$F(000) = 532$
Triclinic, $P\overline{1}$	$D_x = 1.811$ Mg m^{-3}
$a = 8.2215$ (2) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 9.6598$ (4) Å	Cell parameters from 6816 reflections
$c = 13.0019$ (3) Å	$\theta = 0.9$–$29.0°$
$\alpha = 88.038$ (2)°	$\mu = 3.63$ mm^{-1}
$\beta = 75.417$ (2)°	$T = 173$ K
$\gamma = 87.0530$ (12)°	Plate, colourless
$V = 997.76$ (5) Å^3	0.14 × 0.11 × 0.02 mm

Data collection

Bruker-Nonius KappaCCD diffractometer	$R_{int} = 0.029$
Radiation source: fine-focus sealed tube	$\theta_{max} = 29.5°$, $\theta_{min} = 2.5°$
φ and ω scan	$h = -11 \rightarrow 11$
7298 measured reflections	$k = -13 \rightarrow 11$
5297 independent reflections	$l = -17 \rightarrow 17$
4058 reflections with $I > 3.00\ \sigma(I)$	

Refinement

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.035$	Hydrogen site location: geom, diff
$wR(F^2) = 0.070$	H-atom parameters constrained
	Weighting scheme based on measured s.u.'s $w = 1 / (s^2(F_o^2) +$
$S = 1.70$	$0.10000 * F_o^2)$
4057 reflections	$(\Delta/\sigma)_{max} = 0.037$
244 parameters	$\Delta\rho_{max} = 1.32$ e Å^{-3}
0 restraints	$\Delta\rho_{min} = -1.87$ e Å^{-3}
19 constraints	

PIELIKUMS 7

Lubriks, D.; Sokolovs, I.; Suna, E. Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes. *J. Am. Chem. Soc.* **2012**, *134*, 15436-15442

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Indirect C–H Azidation of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes

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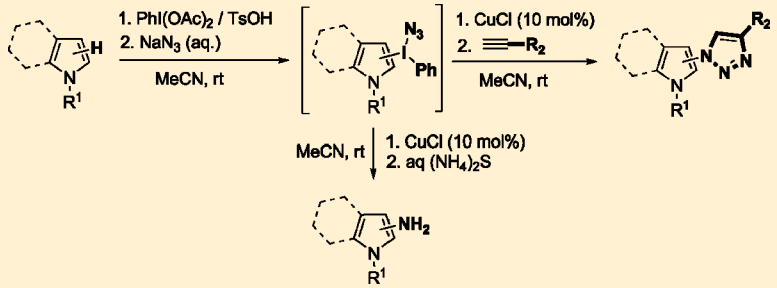
Supporting Information



ABSTRACT: A C–H bond of electron-rich heterocycles is transformed into a C–N bond in a reaction sequence comprising the formation of heteroaryl(phenyl)iodonium azides and their in situ regioselective fragmentation to heteroaryl azides. A Cu(I) catalyst ensures complete regiocontrol in the fragmentation step and catalyzes the subsequent 1,3-dipolar cycloaddition of the formed azido heterocycles with acetylenes. The heteroaryl azides can also be conveniently reduced to heteroarylamines by aqueous ammonium sulfide. The overall C–H to C–N transformation is a mild and operationally simple one-pot sequential multistep process.

INTRODUCTION

Symmetrical diaryliodonium salts have found numerous applications as electrophilic arylating reagents in both transition-metal-catalyzed and metal-free reactions with carbon and heteroatom nucleophiles.[1] Unsymmetrical diaryliodonium salts, however, are less frequently employed, because the presence of two different aromatic moieties in λ^3-iodanes can potentially lead to the formation of product mixtures in the reactions with nucleophiles. Nevertheless, regiocontrol can be achieved by differentiation of electronic and steric properties of aromatic moieties. Thus, a nucleophile would preferentially react with the more electron-deficient and/or sterically hindered *ortho*-substituted aromatic ring of unsymmetrical diaryliodonium salts (Figure 1).[2] In the meantime, regioselective reaction of nucleophiles with electron-rich aromatic or heteroaromatic moieties of unsymmetrical diaryl-λ^3-iodanes is a challenging task. We envisioned, however, that the desired regioselectivity of nucleophile attack can be ensured by a transition-metal catalyst, because in the catalytic cross-coupling reactions electron-rich[3] and/or less sterically hindered[4] aryl moieties are selectively transferred from unsymmetrical iodonium salts to the transition metal (Figure 1).

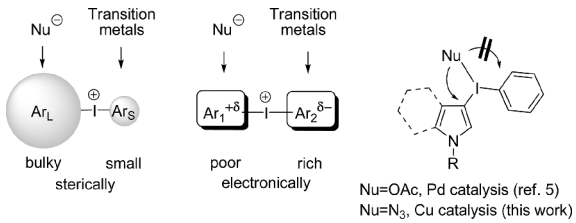


Figure 1. Regioselectivity in the reactions of nonsymmetrical iodonium salts.

We have recently demonstrated that the regioselectivity of acetoxylation of heteroaryl(phenyl)iodonium acetates can be directed to the more electron-rich heteroaryl moiety by a Pd(II) catalyst.[5] We reasoned that use of other counterions instead of acetate would provide straightforward access to differently substituted heterocycles by the transition-metal-catalyzed regioselective fragmentation of unsymmetrical heteroaryliodonium species. Herein we report a one-pot sequential procedure for C–H to C–N transformation in electron-rich heterocycles (pyrroles, pyrrolopyridines, thienopyrroles, pyrrolopyrimidines, and uracil) comprising in situ preparation of heteroaryl(phenyl)iodonium azides and their Cu-catalyzed conversion to heteroaryl azides. The formed azides are not sufficiently stable to be isolated; however, they can be in situ reduced to heteroaromatic amines. The developed one-pot four-step C–H to C–N transformation sequence is a mild and convenient alternative to the transition-metal-catalyzed direct C–H amination of arenes[6] and heteroarenes,[7,8] which usually requires elevated temperatures to proceed. The in situ formed heteroaryl azides can also undergo Cu-catalyzed azide–alkyne cycloaddition to furnish 1,2,3-triazoles,[9] thus allowing for the

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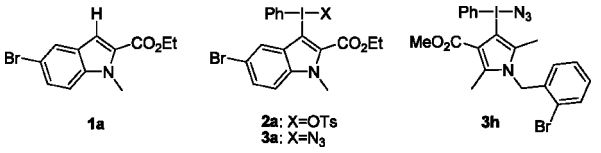
direct ligation of heterocycles to biomolecular frameworks via a triazole linker, an approach that is widely used in bioconjugate chemistry[10] for labeling and modification of oligonucleotides[11] and peptidomimetics.[12] The developed C–H azidation/1,3-dipolar cycloaddition sequence is suitable also for use in discovery of lead compounds by target-directed synthesis[13] as well as in the design of novel peptidomimetics.[14] Furthermore, 1,2,3-triazoles can be employed for synthesis of other heterocyclic systems.[15]

RESULTS AND DISCUSSION

At the outset of the investigation, we examined the regioselectivity of fragmentation of indolyl(phenyl)iodonium azide **3a**. The iodonium salt **3a** was synthesized by the reaction of indole **1a** with a mixture of $PhI(OAc)_2$ and TsOH,[16] followed by exchange of tosylate anion for azide in the intermediate **2a**. The formed iodonium azide **3a** was unstable, and in the crystalline form it slowly decomposed to iodoindole **5a** even at −18 °C. Nevertheless, the indolyl azide **3a** as well as its pyrrole analogue **3h** could be characterized, and their structures were confirmed by X-ray crystallographic analysis (Table 1).[17] In the crystal lattice azides **3a,h** exist in a

Table 1. Selected Crystallographic Parameters for Iodonium Azides 3a,h

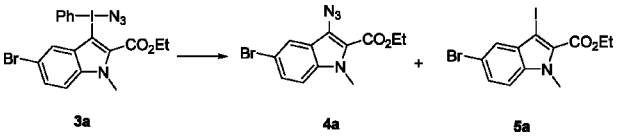


λ^3-iodane	N_3–I–C(Het) angle (deg)	I–N_3 distance (Å)	I–C(Ph) distance (Å)	I–C(Het) distance (Å)
3a	174.1	2.813	2.112	2.083
3h	177.3	2.837	2.129	2.064

characteristic slightly distorted T-shaped geometry with the heterocycle in the equatorial position and Ph moiety and azide anion in axial positions (for selected crystallographic parameters see Table 1). Notably, I–N bonds in the azides **3a,h** are considerably longer than hypervalent I–N bonds in structurally related azidobenziodoxole[18] (2.182 Å) and polymeric iodine azide (2.26–2.30 Å).[19] Furthermore, the distance between the hypervalent iodine in **3h** and the azide anion (2.837 Å, Table 1) is much longer than that between the iodine of the phenyl(pyrrolyl)iodonium moiety of **3h** and the acetate anion (2.592 Å).[5] Apparently, the long hypervalent I–N bond possesses partial ionic character,[20] which accounts for the low stability of iodonium azides **3a,h**.

In MeCN and CH_2Cl_2 solutions at room temperature the iodonium azide **3a** spontaneously decomposed to 3-iodoindole **5a** and phenyl azide (see Table 2, entries 1 and 2). Importantly, the desired indolyl azide **4a** was not formed in MeCN and CH_2Cl_2. The regioselectivity of the noncatalyzed fragmentation of iodonium salt **3a** apparently is controlled by electronic factors, as evidenced by the delivery of the azide nucleophile to the relatively more electron-deficient phenyl ring rather than to the electron-rich indole moiety of **3a**.[21] Notably, λ^3-iodane **3a** was stable in DMSO (entry 3) at room temperature. The addition of $Pd(OAc)_2$ (5 mol %) did not alter the course of the reaction (entries 4 and 5), whereas Cu salts completely reversed the fragmentation regioselectivity, and the iodonium

Table 2. Fragmentation of Indolyliodonium Azide 3a



entry	catalyst (concn, mol %)	solvent	time	conversion[a,b] %	4a:5a ratio[b]
1	none	MeCN	60 h	35[c]	1:99
2	none	CH_2Cl_2	3 h	70	1:99
3	none	DMSO	3 h	<5	
4	$Pd(OAc)_2$ (5)	MeCN	24 h	32	1:5
5	$Pd(OAc)_2$ (5)	CH_2Cl_2	3 h	35	1:99
6	$Cu(OTf)_2$ (10)	CH_2Cl_2	3 h	60	9:1
7	CuOTf·PhH (10)	CH_2Cl_2	30 min	100	9:1
8	CuOTf·PhH (10)	MeCN	30 min	87	9:1
9	CuOTf·PhH (10)	toluene	30 min	85	4:1
10	CuOTf·PhH (10)	THF	30 min	60	5:1
11	CuOTf·PhH (10)	DMSO	30 min	45	9:1
12	CuCl (10)	CH_2Cl_2	5 min	100	9:1
13	CuCl (10)	MeCN	5 min	100	12:1
14	CuCl (10)	DMSO	30 min	78	12:1
15	CuCl (10)	MeCN–DMSO (1:1)	15 min	85	10:1
16	TfOH (200)	CH_2Cl_2	3 h	23	1:99
17	$Zn(OTf)_2$ (10)	CH_2Cl_2	3 h	27	1:99
18	$Sc(OTf)_3$ (10)	CH_2Cl_2	3 h	20	1:99
19	$(Ph_3P)AuCl$ (10)	CH_2Cl_2	3 h	45	1:99

[a]Reactions at room temperature. [b]Determined by LC–MS assay. [c]Conversion of 100% (**4a**:**5a** = 1:99) after 30 min at 80 °C.

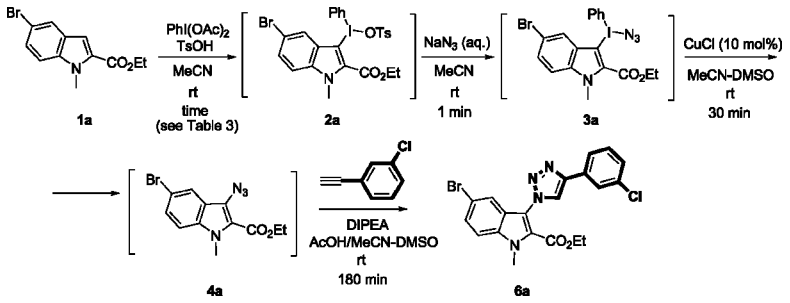
azide **3a** was smoothly converted to the desired indolyl azide **4a** (entries 6–15).

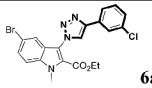
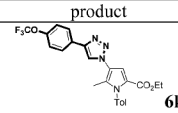
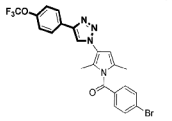
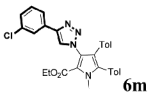
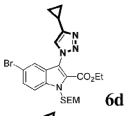
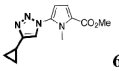
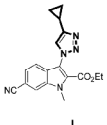
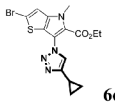
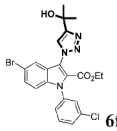
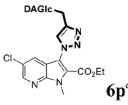
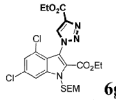
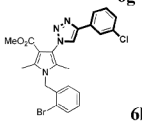
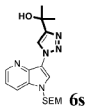
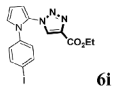
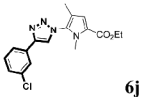
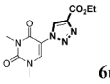
Copper catalysts considerably decreased the reaction time, with CuCl and CuOTf in CH_2Cl_2 being the most efficient (entries 7 and 12). Interestingly, both Cu(I) and Cu(II) salts can be used; however, the Cu(I) species ensured faster reaction (entry 7 vs entry 6). Other solvents either retarded the reaction (entries 10, 11, and 14) or deteriorated the regioselectivity (entries 9 and 10). It should be noted that the conversion of **3a** was faster in CH_2Cl_2 compared to MeCN (entry 2 vs entry 1 and entry 7 vs entry 8). Lewis acids such as $(Ph_3P)AuCl$, $Zn(OTf)_2$, and $Sc(OTf)_3$ as well as TfOH were completely inefficient as catalysts (entries 16–19). Consequently, CuCl (10 mol %) was chosen for all subsequent experiments.

The observed high regioselectivity of the Cu(I)-catalyzed fragmentation of iodonium salt **3a** to azide **4a** (**4a**:**5a** = 9:1) in CH_2Cl_2 is slightly lower than the regioselectivity of the alternative noncatalyzed formation of **5a** from **3a** (**4a**:**5a** = 1:99). The determined initial rates of the noncatalyzed fragmentation of **3a** to iodide **5a** in CH_2Cl_2 (rate coefficient $k = 9 \times 10^{-5}$ s^{-1}, CH_2Cl_2-d_2, 23 °C, and reaction half-life $t_{1/2}$ = 128 min) evidence that spontaneous fragmentation of iodonium azide **3a** delivers ca. 10% **5a** within the first 10 min. By this time, the CuOTf-catalyzed conversion of **3a** to azide **4a** in CH_2Cl_2 is almost 90%.[22] Consequently, the regioselectivity of the Cu-catalyzed conversion of **3a** to **4a** is

dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436–15442

Table 3. Sequential One-Pot Synthesis of Heteroaryl Azides 4a–u and Triazoles 6a–u



entry	product	time	yield (%)[c]	entry	product	time	yield (%)[c]
1	 **6a**	30 min	90	11	 **6k**	10 min	65
2	 **6b**	18 h	71	12	 **6l**	30 min	65
3	 **6c**	5 min	65	13	 **6m**	30 min	73
4	 **6d**	3 h	71	14	 **6n**	5 min	59
5	 **6e**	3 h	75	15	 **6o**	30 min	75
6	 **6f**	3 h	73	16	 **6p**[a]	30 min	62
7	 **6g**	18 h	72	17	 **6r**	5 min	70
8	 **6h**	10 min	64	18	 **6s**	72 h[b]	42
9	 **6i**	5 min	53	19	 **6t**	10 min	47
10	 **6j**	5 min	55	20	 **6u**	18 h	65

[a]DAGlc (diacetone-D-glucose). [b]A 2.2 equiv amount of TsOH–H_2O. [c]Yields were calculated on the basis of the starting heterocycle **1a–u**.

compromised by the competing noncatalyzed fragmentation to **5a**, and this observation renders CH_2Cl_2 inferior as a solvent compared to alternatives such as MeCN and DMSO (entry 2 vs entries 1 and 3, Table 2). The noncatalyzed fragmentation of **3a** in MeCN is considerably less pronounced, and azide **3a** is virtually stable in DMSO. Therefore, MeCN and DMSO are solvents of choice for CuCl-catalyzed fragmentation of iodonium azides (entries 13–15, Table 2).

The formed indolyl azide **4a** decomposed during attempted purification; however, it can be employed in further transformations without isolation. Thus, addition of substituted acetylene directly to azide **4a** and CuCl in the presence of DIPEA and AcOH[23] resulted in the clean formation of 1,4-disubstituted 1,2,3-triazole **6a** as a sole regioisomer.[24] Hence, CuCl catalyzed both the in situ formation of indolyl azide **4a** and its subsequent 1,3-dipolar cycloaddition with (3-chlorophenyl)acetylene (Table 3).[9]

A series of heterocycles was subsequently subjected to an azidation–cycloaddition sequence to show the scope of the developed methodology. All heterocycles that can form iodonium salts in the reaction with a mixture of $PhI(OAc)_2$ and TsOH are suitable substrates,[25] including indoles[26] **1a–g**, pyrroles[27] **1h–n**, thieno[3,2-*b*]pyrrole **1o**, pyrrolo[2,3-*b*]-pyridines **1p,r**, pyrrolo[3,2-*b*]pyridine **1s**, pyrrolo[2,3-*d*]-pyrimidine **1t**, and uracil[28] **1u** (Table 3). In general, the regioselectivity of heteroaryliodonium salt formation is consistent with that of S_EAr reactions. Thus, λ^3-iodanes are formed at the β-position of indoles **1a–g** and fused pyrroles **1o–t** at the α-position of pyrroles **1i,j,n** and at the fifth position of uracil **1u** (Table 3). In 2,5-disubstituted pyrroles **1h,k–m**, however, iodonium salts were formed at the β-position. Importantly, the reaction conditions are compatible with the presence of iodine, bromine, and chlorine, thus rendering feasible their further functionalization. *N*-Alkyl, *N*-aryl, *N*-benzoyl, and *N*-benzyl substituents as well as *N*-SEM protecting groups are tolerated (Table 3).

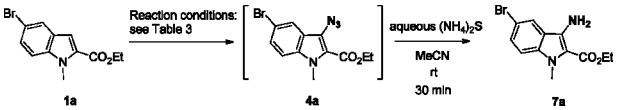
The formed heteroaryl azides **4a–u** could also be converted to the corresponding heteroaromatic amines **7a–u** by the in situ reduction with aqueous $(NH_4)_2S$ at room temperature within 30 min (see Table 4). Other reducing agents such as Ph_3P are equally efficient; however, the use of $(NH_4)_2S$ in the reduction generates less waste, requiring simple extractive workup to obtain crude products **7a–u**. In general, the one-pot three-step azidation–reduction sequence allows for amination of heteroaryl C–H bonds under mild conditions and in high overall yields.

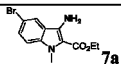
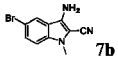
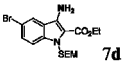
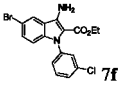
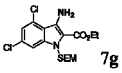
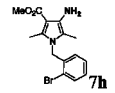
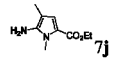
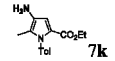
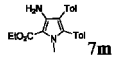
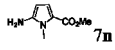
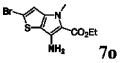
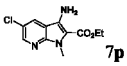
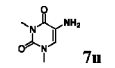
Additional experiments have been carried out to determine the oxidation state of copper species responsible for the catalytic azidation of heterocycles. The considerably faster formation of **4a** in the presence of Cu(I) ions compared to Cu(II) counterparts (entry 7 vs entry 6, Table 2) suggests that Cu(I) salts are catalytically active species. This assumption was supported by the observed inhibition of **4a** formation by neocuproin (2 equiv with respect to CuOTf; see Figure 2). Neocuproin, a highly specific chelating agent for Cu(I) ions, forms a stable bright orange-colored complex of formula $Cu^I(neocuproin)_2$,[29] thus acting as an inhibitor of Cu(I)-catalyzed reactions.[30]

Kinetic studies demonstrated that the CuOTf-catalyzed conversion of **3a** to **4a** in DMSO-d_6 is first-order in CuOTf in the range of 0.25–5 mol % at 25 °C (Figure 3). This indicates that Cu(I) salts are involved in the rate-limiting step of the catalytic cycle. The decomposition of **3a** to **4a** was found to be zeroth-order with respect to the N_3 anion (Figure 4), suggesting that the formation of azide **4a** presumably is an intramolecular process. Finally, a radical inhibition test was also performed to verify the possibility of **3a** fragmentation via the radical chain pathway. Accordingly, the addition of radical scavengers such as 1,1-diphenylethylene[31] and 2,6-di-*tert*-butyl-4-methylphenol[6a] (both 200 mol % with respect to Cu(I)) did not affect the rate of CuOTf-catalyzed **3a** to **4a** conversion in CH_2Cl_2-d_2. Furthermore, we did not observe indole **1a**, which could form by a proton abstraction from solvent by indolyl radical during the decomposition of **3a**. All these data point against the involvement of free radical intermediates.[32]

A working mechanism for the Cu-catalyzed formation of heteroaryl azides is outlined in Scheme 1. Oxidative addition of iodonium azide **I** to Cu(I) salts would generate Cu(III) species **II**.[33] Complex **II** can directly collapse into azide **III** via the highly regioselective coupling of the heterocycle with the azide,

Table 4. Sequential Azidation–Reduction Sequence for One-Pot Synthesis of Heteroarylamines 7a–u



entry	product	yield (%)[a]
1	 7a	84
2	 7b	80
3	 7d	82
4	 7f	84
5	 7g	79
6	 7h	65
7	 7j	60
8	 7k	62
9	 7m	72
10	 7n	53
11	 7o	66
12	 7p	75
13	 7u	50

[a]Yields were calculated on the basis of the starting heterocycle **1a–u**.

and the regioselectivity of azide attack presumably is ensured by the formation of a transient π-complex between the highly electrophilic Cu(III) species and electron-rich heterocycle.[34] Alternatively, complex **II** can undergo regioselective transformation to PhI and heteroarylcopper(III) species **IV**,[35] followed by reductive elimination of **III** and regeneration of Cu(I) species.

To verify the role of putative π-Cu(III) complex **II** in the control of the regioselectivity of azide formation, we envisioned the in situ preparation of a π-complex between a suitable π-acidic transition metal and electron-rich heterocycle moiety of unsymmetrical λ^3-iodane **3a**. Among various transition metals, Os(II) species are known to form well-defined and stable η^2-complexes with pyrroles.[36] We examined the fragmentation of iodonium azide **3a** in the presence of 10 mol % Os-

dx.doi.org/10.1021/ja305574k | J. Am. Chem. Soc. 2012, 134, 15436–15442

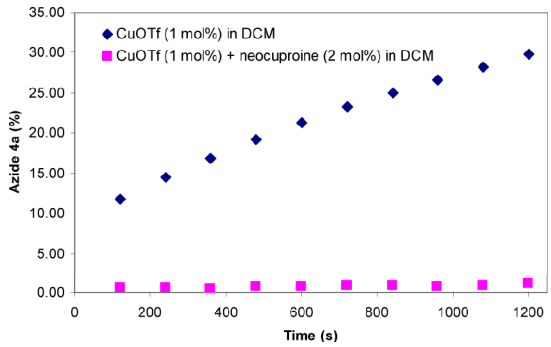


Figure 2. Inhibition of the CuOTf-catalyzed **3a** to **4a** conversion by neocuproin.

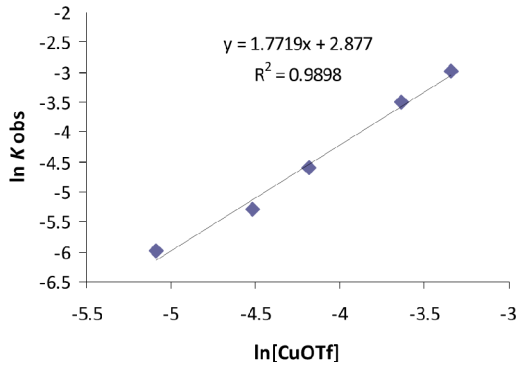


Figure 3. Initial rates vs concentration of CuOTf in DMSO-d_6.

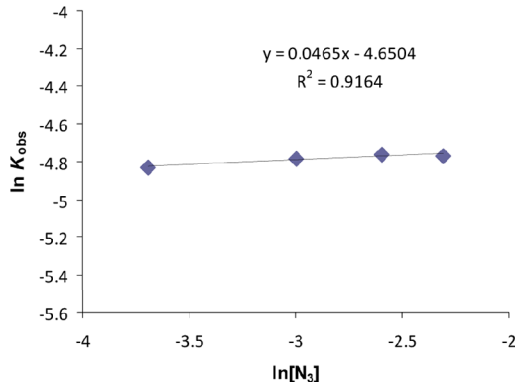


Figure 4. Initial rates vs concentration of azide ion in DMSO-d_6.

$[NH_3]_5(OTf)_3$ in CH_2Cl_2. Notably, indolyl azide **4a** was formed regioselectively (**4a**:**5a** = 7:3) within 30 min as a major product (30% conversion). This result is in sharp contrast to the opposite regioselectivity in the noncatalyzed decomposition of **3a** to **5a** in the presence of representative Lewis acids (entries 4, 5, and 17–19, Table 2). Possibly, π-complexation of a pyrrole ring to the Os(III) facilitates the substitution of the iodonium group by an azide nucleophile in transient complex **V** (Scheme 1); however, additional experiments are needed to support such a scenario.[37,38] The involvement of Cu(I) complex **V** (M = Cu(I)) to activate the heterocycle toward azide attack seems less likely because of insufficient electrophilicity of the Cu(I) species. Finally, Lewis acid activation of hypervalent iodonium species by Cu(I) or Cu(III) salts was shown to be kinetically insensitive to the concentration of copper species,[6a] an observation that contradicts our results.

CONCLUSIONS

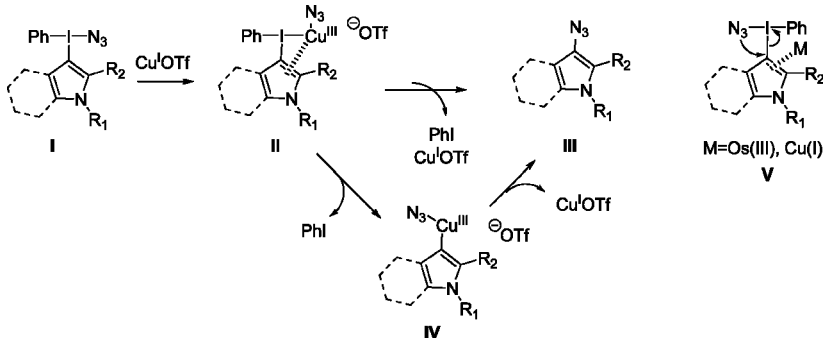
In summary, a rapid and versatile approach to heteroaryl azides via C–H to C–N bond transformation has been developed. The one-pot sequential procedure comprises formation of heteroaryl(phenyl)iodonium azides, followed by Cu(I)-catalyzed fragmentation to heteroaryl azides. The regioselectivity of the fragmentation is controlled by Cu(I) salts. The formed heteroaryl azides can be in situ reduced to heteroarylamines. Alternatively, the heteroaryl azides can undergo Cu-catalyzed click chemistry with a range of acetylenes to furnish 1,2,3-triazoles. The developed procedure is suitable for a variety of electron-rich heterocycles such as pyrroles, indoles, thienopyrroles, pyrrolopyridines, pyrrolopyrimidines, and uracil. Further studies to expand the scope of nucleophiles in the Cu-catalyzed regioselective fragmentation of heteroaryl(phenyl)iodonium salts are ongoing in our laboratory.

EXPERIMENTAL SECTION

Preparation of Iodonium Azides 3a and 3h. *Caution: Azides **3a,h** are thermally unstable and possess high thermal hazard potential.[39] Therefore, care must be taken during handling of azides **3a,h**, and a small scale is strongly encouraged.*

Ethyl 3-[(Azido)(phenyl)-λ^3-iodanyl]-1,5-dimethyl-1*H*-indole-2-carboxylate (3a). To a solution of $PhI(OAc)_2$ (509 mg, 1.58 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added $TsOH{\cdot}H_2O$ (342 mg, 1.80 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of indole **1a** (423 mg, 1.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added rapidly to the stirred suspension. The progress of the reaction was monitored by TLC, and within 30 min complete conversion of the starting **1a** was observed. The reaction was then poured into a solution of NaN_3 (146

Scheme 1. Working Mechanism for Azidation of Heterocycles



mg, 2.25 mmol, 1.5 equiv) in water (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The solid residue was washed with diethyl ether to afford **3a** as a white powder (727 mg, 92% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.56. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 102−103 °C dec; IR (film, cm^{-1}) 1999 (N═N═N), 1716 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 8.13−8.07 (3H, m), 7.73 (1H, d, J = 9.0 Hz), 7.60 (1H, dd, J = 9.0, 1.6 Hz), 7.55−7.50 (1H, m), 7.45−7.40 (2H, m), 4.51 (2H, q, J = 7.1 Hz), 4.07 (3H, s), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 159.1, 137.0, 133.9, 131.3, 131.2, 131.0, 129.1, 128.6, 123.5, 115.9, 114.6, 62.4, 33.5, 14.0; HRMS-ESI (m/z) calcd for $C_{18}H_{16}NO_2BrI$ $[M - N_3]^+$ 483.9409, found 483.9419.

Methyl 4-[(Azido)(phenyl)-λ^3-iodanyl]-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (3h). The same procedure was used as for **3a**. Accordingly, 3-[1-(2-bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1*H*-pyrrole (**1h**; 482 mg, 1.50 mmol) was converted to iodonium azide **3h**. Purification of the crude **3h** by washing with diethyl ether afforded product as a white powder (723 mg, 85% yield): analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.54. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 96−97 °C dec; IR (film, cm^{-1}) 2002 (N═N═N), 1696 (C═O); ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 7.95−7.91 (2H, m), 7.73−7.68 (1H, m), 7.61−7.55 (1H, m), 7.50−7.45 (2H, m), 7.29−7.24 (2H, m), 6.19−6.14 (1H, m), 5.30 (2H, s), 3.80 (3H, s), 2.43 (3H, s), 2.37 (3H, s); ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 162.3, 138.2, 137.5, 134.9, 133.5, 133.0, 131.2, 131.0, 129.7, 128.4, 126.1, 121.1, 110.4, 109.6, 51.3, 48.5, 12.6, 11.8; HRMS-ESI (m/z) calcd for $C_{21}H_{20}NO_2BrI$ $[M - N_3]^+$ 523.9722, found 523.9734.

Experimental Procedures for Substituted 1,2,3-Triazoles 6a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (1.5 mL) was added $TsOH·H_2O$ (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by DMSO (2.5 mL) and solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, acetylene (0.75 mmol, 1.5 equiv), DIPEA (1.00 mmol, 2 equiv), and AcOH (1.00 mmol, 2 equiv) were added, and stirring was continued for 3 h at room temperature. The reaction mixture was poured into 50 mL of water and 25 mL of saturated $NaHCO_3$ and extracted with DCM (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

Experimental Procedures for Heteroarylamines 7a−u. To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (4 mL) was added $TsOH·H_2O$ (0.60 mmol, 1.2 equiv), and the resulting suspension was stirred for 5 min at room temperature. Then a solution of heterocycle **1a−u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether:EtOAc = 3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a−u** (see Table 3 for the appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed by solid CuCl (5 mg, 10 mol %; *CuCl must be added immediately after NaN_3 to avoid the noncatalyzed decomposition of iodonium azide*), whereupon the color of the reaction mixture changed to brown. After the reaction mixture was stirred for 30 min at room temperature, aqueous $(NH_4)_2S$ (40−48 wt % solution in water, Aldrich, 1.25 mmol, 200 μL, 2.5 equiv) was added. After being stirring for another 30 min at room temperature, the reaction mixture was poured into a mixture of water (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra, X-ray crystallographic data for iodonium azides **3a** and **3h** (CIF), and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(38) Control experiments supported the importance of electronic effects in the regiocontrol of the Cu-catalyzed fragmentation of iodonium azide **3a**. Thus, replacement of the Ph group in **3a** with an electron-poor 4-$NO_2C_6H_4$ moiety altered the regioselectivity of azide attack and favored the formation of aryl azide 4-$NO_2C_6H_4N_3$ (**4a**:**5a** = 1:1 in MeCN and **4a**:**5a** = 1:3 in DCM). In the meantime, substitution of the Ph ring with a more electron-rich mesityl moiety in **3a** did not change the fragmentation regioselectivity (**4a**:**5a** = 9:1 in MeCN). Likewise, CuOTf-catalyzed decomposition of **3a** possessing a 4-$MeOC_6H_4$ moiety instead of a Ph ring afforded **4a**, albeit with diminished regioselectivity (**4a**:**5a** = 4:1 in DCM).

(39) The decomposition of indolyl azide **3a** was investigated by differential scanning calorimetry (DSC) and thermogravimetry methods. The DSC analysis of **3a** (heating rate 5 K/min) showed two exotherms: from 100 to 120 °C with a heat release of 122.0 J/g and from 212 to 263 °C with a heat release of 1842.7 J/g. The total decomposition enthalpy of 1964.7 J/g points toward a high thermal hazard potential for iodonium azide **3a**.

Indirect C–H Amination of Heterocycles via Copper-Catalyzed Regioselective Fragmentation of Unsymmetrical λ^3-Iodanes

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CONTENTS

Materials and Methods

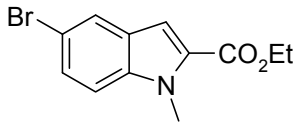
All reactions were carried out under an argon atmosphere. Progress of reactions was monitored by thin-layer chromatography on Merck Kieselgel $60F_{254}$. Flash column chromatography was performed using Biotage SP1 Flash Purification System and Biotage KP-Sil 25+M or Biotage KP-Sil 12+M silica cartridges.

^{1}H NMR spectra were recorded on Varian Inova 400 MHz NMR spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Melting points were uncorrected. Elemental analyses were performed using Carlo-Erba CHNS-0 EA1108 instrument. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

All reagents were obtained commercially and used as received.

Experimental Data

Synthesis of Starting Pyrroles and Indoles 1a-u.



Ethyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (1a). Ethyl 5-bromo-1*H*-indole-2-carboxylate (2.00 g, 14.40 mmol) was converted to indole **1a** in accordance to literature procedure.[7] Purification of the crude product by column chromatography (Biotage Si 40+M) using gradient elution from 10% EtOAc/light petroleum ether to 40% EtOAc/light petroleum ether afforded product as a white solid (1.96 g, 93% yield); analytical TLC on silica gel, 1:5 EtOAc/light petroleum ether, Rf=0.55. Pure material was obtained by crystallization from EtOAc/light petroleum ether: mp 91-92 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, dd, J = 1.8, 0.8 Hz), 7.41 (1H, dd, J = 8.9, 1.8 Hz), 7.27-7.24 (1H, m, overlapped with $CHCl_3$), 7.21 (1H, d, J = 0.8 Hz), 4.38 (2H, q, J = 7.1 Hz), 4.06 (3H, s), 1.41 (3H, t, J = 7.1 Hz).

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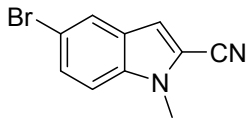
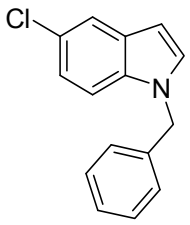
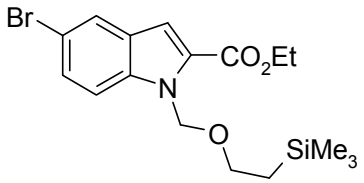


5-Bromo-1-methyl-1*H*-indole-2-carbonitrile (1b). The same procedure was used as for **1a**. Accordingly, 5-bromo-1*H*-indole-2-carbonitrile (1.50 g, 6.78 mmol) was converted to 1-methyl-1*H*-indole **1b**. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow solid (1.44 g, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 122-123 ^{o}C . IR (film, cm^{-1}) 2217 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 (1H, dd, *J*=1.8, 0.6 Hz), 7.48 (1H, dd, *J*=8.9, 1.8 Hz), 7.25-7.20 (1H, m), 7.07 (1H, d, *J*=0.8 Hz), 3.89 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 136.7, 129.0, 127.7, 124.8, 114.9, 113.1, 111.9, 111.7, 111.5, 31.9. Anal. Calcd for $C_{10}H_7BrN_2$: C, 51.09; H, 3.00; N, 11.92 Found: C, 51.09; H, 3.03; N, 11.80.

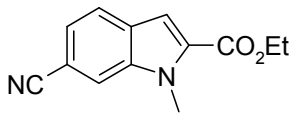


1-Benzyl-5-chloro-1*H*-indole (1c). The same procedure was used as for **1a**. Accordingly, 5-chloro-1*H*-indole (1.00 g, 6.60 mmol) was converted to 1-benzyl-1*H*-indole **1c**. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow solid (1.44 g, 90% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, Rf=0.46. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 63-64 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (1H, d, *J*=2.0 Hz), 7.35-7.28 (3H, m), 7.19 (1H, d, *J*=8.7 Hz), 7.16 (1H, d, *J*=3.2 Hz), 7.13 (1H, dd, *J*=8.7, 2.0 Hz), 7.11-7.08 (2H, m), 6.51 (1H, d, *J*=3.2 Hz), 5.31 (2H, s).

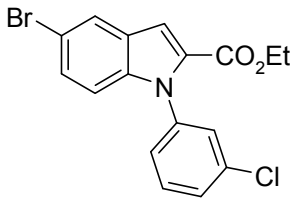


Ethyl 5-bromo-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (1d). The same procedure was used as for **1a**. Accordingly, ethyl 5-bromo-1*H*-indole-2-carboxylate (500 mg, 1.87 mmol) was converted to 1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole **1d**. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0%

EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow oil (685 mg, 92% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.58. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, dd, *J*=1.4, 1.0 Hz), 7.44 (2H, d, *J*=1.4 Hz), 7.26 (1H, d, *J*=1.0 Hz), 5.99 (2H, s), 4.38 (2H, q, *J*=7.1 Hz), 3.51 (2H, dd, *J*=8.2, 8.2 Hz), 1.41 (3H, t, *J*=7.1 Hz), 0.86 (2H, dd, *J*=8.2, 8.2 Hz), –0.08 (9H, s).



Ethyl 6-cyano-1-methyl-1*H*-indole-2-carboxylate (1e) was synthesized according to the method of Andersen et al.[8] Thus, a solution of ethyl 6-bromo-1-methyl-1*H*-indole-2-carboxylate (3.16 g, 11.2 mmol) and $Zn(CN)_2$ (990 mg, 8.4 mmol) in dry DMF (20 mL) was stirred at room temperature for 20 min under argon. $Pd(PPh_3)_4$ (650 mg, 0.56 mmol, 5 mol %) was added, and the solution was stirred for 24 h at 95 °C. After cooling to room temperature, the mixture was poured into aqueous saturated Na_2CO_3 solution (150 mL) and extracted with EtOAc (4x50 mL). Combined organic extracts were washed with water, brine and dried over Na_2SO_4.Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a colourless solid (2.10 g; 82% yield); analytical TLC on silica gel, 1:9 EtOAc/petroleum ether, Rf=0.26. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 141-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.77-7.70 (2H, m), 7.39-7.28 (2H, m), 4.40 (2H, q, *J*=7.1 Hz), 4.10 (3H, s), 1.42 (3H, t, *J*=7.1 Hz).

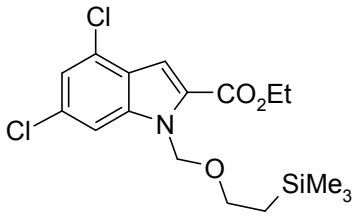


Ethyl 5-bromo-1-(3-chlorophenyl)-1*H*-indole-2-carboxylate (1f). Ethyl 5-bromo-1*H*-indole-2-carboxylate (804 mg, 3.00 mmol) was converted to indole **1f** in accordance to literature procedure.[9] Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a colourless solid (1.10 g; 97% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.53. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 85-86 °C. ^{1}H NMR (400

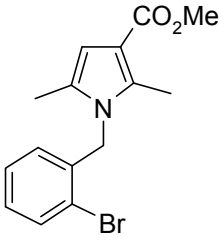
[8] Balle, T.; Perregaard, J.; Ramirez, M. T.; Larsen, A. K.; Søby, K. K.; Liljefors, T.; Andersen, K. *J.Med. Chem.* **2003**, *46,* 265.

[9] Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem*. **2009**, *74*, 7195.

MHz, $CDCl_3$, ppm) 7.84 (1H, d, *J*=1.8 Hz), 7.48-7.40 (2H, m), 7.37-7.30 (3H, m), 7.23-7.19 (1H, m), 6.95 (1H, d, *J*=8.8 Hz), 4.22 (2H, q, *J*=7.0 Hz), 1.22 (3H, t, *J*=7.0 Hz).

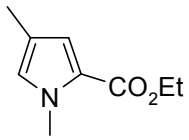


Ethyl 4,6-dichloro-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (1g). The same procedure was used as for **1a**. Accordingly, 4,6-dichloro-1*H*-indole-2-carboxylate (500 mg, 1.94 mmol) was converted to 1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole **1g**. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a colourless solid (687 mg, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.56. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 58-59 ^oC. IR (film, cm^{-1}) 1715 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49-7.47 (1H, m), 7.37 (1H, d, *J*=0.8 Hz), 7.20 (1H, d, *J*=1.6 Hz), 5.96 (2H, s), 4.39 (2H, q, *J*=7.1 Hz), 3.53 (2H, dd, *J*=8.2, 8.2 Hz), 1.42 (3H, t, *J*=7.1 Hz), 0.88 (2H, dd, *J*=8.2, 8.2 Hz), -0.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.5, 140.1, 131.4, 129.1, 128.4, 124.2, 121.9, 110.5, 110.3, 73.5, 66.1, 61.3, 17.9, 14.5, -1.3. Anal. Calcd for $C_{17}H_{23}Cl_2NO_3Si$: C, 52.58; H, 5.97; N, 3.61 Found: C, 52.59; H, 5.99; N, 3.50.

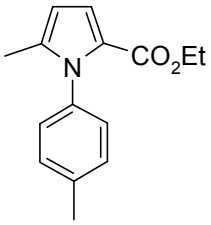


Methyl 1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (1h). Methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate (766 mg, 5.00 mmol) was converted to 1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole **1h** in accordance to literature procedure.[10] Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow oil (1.48 g, 92% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.31. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 95-96 ^oC. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.58 (1H, dd, *J*=7.7, 1.4 Hz), 7.18 (1H, td, *J*=7.5, 1.4 Hz), 7.13 (1H, td, *J*=7.7, 1.9 Hz), 6.36 (1H, d, *J*=1.0 Hz), 6.25-6.21 (1H, m), 5.02 (2H, s), 3.80 (3H, s), 2.41 (3H, s), 2.09 (3H, s).

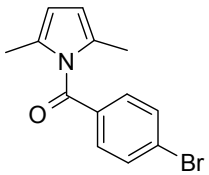
[10] Lubriks, D.; Sokolovs, I.; Suna, E. *Org. Lett.* **2011**, *13,* 4324.



Ethyl 1,4-dimethyl-1*H*-pyrrole-2-carboxylate (1j). The same procedure was used as for **1h**. Accordingly, ethyl 4-methyl-1*H*-pyrrole-2-carboxylate (500 mg, 3.26 mmol) was converted to 1,4-dimethyl-1*H*-pyrrole **1j.** Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow oil (472 mg, 87% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, Rf=0.59. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.68 (1H, d, *J*=2.0 Hz), 6.51-6.44 (1H, m), 4.18 (2H, q, *J*=7.1 Hz), 3.78 (3H, s), 1.98 (3H, s), 1.26 (3H, t, *J*=7.1 Hz).

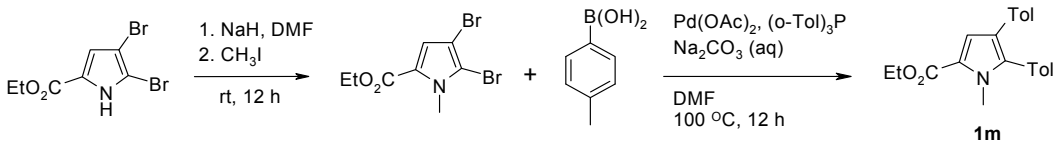


Ethyl 5-methyl-1-(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (1k). Ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (460 mg, 3.00 mmol) was converted to 1-(4-methylphenyl)-1*H*-pyrrole **1k** in accordance to literature procedure.[4] Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow oil (672 mg, 92% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.37. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28-7.25 (2H, m, overlapped with $CDCl_3$), 7.14-7.07 (2H, m), 7.03 (1H, d, *J*=3.8 Hz), 6.05 (1H, dd, *J*=3.8, 1.0 Hz), 4.13 (2H, q, *J*=7.1 Hz), 2.44 (3H, s), 2.04 (3H, s), 1.20 (3H, t, *J*=7.1 Hz).



1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrole (1l). 2,5-Dimethyl-1*H*-pyrrole (1.00 g, 10.51 mmol) was converted to 1-[(4-bromophenyl)carbonyl]-1*H*-pyrrole **1l** in accordance to literature procedure.[4] Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a brown solid (1.90 g, 65% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.59. Pure material was obtained by crystallization from diethylether/petroleum ether: mp

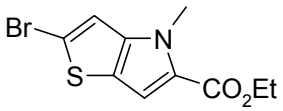
48-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64-7.60 (2H, m), 7.58-7.54 (2H, m), 5.88 (2H, s), 2.07 (6H, s).



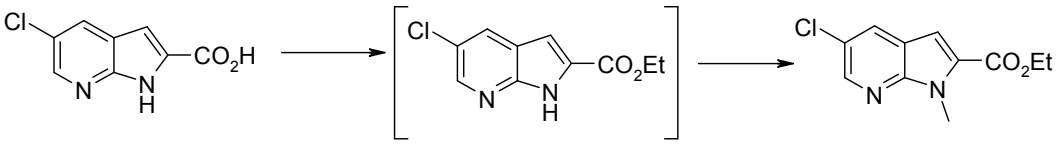
1m

Ethyl 1-methyl-4,5-bis(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (1m). Ethyl 4,5-dibromo-1*H*-pyrrole-2-carboxylate (1.50 g, 5.06 mmol) was converted to ethyl 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylate in accordance to literature procedure.[4] Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a colourless solid (1.38 g, 88% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.52. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 86-87 °C. IR (film, cm^{-1}) 1707 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.02 (1H, s), 4.28 (2H, q, *J*=7.1, Hz), 3.97 (3H, s), 1.34 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.9, 124.3, 119.4, 113.6, 98.9, 60.6, 36.0, 14.5. Anal. Calcd for $C_8H_9Br_2NO_2$: C, 30.90; H, 2.92; N, 4.50 Found: C, 30.97; H, 2.97; N, 4.46.

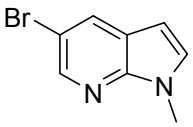
An oven-dried screw-cap pressure tube was charged with ethyl 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylate (from above; 400 mg, 1.29 mmol, 1 equiv), *p*-tolylboronic acid (437 mg, 3.22 mmol, 2.5 equiv), $Pd(OAc)_2$ (16 mg, 0.06 mmol, 5 mol%) and (*o*-Tol)$_3$P (39 mg, 0.13 mmol, 10 mol%). Then, aqueous Na_2CO_3 (1.37 g, 12.9 mmol, 10 equiv in 7 mL of water) and DMF (10 mL) were added successively under a stream of argon. After stirring at 100 °C for 12 h and cooling to room temperature, the reaction was poured into water (50 mL) and extracted with MeO*t*-Bu (3x30 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated with 5 mL of silica gel. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a colourless solid (363 mg, 84% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.44. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 117- 118 °C. IR (film, cm^{-1}) 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.24-7.14 (5H, m), 7.06-6.97 (4H, m), 4.34 (2H, q, *J*=7.1 Hz), 3.76 (3H, s), 2.41 (3H, s), 2.28 (3H, s), 1.39 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.7, 138.4, 137.8, 135.3, 132.6, 131.0, 129.5, 129.0, 128.9, 127.8, 123.0, 122.7, 116.9, 60.0, 34.2, 21.5, 21.2, 14.7. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20 Found: C, 78.85; H, 7.01; N, 4.30.



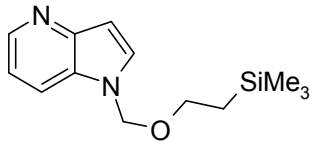
Ethyl 2-bromo-4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (1o). The same procedure was used as for **1a**. Accordingly, 2-bromo-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (350 mg, 1.28 mmol) was converted to 4-methyl-4*H*-thieno[3,2-*b*]pyrrole **1o**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a colourless solid (330 mg, 89% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.42. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 86-87 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.08 (1H, s), 7.00 (1H, s), 4.32 (2H, q, *J*=7.1 Hz), 4.00 (3H, s), 1.37 (3H, t, *J*=7.1 Hz).



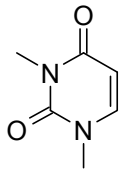
Ethyl 5-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (1p). A mixture of 5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (500 mg, 2.54 mmol, 1 equiv), EtOH (15 mL) and $SOCl_2$ (922 µL, 12.70 mmol, 5 equiv) was refluxed for 4 h, cooled to room temperature and evaporated. Brown solid residue was dissolved in DMF (15 mL), K_2CO_3 (878 mg, 6.35 mmol, 2.5 equiv) was added, followed by CH_3I (190 µL, 3.05 mmol, 1.2 equiv). After stirring for 12 h at room temperature the solvent was evaporated and the residue was partitioned between water (50 mL) and EtOAc. Aqueous layer was extracted with EtOAc (2x30 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and evaporated with 5 mL of silica gel. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded product as a yellow solid (460 mg, 76% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 89-90 ^{o}C. IR (film, cm^{-1}) 1717 (C=O), 1237 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (1H, d, *J*=2.3 Hz), 7.93 (1H, d, *J*=2.3 Hz), 7.16 (1H, s), 4.40 (2H, q, *J*=7.1 Hz), 4.13 (3H, s), 1.42 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.6, 147.5, 145.3, 130.0, 129.7, 124.7, 119.1, 107.1, 61.2, 30.7, 14.5. Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74 Found: C, 55.41; H, 4.63; N, 11.60.



5-Bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1r). The same procedure was used as for **1a**. Accordingly, 5-bromo-1-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 2.54 mmol) was converted to 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine **1r**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a colourless solid (485 mg, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, Rf=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 62-63 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.35 (1H, d, *J*=2.1 Hz), 8.02 (1H, d, *J*=2.1 Hz), 7.19 (1H, d, *J*=3.5 Hz), 6.40 (1H, d, *J*=3.5 Hz), 3.87 (3H, s).



1-[2-(Trimethylsilyl)ethoxymethyl]-1*H*-pyrrolo[3,2-*b*]pyridine (1s). The same procedure was used as for **1a**. Accordingly, 1*H*-pyrrolo[3,2-*b*]pyridine (300 mg, 2.54 mmol) was converted to 1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-pyrrolo[3,2-*b*]pyridine **1s**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 30% EtOAc/petroleum ether to 80% EtOAc/petroleum ether afforded product as a yellow oil (430 mg, 68% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.43. IR (film, cm^{-1}) 1289 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.48 (1H, dd, *J*=4.6, 1.4 Hz), 7.77 (1H, ddd, *J*=8.2, 1.4, 1.0 Hz), 7.39 (1H, d, *J*=3.4 Hz), 7.13 (1H, dd, *J*=8.2, 4.6 Hz), 6.72 (1H, dd, *J*=3.4, 1.0 Hz), 5.46 (2H, s), 3.43 (2H, dd, *J*=8.2, 8.2 Hz), 0.86 (2H, dd, *J*=8.2, 8.2 Hz), -0.08 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 147.6, 144.0, 131.2, 129.4, 117.3, 117.0, 103.6, 76.2, 66.2, 17.8, -1.3. HRMS-ESI (m/z) calcd for $C_{13}H_{21}N_2OSi$ $[M+H]^+$ 249.1423, found 249.1415.

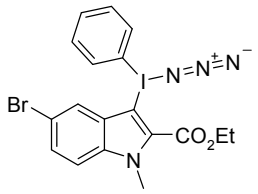


1,3-Dimethylpyrimidine-2,4(1*H*,3*H*)-dione (1u). Pyrimidine-2,4(1*H*,3*H*)-dione (500 mg, 4.46 mmol) was converted to pyrimidine-2,4(1*H*,3*H*)-dione **1u** in accordance to literature procedure.[11]

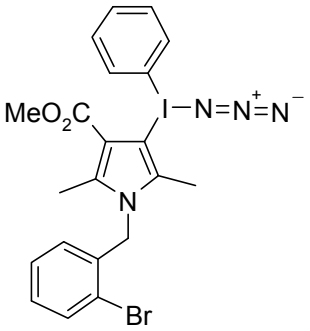
[11] Hannon, S. J.; Kundu N. G.; Hertzberg R. P.; Bhatt R. S.; Heidelberger, C. *Tetrahedron Lett.* **1980**, *21*, 1105.

Purification of the crude product by column chromatography (Biotage M+25) using isocratic elution 10% MeOH/CH_2Cl_2 afforded product as a colourless solid (534 g; 85% yield); analytical TLC on silica gel, 1:10 MeOH/CH_2Cl_2, Rf=0.47. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.12 (1H, d, *J*=7.8 Hz), 5.73 (1H, d, *J*=7.8 Hz), 3.40 (3H, s), 3.34 (3H, s).

Preparation of Iodonium Azides 3a and 3h.



3-[5-Bromo-2-(ethoxycarbonyl)-1-methyl-1*H*-indol-3-yl](phenyl)-λ^3-iodanyltriaza-1,2-dien-2-ium-1-ide (3a). To a solution of $PhI(OAc)_2$ (509 mg, 1.58 mmol, 1.05 equiv) in CH_2Cl_2 (10 mL) was added TsOH●H_2O (342 mg, 1.80 mmol, 1.2 equiv) and the resulting suspension was stirred for 5 min at room temperature. Then, a solution of indole **1a** (423 mg, 1.50 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added rapidly to the stirred suspension. The progress of the reaction was monitored by TLC, and within 30 min complete conversion of the starting **1a** was observed. The reaction was then poured into the solution of NaN_3 (146 mg, 2.25 mmol, 1.5 equiv) in water (50 mL) and extracted with CH_2Cl_2 (3x30 mL). Organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The solid residue was washed with diethylether to afford **3a** as a white powder (727 mg, 92% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.56. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 102-103 ºC (dec). IR (film, cm^{-1}) 1999 (N=N=N), 1716 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.13-8.07 (3H, m), 7.73 (1H, d, *J*=9.0 Hz), 7.60 (1H, dd, *J*=9.0, 1.6 Hz), 7.55-7.50 (1H, m), 7.45-7.40 (2H, m), 4.51 (2H, q, *J*=7.1 Hz), 4.07 (3H, s), 1.43 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, pmm) δ 159.1, 137.0, 133.9, 131.3, 131.2, 131.0, 129.1, 128.6, 123.5, 115.9, 114.6, 62.4, 33.5, 14.0. HRMS-ESI (m/z) calcd for $C_{18}H_{16}NO_2BrI$ $[M-N_3]^+$ 483.9409, found 483.9419.

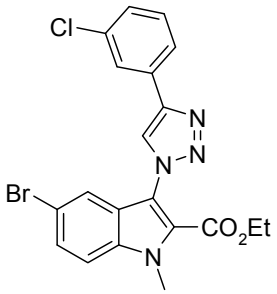


3-[1-(2-Bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1*H*-pyrrol-3-yl](phenyl)-λ^3-iodanyltriaza-1,2-dien-2-ium-1-ide (3h). The same procedure was used as for **3a**. Accordingly, 3-[1-(2-bromobenzyl)-4-(methoxycarbonyl)-2,5-dimethyl-1H-pyrrole **1h** (482 mg, 1.50 mmol) was converted to iodonium azide **3h**. Purification of the crude **3h** by washing with diethylether afforded product as a white powder (723 mg, 85% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, Rf=0.54. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 96-97 ^oC (dec). IR (film, cm^{-1}) 2002 (N=N=N), 1696 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.95-7.91 (2H, m), 7.73-7.68 (1H, m), 7.61-7.55 (1H, m), 7.50-7.45 (2H, m), 7.29-7.24 (2H, m), 6.19-6.14 (1H, m), 5.30 (2H, s), 3.80 (3H, s), 2.43 (3H, s), 2.37 (3H, s). ^{13}C NMR (100.6 MHz, DMSO-d_6, pmm) δ 162.3, 138.2, 137.5, 134.9, 133.5, 133.0, 131.2, 131.0, 129.7, 128.4, 126.1, 121.1, 110.4, 109.6, 51.3, 48.5, 12.6, 11.8.. HRMS-ESI (m/z) calcd for $C_{21}H_{20}NO_2BrI$ $[M-N_3]^+$ 523.9722, found 523.9734.

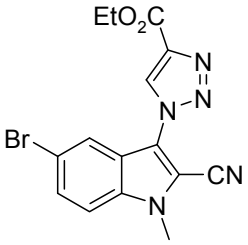
Experimental Procedures for Substituted 1,2,3-Triazoles 6a–u.

To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (1.5 mL) was added TsOH●H_2O (0.60 mmol, 1.2 equiv) and the resulting suspension was stirred for 5 min at room temperature. Then, a solution of heterocycle **1a-u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether/EtOAc=3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a–u** (see Table 3 for appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed with DMSO (2.5 mL), and solid CuCl (5 mg, 10 mol%; *CuCl must be added immediately after NaN_3 in order to avoid the non-catalyzed decomposition of iodonium azide*) whereupon the color of reaction changed to brown. After stirring for 30 min at room temperature, acetylene (0.75 mmol, 1.5 equiv), DIPEA (1.00 mmol, 2 equiv) and AcOH (1.00 mmol, 2 equiv) were added and stirring was continued for 3 h at room temperature. Reaction mixture was poured into 50 mL of

water and 25 mL of saturated $NaHCO_3$, extracted with DCM (3x30 mL). Organic extracts were combined, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel.

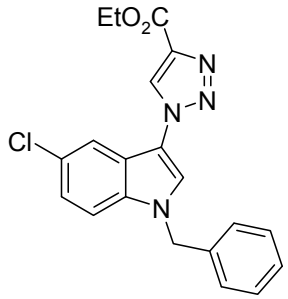


Ethyl 5-bromo-3-[4-(3-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-1-methyl-1*H*-indole-2-carboxylate (6a). Following the general procedure, indole **1a** (141 mg, 0.5 mmol) was converted into triazole **6a**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow solid (207 mg, 90% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.37. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 146-147 ^oC. IR (film, cm^{-1}), 1717 (C=O), 1484 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09 (1H, s), 7.93 (1H, dd, *J*=1.8, 1.8 Hz), 7.84-7.79 (1H, m), 7.66 (1H, d, *J*=1.8 Hz), 7.53 (1H, dd, *J*=9.0, 1.8 Hz), 7.42-7.33 (3H, m), 4.21 (2H, q, *J*=7.1 Hz), 4.13 (3H, s), 1.08 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.0, 145.7, 135.3, 134.9, 132.2, 130.3, 129.6, 128.3, 125.8, 124.0, 123.8, 123.7, 123.5, 122.0, 117.6, 115.9, 112.3, 61.8, 32.7, 14.1. Anal. Calcd for $C_{20}H_{16}BrClN_4O_2$: C, 52.25; H, 3.51; N, 12.19 Found: C, 52.26; H, 3.49; N, 12.17.

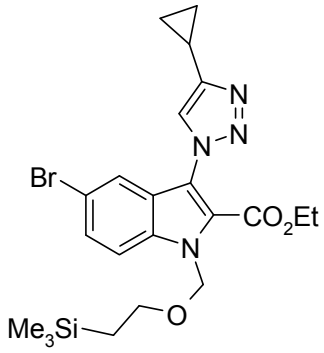


Ethyl 1-(5-bromo-2-cyano-1-methyl-1*H*-indol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (6b). Following the general procedure, indole **1b** (118 mg, 0.50 mmol) was converted into triazole **6b**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 75% EtOAc/petroleum ether afforded product as a yellow solid (133 mg, 71% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 188-189 ^oC (dec). IR (film, cm^{-1}) 1730 (C=O), 1472 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.66 (1H, s), 8.16

(1H, d, *J*=1.8 Hz), 7.60 (1H, dd, *J*=9.0, 1.8 Hz), 7.32 (1H, d, *J*=9.0 Hz), 4.49 (2H, q, *J*=7.2 Hz), 4.00 (3H, s), 1.46 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.3, 140.8, 135.5, 131.2, 127.0, 123.6, 121.0, 120.8, 117.2, 112.2, 110.8, 104.0, 61.9, 32.6, 14.5. HRMS-ESI (m/z) calcd for $C_{15}H_{12}N_5O_2BrNa$ $[M+Na]^+$ 396.0072, found 396.0070.

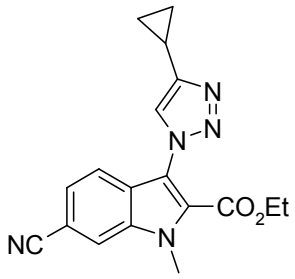


Ethyl 1-(1-benzyl-5-chloro-1*H*-indol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (6c). Following the general procedure, indole **1c** (121 mg, 0.50 mmol) was converted into triazole **6c**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (124 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.23. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 117-118 ^{o}C. IR (film, cm^{-1}) 1730 (C=O), 1471 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (1H, s), 7.75 (1H, d, *J*=1.9 Hz), 7.54 (1H, s), 7.33-7.27 (3H, m), 7.26-7.19 (2H, m), 7.17-7.10 (2H, m), 5.32 (2H, s), 4.44 (2H, q, *J*=7.2 Hz), 1.41 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.9, 149.2, 146.4, 139.1, 135.6, 131.6, 129.9, 129.4, 127.5, 127.3, 122.6, 121.6, 120.8, 120.3, 112.0, 60.3, 21.4, 14.3, 11.0. Anal. Calcd for $C_{20}H_{17}ClN_4O_2$: C, 63.08; H, 4.50; N, 14.71 Found: C, 63.81; H, 4.44; N, 14.42.

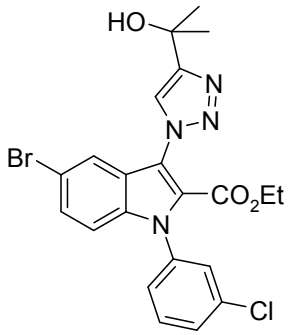


Ethyl 5-bromo-3-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-1-[2-(trimethylsilyl) ethoxymethyl]-1*H*-indole-2-carboxylate (6d). Following the general procedure, indole **1d** (200 mg, 0.50 mmol) was converted into triazole **6d**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether

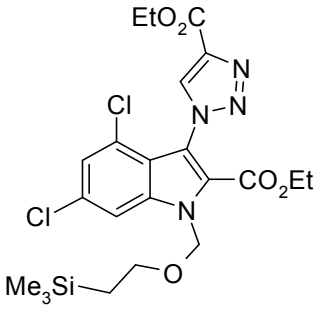
afforded product as a yellow powder (179 mg, 71% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.50. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 75-76 °C. IR (film, cm^{-1}) 1718 (C=O), 1482 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (1H, dd, *J*=1.2, 1.2 Hz), 7.56 (1H, s), 7.52 (2H, d, *J*=1.2 Hz), 5.99 (2H, s), 4.20 (2H, q, *J*=7.2 Hz), 3.57 (2H, dd, *J*=8.2, 8.2 Hz), 2.10-2.03 (1H, m), 1.11 (3H, t, *J*=7.2 Hz), 1.06-1.01 (2H, m), 0.99-0.94 (2H, m), 0.90 (2H, dd, *J*=8.2, 8.2 Hz), -0.05 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.1, 149.6, 135.6, 130.0, 124.7, 123.4, 123.2, 122.4, 119.7, 116.4, 113.3, 73.9, 66.6, 61.8, 18.0, 13.8, 7.9, 6.8, 1.3. Anal. Calcd for $C_{22}H_{29}BrN_4O_3Si$: C, 52.27; H, 5.78; N, 11.08 Found: C, 52.38; H, 5.62; N, 11.09.



Ethyl 6-cyano-3-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1*H*-indole-2-carboxylate (6e). Following the general procedure, indole **1e** (114 mg, 0.50 mmol) was converted into triazole **6e**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a white off powder (126 mg, 75% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 163-164 °C. IR (film, cm^{-1}) 1707 (C=O), 2224 (C≡N), 1464 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86-7.82 (1H, m), 7.58 (1H, d, *J*=8.4 Hz), 7.55 (1H, m), 7.42 (1H, dd, *J*=8.4, 1.0 Hz), 4.23 (2H, q, *J*=7.2 Hz), 4.15 (3H, s), 2.10-2.01 (1H, m), 1.13 (3H, s), 1.07-1.00 (2H, m), 0.98-0.91 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.7, 149.5, 135.3, 125.8, 125.3, 124.4, 123.4, 121.1, 119.3, 118.9, 115.9, 109.1, 62.0, 32.8, 14.0, 8.1, 6.9. HRMS-ESI (m/z) calcd for $C_{18}H_{18}N_5O_2$ $[M+H]^+$ 336.1461, found 336.1457.

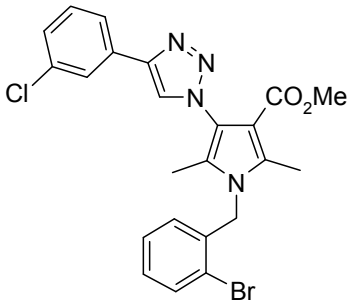


Ethyl 5-bromo-1-(3-chlorophenyl)-3-[4-(1-hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-1-yl]-1*H*-indole-2-carboxylate (6f). Following the general procedure, indole **1f** (189 mg, 0.50 mmol) was converted into triazole **6f**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded product as a white powder (184 mg, 73% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.39. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 161-162 ^{o}C. IR (film, cm^{-1}) 1723 (C=O), 1481 (N=N), 1180 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.94 (1H, s), 7.79 (1H, d, *J*=1.9 Hz), 7.55-7.48 (2H, m), 7.45 (1H, dd, *J*=9.0, 1.9 Hz), 7.39 (1H, dd, *J*=2.0, 1.8 Hz), 7.28 (1H, ddd, *J*=7.2, 2.0, 1.8 Hz), 7.01 (1H, d, *J*=9.0 Hz), 4.07 (2H, q, *J*=7.1 Hz), 2.65-2.61 (1H, m), 1.76 (6H, s), 0.98 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.1, 155.0, 138.4, 136.2, 135.2, 130.5, 130.5, 129.5, 128.4, 126.3, 124.2, 123.7, 123.0, 122.7, 119.7, 116.7, 113.3, 68.8, 61.8, 30.7, 13.7. HRMS-ESI (m/z) calcd for $C_{22}H_{21}N_4O_3ClBr$ $[M+H]^+$ 503.0486, found 503.0500.

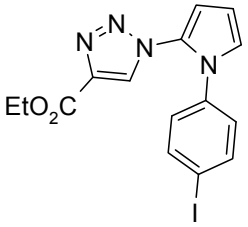


Ethyl 4,6-dichloro-3-[4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (6g). Following the general procedure, indole **1g** (194 mg, 0.50 mmol) was converted into triazole **6g**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow oil (190 mg, 72% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.38. IR (film, cm^{-1}) 1722 (C=O), 1719 (C=O), 1456 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, s), 7.63 (1H, d, *J*=1.6 Hz), 7.24 (1H, d, *J*=1.6 Hz), 6.01 (2H, s), 4.48 (2H, q, *J*=7.1 Hz), 4.13 (2H, q, *J*=7.1 Hz), 3.61 (2H, dd, *J*=8.2, 8.2

Hz), 1.45 (3H, t, *J*=7.1 Hz), 1.00 (3H, t, *J*=7.1 Hz), 0.92 (2H, dd, *J*=8.2, 8.2 Hz), -0.03 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.9, 159.4, 139.7, 137.8, 132.9, 132.3, 127.0, 125.7, 124.8, 119.0, 117.9, 111.1, 74.1, 66.9, 62.1, 61.6, 18.0, 14.5, 13.7, 1.3. HRMS-ESI (m/z) calcd for $C_{22}H_{29}N_4O_5SiCl_2$ $[M+H]^+$ 527.1284, found 527.1287.

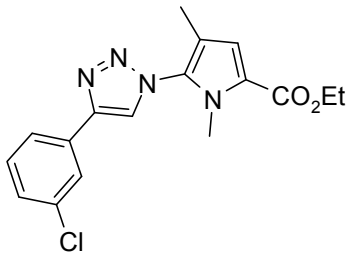


Methyl 1-(2-bromobenzyl)-2,5-dimethyl-4-(4-(3-chlorophenyl)-1*H*-1,2,3-triazol-1-yl)-1*H*-pyrrole-3-carboxylate (6h). Following the general procedure, pyrrole **1h** (140 mg, 0.50 mmol) was converted into triazole **6h**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (160 mg, 64% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.37. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 177-178 ^{o}C. IR (film, cm^{-1}) 1702 (C=O), 1437 (N=N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00-7.95 (1H, m), 7.94-7.88 (1H, m), 7.81 (1H, d, *J*=7.6 Hz), 7.62 (1H, d, *J*=7.8 Hz), 7.38 (1H, dd, *J*=7.8, 7.8 Hz), 7.33-7.27 (2H, m), 7.20 (1H, dd, *J*=7.6, 7.6 Hz), 6.43 (1H, d, *J*=7.6 Hz), 5.13 (2H, s), 3.61 (3H, s), 2.49 (3H, s), 2.01 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 164.2, 145.6, 135.6, 134.9, 133.1, 132.8, 130.2, 129.6, 128.5, 128.1, 126.8, 126.5, 125.9, 124.1, 123.9, 121.7, 118.6, 108.2, 51.1, 47.9, 11.4, 9.3. Anal. Calcd for $C_{23}H_{20}BrClN_4O_2$: C, 55.27; H, 4.03; N, 11.21 Found: C, 55.63; H, 4.04; N, 10.89.

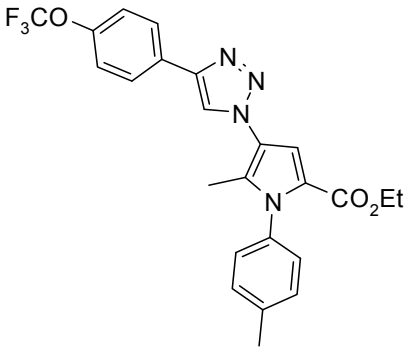


Ethyl 1-[1-(4-iodophenyl)-1*H*-pyrrol-2-yl]-1*H*-1,2,3-triazole-4-carboxylate (6i). Following the general procedure, pyrrole **1i** (135 mg, 0.50 mmol) was converted into triazole **6i**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a brown powder (108 mg, 53% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.34. Pure material

was obtained by crystallization from diethylether/petroleum ether: mp 142-143 °C. IR (film, cm^{-1}) 1721 (C=O), 1485 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, s), 7.80-7.77 (2H, m), 7.54 (1H, dd, *J*=2.5, 1.8 Hz), 7.20-7.16 (2H, m), 7.07 (1H, dd, *J*=3.2, 2.5 Hz), 6.62 (1H, dd, *J*=3.2, 1.8 Hz), 4.45 (2H, q, *J*=7.1 Hz), 1.42 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.8, 140.3, 139.5, 139.0, 125.7, 124.9, 122.6, 119.9, 111.7, 104.3, 91.3, 61.5, 14.5. Anal. Calcd for $C_{15}H_{13}IN_4O_2$: C, 44.14; H, 3.21; N, 13.73 Found: C, 44.02; H, 3.30; N, 13.46.

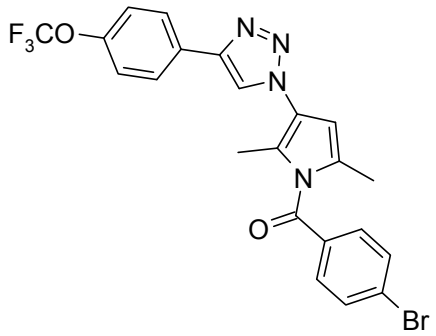


Ethyl 5-[4-(3-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-1,4-dimethyl-1*H*-pyrrole-2-carboxylate (6j). Following the general procedure, pyrrole **1j** (84 mg, 0.50 mmol) was converted into triazole **6j**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a brown powder (95 mg, 55% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.30. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 135-136 °C. IR (film, cm^{-1}) 1706 (C=O), 1425 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.92-7.87 (2H, m), 7.78 (1H, d, *J*=7.6 Hz), 7.37 (1H, dd, *J*=7.8, 7.6 Hz), 7.31 (1H, d, *J*=7.8 Hz), 6.67 (1H, s), 4.04 (2H, q, *J*=7.1 Hz), 3.94 (3H, s), 1.93 (3H, s), 0.95 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.6, 145.3, 134.8, 132.5, 130.2, 128.0, 126.1, 126.1, 125.7, 123.7, 123.4, 117.6, 116.6, 60.4, 37.8, 14.1, 8.8. HRMS-ESI (m/z) calcd for $C_{17}H_{18}N_4O_2Cl$ $[M+H]^+$ 345.1118, found 345.1130.

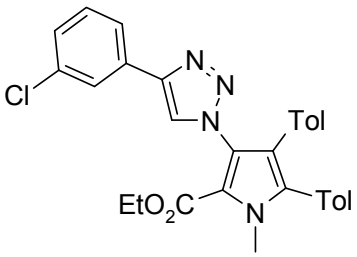


Ethyl 5-methyl-1-(4-methylphenyl)-4-[4-(trifluoromethoxy)phenyl-1*H*-1,2,3-triazol-1-yl]-1*H*-pyrrole-2-carboxylate (6k). Following the general procedure, pyrrole **1k** (122 mg, 0.50 mmol) was converted into triazole **6k**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether

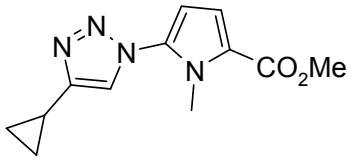
afforded product as a yellow powder (153 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.56. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 85-86 ºC. IR (film, cm^{-1}) 1718 (C=O), 1492 (N=N), 1262 (C–F), 1223 (C–F), 1206 (C–F), 1165 (C–F); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (1H, s), 7.94-7.91 (2H, m), 7.32-7.29 (4H, m), 7.21 (1H, s), 7.17-7.13 (2H, m), 4.15 (2H, q, *J*=7.1 Hz), 2.44 (3H, s), 2.14 (3H, s), 1.20 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.9, 149.2, 146.4, 139.1, 135.6, 131.6, 129.9, 129.4, 127.5, 127.3, 122.6, 121.6, 120.8, 120.7, 120.3, 112.0, 60.3, 21.4, 14.3, 11.0. Anal. Calcd for $C_{24}H_{21}F_3N_4O_3$: C, 61.27; H, 4.50; N, 11.91 Found: C, 61.38; H, 4.44; N, 11.86.



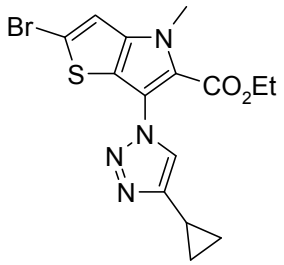
1-1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrol-3-yl-4-[4-(trifluoromethoxy)phenyl]-1*H*-1,2,3-triazole (6l). Following the general procedure, pyrrole **1l** (139 mg, 0.50 mmol) was converted into triazole **6l**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (164 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 113-114 ºC. IR (film, cm^{-1}) 1705 (C=O), 1484 (N=N), 1261 (C–F), 1222 (C–F), 1209 (C–F), 1166 (C–F); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93-7.90 (3H, m), 7.71-7.67 (2H, m), 7.67-7.63 (2H, m), 7.32-7.27 (2H, m), 6.22 (1H, s), 2.17 (3H, s), 2.16 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 169.5, 149.2, 133.3, 132.7, 131.9, 130.0, 129.9, 129.8, 129.3, 127.3, 123.3, 122.3, 121.6, 120.7, 120.7, 106.5, 14.4, 12.4. HRMS-ESI (m/z) calcd for $C_{22}H_{17}N_4O_2BrF_3$ $[M+H]^+$ 505.0487, found 505.0477.



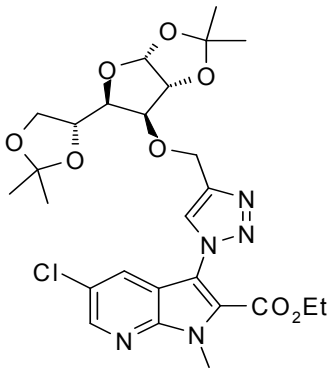
Ethyl 3-[4-(3-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-1-methyl-4,5-bis(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (6m). Following the general procedure, pyrrole **1m** (167 mg, 0.50 mmol) was converted into triazole **6m**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a white off powder (187 mg, 73% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 99-100 °C. IR (film, cm^{-1}) 1704 (C=O), 1449 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.82 (1H, dd, *J*=1.8, 1.6 Hz), 7.74 (1H, s), 7.71 (1H, ddd, *J*=7.6, 1.6, 1.6 Hz), 7.34 (1H, dd, *J*=7.8, 7.6 Hz), 7.28 (1H, ddd, *J*=7.8, 1.8, 1.8 Hz), 7.21-7.17 (2H, m), 7.15-7.12 (2H, m), 6.87-6.83 (2H, m), 6.80-6.76 (2H, m), 4.06 (2H, q, *J*=7.1 Hz), 3.86 (3H, s), 2.38 (3H, s), 2.17 (3H, s), 0.94 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.0, 145.4, 138.8, 136.9, 136.4, 134.8, 132.5, 130.9, 130.1, 129.4, 129.1, 128.9, 128.1, 128.0, 127.1, 125.7, 124.7, 123.7, 123.5, 121.3, 118.7, 60.6, 35.0, 21.7, 21.3, 14.1. Anal. Calcd for $C_{30}H_{27}ClN_4O_2$: C, 70.51; H, 5.33; N, 10.96 Found: C, 70.12; H, 5.49; N, 10.56.



Methyl 5-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-1-methyl-1*H*-pyrrole-2-carboxylate (6n). Following the general procedure, pyrrole **1n** (70 mg, 0.50 mmol) was converted into triazole **6n**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded product as a yellow powder (73 mg, 59% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.12. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 107-108 °C. IR (film, cm^{-1}) 1712 (C=O), 1477 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44 (1H, s), 7.20 (1H, d, *J*=2.0 Hz), 7.04 (1H, d, *J*=2.0 Hz), 3.96 (3H, s), 3.83 (3H, s), 2.01-1.93 (1H, m), 0.99-0.93 (2H, m), 0.89-0.84 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.2, 150.4, 122.6, 122.0, 120.8, 118.5, 109.0, 51.6, 37.3, 7.9, 6.8. HRMS-ESI (m/z) calcd for $C_{12}H_{15}N_4O_2$ $[M+H]^+$ 247.1195, found 247.1190.

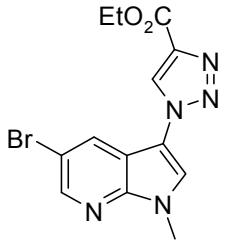


Ethyl 2-bromo-6-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (6o). Following the general procedure, thieno[3,2-*b*]pyrrole **1o** (144 mg, 0.50 mmol) was converted into triazole **6o**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (148 mg, 75% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.35. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 137-138 °C. IR (film, cm^{-1}) 1684 (C=O), 1459 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93 (1H, s), 7.00 (1H, s), 4.26 (2H, q, *J*=7.1 Hz), 4.00 (3H, s), 2.05-1.98 (1H, m), 1.24 (3H, t, *J*=7.1 Hz), 1.04-0.89 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.2, 149.2, 141.0, 122.4, 120.8, 118.7, 118.6, 117.2, 113.5, 61.2, 36.1, 14.3, 8.0, 7.0. HRMS-ESI (m/z) calcd for $C_{15}H_{16}N_4O_2BrS$ $[M+H]^+$ 395.0177, found 395.0190.

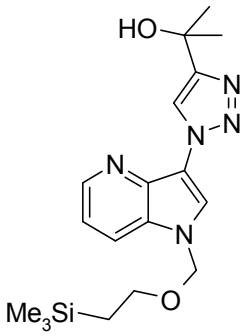


Ethyl 5-chloro-1-methyl-3--[4-((3a*R*,5*R*,6*S*,6a*R*)-5-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yloxy)methyl-1*H*-1,2,3-triazol-1-yl]-1*H*-pyrrolo[*2,3-b*]pyridine-2-carboxylate (6p). Following the general procedure, pyrrolo[2,3-*b*]pyridine **1p** (106 mg, 0.50 mmol) was converted into triazole **6p**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow foam (179 mg, 62% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.17. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 64-65 °C. IR (, cm^{-1}) 1721 (C=O), 1489 (N=N), 1244 (C=N), 1074 (C–O), 1041 (C–O), 1019 (C–O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (1H, d, *J*=2.2 Hz), 8.00 (1H, s), 7.92 (1H, d, *J*=2.2 Hz), 5.89 (1H, d, *J*=3.6 Hz), 4.98-4.89 (2H,

m), 4.66 (1H, d, *J*=3.6 Hz), 4.37-4.32 (1H, m), 4.27 (2H, q, *J*=7.1 Hz), 4.22 (3H, s), 4.16-4.08 (3H, m), 4.01 (1H, dd, *J*=5.5, 5.5 Hz), 1.50 (3H, s), 1.39 (3H, s), 1.33 (3H, s), 1.30 (3H, s), 1.18 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 159.9, 147.4, 144.6, 144.3, 127.8, 126.7, 126.3, 123.6, 116.2, 115.8, 112.1, 109.3, 105.4, 82.9, 82.1, 81.3, 72.5, 67.6, 64.3, 62.0, 31.3, 27.0, 26.0, 26.4, 25.6, 13.4. HRMS-ESI (m/z) calcd for $C_{26}H_{32}N_5O_8NaCl$ $[M+Na]^+$ 600.1837, found 600.1857.

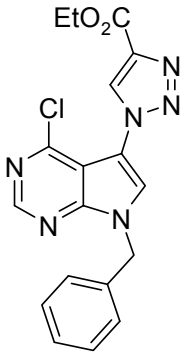


Ethyl 1-(5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (6r). Following the general procedure, pyrrolo[2,3-*b*]pyridine **1r** (106 mg, 0.50 mmol) was converted into triazole **6r**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded product as a yellow powder (123 mg, 70% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.26. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 97-98 ^{o}C. IR (film, cm^{-1}) 1709 (C=O), 1221 (C=N), 1440 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51-8.44 (1H, m), 8.42 (1H, s), 8.36-8.26 (1H, m), 7.68-7.61 (1H, m), 4.47 (2H, q, *J*=7.1 Hz), 3.96 (3H, s), 1.44 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.7, 146.0, 144.5, 140.5, 129.6, 126.4, 122.5, 114.7, 113.6, 112.1, 61.7, 31.9, 14.5. HRMS-ESI (m/z) calcd for $C_{13}H_{13}N_5O_2Br$ $[M+H]^+$ 350.0253, found 350.0248.

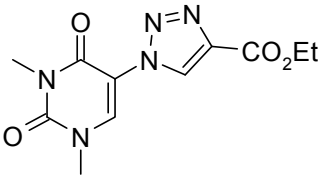


2-[1-(1-2-(Trimethylsilyl)ethoxymethyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol (6s). Following the general procedure, pyrrolo[3,2-*b*]pyridine **1s** (124 mg, 0.50 mmol) was converted into triazole **6s**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a white powder (78 mg, 42% yield); analytical TLC on

silica gel, 1:1 EtOAc/petroleum ether, Rf=0.23. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 74-75 °C. IR (film, cm^{-1}) 1249 (C=N), 1086 (C–O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.85 (1H, s), 8.59 (1H, dd, *J*=4.6, 1.3 Hz), 8.08 (1H, s), 7.88 (1H, dd, *J*=8.4, 1.3 Hz), 7.28 (1H, dd, *J*=8.4, 4.6 Hz), 5.55 (2H, s), 3.52 (2H, dd, *J*=8.2, 8.2 Hz), 2.71-2.62 (1H, m), 1.74 (6H, s), 0.90 (2H, dd, *J*=8.2, 8.2 Hz), -0.06 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 155.4, 145.0, 137.8, 128.6, 122.3, 119.4, 118.5, 118.5, 116.1, 76.8, 68.7, 66.8, 30.6, 17.9, -1.3. HRMS-ESI (m/z) calcd for $C_{18}N_{27}N_5O_2SiNa$ $[M+Na]^+$ 396.1832, found 396.1830.



Ethyl 1-(7-benzyl-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1*H*-1,2,3-triazole-4-carboxylate (6t). Following the general procedure, pyrrolo[2,3-*d*]pyrimidine **1t** (122 mg, 0.50 mmol) was converted into triazole **6t**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 15% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded product as a yellow foam (90 mg, 47% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.10. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 105-106 °C. IR (film, cm^{-1}) 1730 (C=O), 1456 (N=N), 1244 (C=N), 1233 (C=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.79 (1H, s), 8.44 (1H, s), 7.64 (1H, s), 7.38-7.34 (3H, m), 7.33-7.30 (2H, m), 5.54 (2H, s), 4.46 (2H, q, *J*=7.2 Hz), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.6, 152.3, 151.2, 149.9, 140.3, 134.9, 131.1, 129.4, 129.0, 128.4, 126.2, 111.9, 111.5, 61.7, 49.1, 14.4. HRMS-ESI (m/z) calcd for $C_{18}H_{16}N_6O_2Cl$ $[M+H]^+$ 383.1023, found 383.1031.

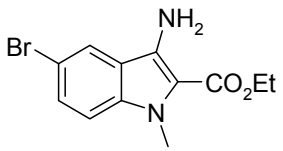


Ethyl 1-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1*H*-1,2,3-triazole-4-carboxylate (6u). Following the general procedure, pyrimidine **1u** (70 mg, 0.50 mmol) was converted into triazole **6u**. Purification of the crude product by column chromatography (Biotage

M+12) using gradient elution from 30% EtOAc/petroleum ether to 90% EtOAc/petroleum ether afforded product as a white powder (91 mg, 65% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.13. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 166-167 °C. IR (film, cm^{-1}) 1718 (C=O), 1678 (C=O), 1674 (C=O), 1488 (N=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.91 (1H, s), 8.28 (1H, s), 4.42 (2H, q, *J*=7.1 Hz), 3.58 (3H, s), 3.45 (3H, s), 1.40 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.5, 157.7, 150.3, 140.3, 138.0, 128.4, 112.4, 61.5, 38.0, 28.9, 14.4. HRMS-ESI (m/z) calcd for $C_{11}H_{13}N_5O_4Na$ $[M+Na]^+$ 302.0865, found 302.0866.

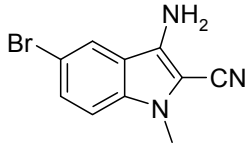
Synthesis of Aminoheterocycles 7a–u.

To a solution of $PhI(OAc)_2$ (0.53 mmol, 1.05 equiv) in MeCN (4 mL) was added $TsOH\bullet H_2O$ (0.60 mmol, 1.2 equiv) and the resulting suspension was stirred for 5 min at room temperature. Then, a solution of heterocycle **1a-u** (0.50 mmol, 1 equiv) in MeCN (1 mL) was added to the stirred suspension and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether/EtOAc=3:1; the formed heteroaryliodonium salt does not migrate from the application point). Immediately upon full conversion of the starting **1a–u** (see Table 3 for appropriate time), a solution of NaN_3 (0.75 mmol, 1.5 equiv) in water (500 μL) was added (*decomposition of the formed iodonium salt begins if the addition of NaN_3 is delayed*), followed with solid CuCl (5 mg, 10 mol%; *CuCl must be added immediately after NaN_3 in order to avoid the non-catalyzed decomposition of iodonium azide*) whereupon the color of reaction changed to brown. After stirring for 30 min at room temperature, aqueous $(NH_4)_2S$ (40-48 wt% solution in water, Aldrich, 1.25 mmol, 200 μL, 2.5 equiv) was added. After stirring for another 30 min at room temperature the reaction was poured into a mixture of water (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3x30 mL). Organic extracts were combined, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel.

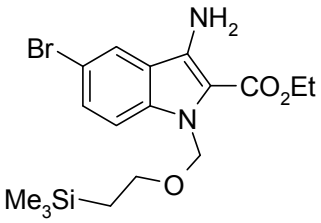


Ethyl 3-amino-5-bromo-1-methyl-1*H*-indole-2-carboxylate (7a). Following the general procedure, indole **1a** (142 mg, 0.50 mmol) was converted into amine **7a**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow powder (125 mg, 84% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.46. Pure material

was obtained by crystallization from diethylether/petroleum ether: mp 107-108 °C. IR (film, cm^{-1}) 3466 (NH_2), 3362 (NH_2), 1672 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.66 (1H, d, *J*=1.8 Hz), 7.38 (1H, dd, *J*=8.9, 1.8 Hz), 7.09 (1H, d, *J*=8.9 Hz), 4.88-4.69 (2H, br s), 4.41 (2H, q, *J*=7.2 Hz), 3.85 (3H, s), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 163.1, 137.3, 135.0, 129.5, 122.0, 119.6, 111.7, 111.0, 60.3, 32.3, 14.7. HRMS-ESI (m/z) calcd for $C_{12}H_{14}N_2O_2Br$ $[M+H]^+$ 297.0239, found 297.0202.

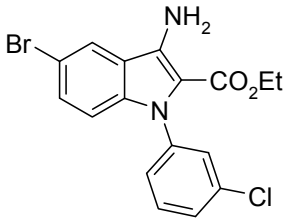


3-Amino-5-bromo-1-methyl-1*H*-indole-2-carbonitrile (7b). Following the general procedure, indole **1b** (118 mg, 0.50 mmol) was converted into amine **7b**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow powder (100 mg, 80% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.42. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 147-148 °C. IR (film, cm^{-1}) 3442 (NH_2), 3349 (NH_2), 2201 (C≡N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (1H, d, *J*=1.9 Hz), 7.42 (1H, dd, *J*=8.9, 1.9 Hz), 7.07 (1H, d, *J*=8.9 Hz), 4.00-3.93 (2H, br s), 3.68 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 136.1, 135.3, 129.7, 121.8, 119.7, 113.8, 112.3, 111.5, 96.7, 31.4. HRMS-ESI (m/z) calcd for $C_{10}H_9N_3Br$ $[M+H]^+$ 249.9980, found 249.9996.

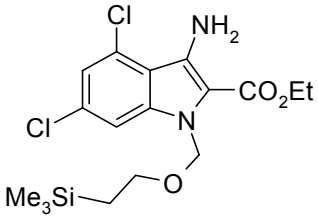


Ethyl 3-amino-5-bromo-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (7d). Following the general procedure, indole **1d** (200 mg, 0.50 mmol) was converted into amine **7d**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow oil (169 mg, 82% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.60. IR (film, cm^{-1}) 3363 (NH_2), 2952 (NH_2), 1674 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.67 (1H, d, *J*=1.9 Hz), 7.42 (1H, dd, *J*=8.9, 1.9 Hz), 7.30 (1H, d, *J*=8.9 Hz), 5.78 (2H, s), 4.97-4.77 (2H, br s), 4.42 (2H, q, *J*=7.2 Hz), 3.45 (2H, dd, *J*=8.2, 8.2 Hz), 1.43 (3H, t, *J*=7.2 Hz), 0.84 (2H, dd, *J*=8.2, 8.2 Hz), -0.09 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 162.9, 137.9, 136.4, 130.0, 122.0,

120.9, 112.8, 112.3, 109.9, 73.6, 65.7, 60.4, 18.1, 14.7, -1.3. HRMS-ESI (m/z) calcd for $C_{17}H_{25}N_2O_3SiBrNa$ $[M+Na]^+$ 435.0716, found 435.0744.

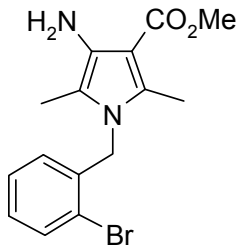


Ethyl 3-amino-5-bromo-1-(3-chlorophenyl)-1*H*-indole-2-carboxylate (7f). Following the general procedure, indole **1f** (189 mg, 0.50 mmol) was converted into amine **7f**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yelow oil (165 mg, 84% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 96-97 ^oC. IR (film, cm^{-1}) 3466 (NH_2), 3361 (NH_2), 1682 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.73 (1H, d, *J*=1.9 Hz), 7.39-7.33 (3H, m), 7.28-7.26 (1H, m), 7.19-7.15 (1H, m), 6.92 (1H, d, *J*=8.9 Hz), 5.09-4.98 (2H, br s), 4.16 (2H, q, *J*=7.2 Hz), 1.07 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 162.5, 140.7, 138.1, 137.3, 134.4, 130.4, 129.8, 128.3, 127.7, 126.2, 122.1, 120.1, 112.9, 112.6, 111.2, 60.1, 14.1. HRMS-ESI (m/z) calcd for $C_{17}H_{15}N_2O_2ClBr$ $[M+H]^+$ 393.0005, found 392.9968.

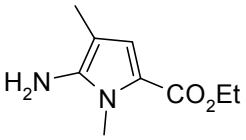


Ethyl 3-amino-4,6-dichloro-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (7g). Following the general procedure, indole **1g** (130 mg, 0.33 mmol) was converted into amine **7g**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (105 mg, 79% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.65. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 63-64 ^oC. IR (film, cm^{-1}) 3502 (NH_2), 3372 (NH_2), 1675 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.30 (1H, d, *J*=1.6 Hz), 6.98 (1H, d, *J*=1.6 Hz), 5.73 (2H, s), 5.63-5.57 (2H, br s), 4.41 (2H, q, *J*=7.2 Hz), 3.48 (2H, dd, *J*=8.2, 8.2 Hz), 1.42 (3H, t, *J*=7.2 Hz), 0.86 (2H, dd, *J*=8.2, 8.2 Hz), -0.06 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 162.7, 140.4, 138.1, 132.8, 128.4, 120.7, 114.6, 110.2, 110.1,

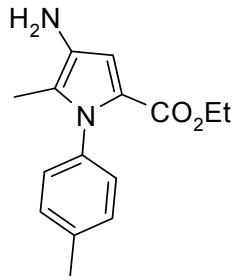
109.2, 73.7, 65.8, 60.4, 18.1, 14.7, -1.3. HRMS-ESI (m/z) calcd for $C_{17}H_{25}N_2O_3Cl_2Si$ $[M+H]^+$ 403.1012, found 403.1013.



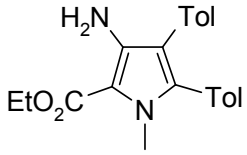
Methyl 4-amino-1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (7h). Following the general procedure, pyrrole **1h** (161 mg, 0.50 mmol) was converted into amine **7h**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 50% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a yellow powder (110 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.15. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 77-78 ^oC. IR (film, cm^{-1}) 3334 (NH_2), 3059 (NH_2), 1675 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.56 (1H, dd, *J*=7.8, 1.3 Hz), 7.17 (1H, ddd, *J*=7.6, 7.6, 1.3 Hz), 7.12 (1H, ddd, *J*=7.8, 7.8, 1.6 Hz), 6.28 (1H, ddd, *J*=7.8, 7.6, 1.6 Hz), 4.95 (2H, s), 3.83 (3H, s), 2.55 (2H, s), 2.35 (3H, s), 1.94 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 166.9, 136.4, 132.6, 132.2, 129.3, 129.0, 128.2, 127.0, 121.5, 110.4, 102.8, 50.6, 47.3, 11.6, 8.5. HRMS-ESI (m/z) calcd for $C_{15}H_{17}N_2O_2BrNa$ $[M+Na]^+$ 359.0371, found 359.0439.



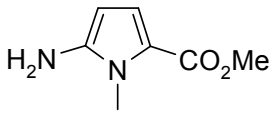
Ethyl 5-amino-1,4-dimethyl-1*H*-pyrrole-2-carboxylate (7j). Following the general procedure, pyrrole **1j** (84 mg, 0.50 mmol) was converted into amine **7j**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 50% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a brown powder (55 mg, 60% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 58-59 ^oC. IR (film, cm^{-1}) 3345 (NH_2), 3239 (NH_2), 1668 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.74 (1H, d, *J*=0.6 Hz), 4.21 (2H, q, *J*=7.1 Hz), 3.74 (3H, s), 3.43-3.26 (2H, br s), 1.93 (3H, d, *J*=0.6 Hz), 1.31 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.4, 140.0, 118.8, 114.5, 101.8, 59.1, 30.9, 14.7, 10.1. HRMS-ESI (m/z) calcd for $C_9H_{15}N_2O_2$ $[M+H]^+$ 183.1134, found 183.1121.



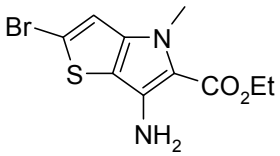
Ethyl 4-amino-5-methyl-1-(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (7k). Following the general procedure, pyrrole **1k** (122 mg, 0.50 mmol) was converted into amine **7k**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 50% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a yellow oil (80 mg, 62% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.27. IR (film, cm^{-1}) 3403 (NH_2), 3341 (NH_2), 1699 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.24-7.21 (2H, m), 7.08-7.04 (2H, m), 6.64 (1H, s), 4.08 (2H, q, *J*=7.1 Hz), 2.90-2.77 (2H, br s), 2.40 (3H, s), 1.91 (3H, s), 1.15 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 160.5, 137.8, 136.9, 129.4, 127.7, 127.7, 124.6, 120.2, 109.4, 59.5, 21.4, 14.4, 9.8. HRMS-ESI (m/z) calcd for $C_{15}H_{19}N_2O_2$ $[M+H]^+$ 259.1447, found 259.1430.



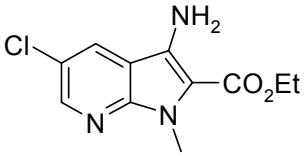
Ethyl 3-amino-1-methyl-4,5-bis(4-methylphenyl)-1*H*-pyrrole-2-carboxylate (7m). Following the general procedure, pyrrole **1m** (126 mg, 0.38 mmol) was converted into amine **7m**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 50% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a white powder (95 mg, 72% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 162-163 ^oC. IR (film, cm^{-1}) 3479 (NH_2), 3365 (NH_2), 1683 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.14-6.99 (8H, m), 4.66-4.51 (2H, br s), 4.37 (2H, q, *J*=7.1 Hz), 3.65 (3H, s), 2.35 (3H, s), 2.29 (3H, s), 1.40 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 162.5, 139.2, 138.0, 135.5, 130.8, 130.7, 129.7, 129.3, 129.1, 128.3, 111.6, 107.5, 59.4, 34.6, 21.5, 21.3, 14.9. HRMS-ESI (m/z) calcd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1916, found 349.1890.



Methyl 5-amino-1-methyl-1*H*-pyrrole-2-carboxylate (7n). Following the general procedure, pyrrole **1n** (139 mg, 1.0 mmol) was converted into amine **7n**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 50% EtOAc/petroleum ether to 100% EtOAc/petroleum ether afforded product as a brown oil (81 mg, 53% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, Rf=0.15. IR (film, cm^{-1}) 3402 (NH_2), 3345 (NH_2), 1695 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.44 (1H, d, *J*=2.2 Hz), 6.34 (1H, d, *J*=2.2 Hz), 3.79 (3H, s), 3.76 (3H, s), 3.01-2.94 (2H, br s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.6, 130.3, 120.2, 117.9, 108.3, 51.0, 36.4. HRMS-ESI (m/z) calcd for $C_7H_{11}N_2O_2$ $[M+H]^+$ 155.0821, found 155.0817.

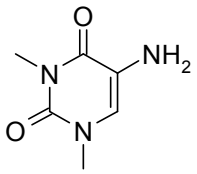


Ethyl 6-amino-2-bromo-4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (7o). Following the general procedure, thieno[3,2-*b*]pyrrole **1o** (144 mg, 0.50 mmol) was converted into amine **7o**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow powder (100 mg, 66% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.46. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 131-132 °C. IR (film, cm^{-1}) 3433 (NH_2), 3301 (NH_2), 1681 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.89 (1H, m), 4.69-4.48 (2H, br s), 4.36 (2H, q, *J*=7.2 Hz), 3.81 (3H, s), 1.39 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 162.9, 142.7, 116.8, 114.2, 110.4, 110.4, 59.8, 35.2, 14.8. Anal. Calcd for $C_{10}H_{11}BrN_2O_2S$: C, 39.62; H, 3.66; N, 9.24 Found: C, 39.64; H, 3.63; N, 9.06.



Ethyl 3-amino-5-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (7p). Following the general procedure, pyrrolo[2,3-*b*]pyridine **1p** (106 mg, 0.50 mmol) was converted into amine **7p**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow

powder (95 mg, 75% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.42. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 171-172 °C. IR (film, cm^{-1}) 3469 (NH_2), 3359 (NH_2), 1667 (C=O), 1250 (C=N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.35 (1H, d, *J*=1.9 Hz), 7.82 (1H, d, *J*=1.9 Hz), 4.94-4.80 (2H, br s), 4.42 (2H, q, *J*=7.2 Hz), 3.96 (3H, s), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 163.2, 146.9, 146.0, 133.3, 127.2, 121.9, 111.4, 110.9, 60.5, 30.8, 14.7. HRMS-ESI (m/z) calcd for $C_{11}H_{13}N_3O_2Cl$ $[M+H]^+$ 254.0696, found 254.0730.



5-Amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (7u). Following the general procedure, pyrimidine **1u** (140 mg, 1.0 mmol) was converted into amine **7u**. Purification of the crude product by column chromatography (Biotage M+12) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a white powder (77 mg, 50% yield); analytical TLC on silica gel, 1:10 MeOH/CH_2Cl_2, Rf=0.38. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 94-95 °C. IR (film, cm^{-1}) 3425 (NH_2), 3342 (NH_2), 1670 (C=O), 1635 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.64 (1H, s), 3.38 (3H, s), 3.33 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, pmm) δ 161.2, 150.4, 121.6, 121.4, 36.8, 28.4. HRMS-ESI (m/z) calcd for $C_6H_{10}N_3O_2$ $[M+H]^+$ 156.0773, found 156.0773.

Kinetic Experiments

The non-catalyzed fragmentation of 3a in CH_2Cl_2-d_2 at 23 °C.

Iodonium salt **3a** (13.18 mg, 0.025 mmol) was weighted in an oven-dried NMR-tube and CH_2Cl_2-d_2 (1 mL) was added shortly before the beginning of ^{1}H-NMR experiment. The amount of product **5a** was determined by integrating a peak at 4.03 ppm corresponding to the *N*-methyl group of **5a** (see Table S1).

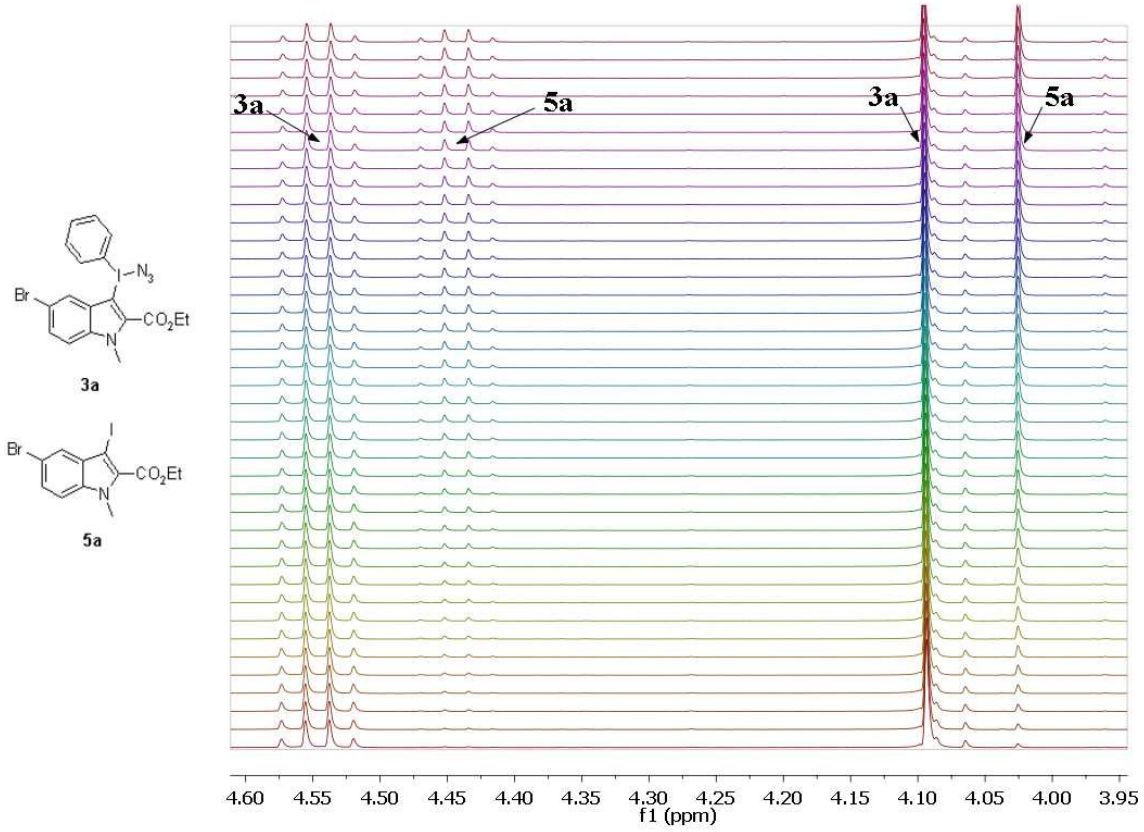


Figure S1. The non-catalyzed fragmentation **3a** in CH_2Cl_2-d_2 at 23 °C.

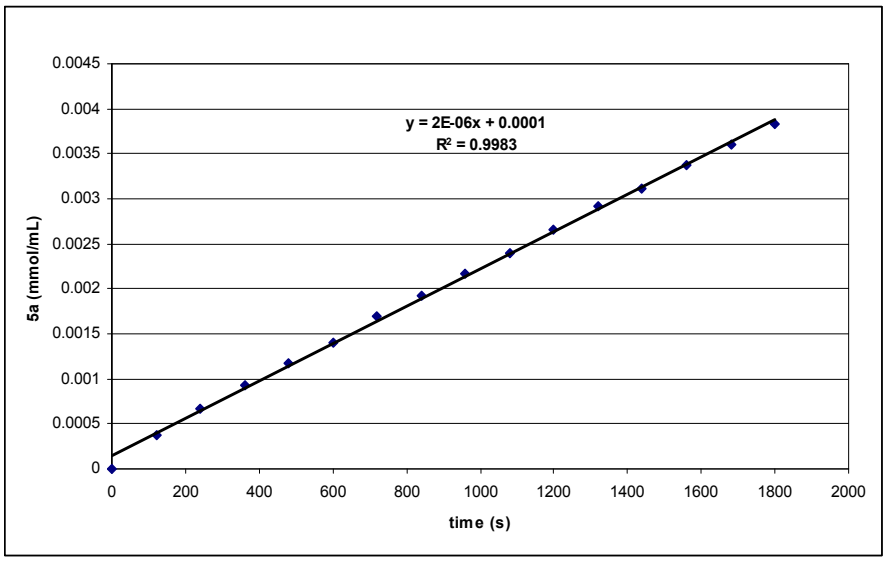


Figure S2. Kinetic data for the non-catalyzed fragmentation of **3a** in CH_2Cl_2-d_2 at 23 °C.

Kinetic profile of 3a in DMSO-d$_6$.

Iodonium salt **3a** (13.18 mg, 0.025 mmol) was weighted in an oven-dried NMR-tube and CH_2Cl_2-d_2 (1 mL) was added shortly before the beginning of ^{1}H-NMR experiment. The salt **3a** was stable in Formation of **5a** was not observed even after 1.5 h.

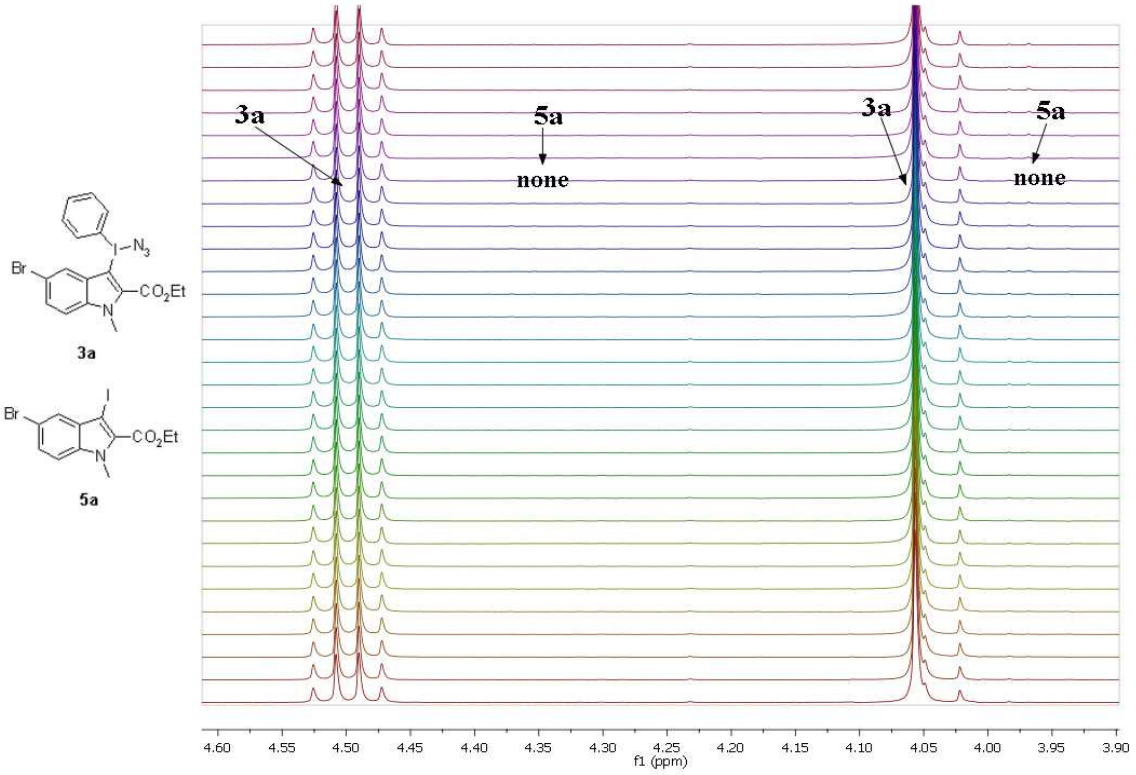


Figure S3. Non-catalyzed fragmentation ^{1}H-NMR experiment of **3a** in DMSO-d_6

Cu-Catalyzed Fragmentation of 3a in DMSO-d_6 at 23 °C

Order of the reaction in Cu(I) catalyst

The order in Cu(I) catalyst was determined by studying the initial rates of the **3a** decomposition at 23 °C in DMSO-d_6 at different concentrations of $(CuOTf)_2$●PhH.

To the iodonium salt **3a** (13.18 mg, 0.025 mmol) was added a certain amount of $(CuOTf)_2$●PhH stock solution [prepared by dissolving $(CuOTf)_2$●PhH (2.52 mg, 0.005 mmol) in DMSO-d_6 (4 mL)], followed with DMSO-d_6 (for volumes of the stock solution and amounts of DMSO-d_6 see Table S1).

Table S1. Volumes of the $(CuOTf)_2$●PhH stock solution and DMSO-d_6 used in experiments to obtain the reaction order in $(CuOTf)_2$PhH

entry	$(CuOTf)_2$●PhH, mol%	Volume of stock solution, µL	Volume of DMSO-d_6, µL
1	0.25	25	975
2	0.50	50	950
3	1.00	100	900
4	3.00	300	700
5	5.00	500	500

The amount of indolylazide **4a** was determined by integrating a peak at 3.93 ppm corresponding to the *N*-methyl group of **4a** (see Table S2).

Kinetic curves for reactions at different concentrations of $(CuOTf)_2$●PhH were constructed by *TableCurve* software and described by equation ($y = a + b \cdot x^c$); see Figure S9. To obtain values of rate coeficients $k_{obs.}$, each of the equations ($y = a + b \cdot x^c$) was differentiated by time and evaluated at x=120 sec. A plot of the initial rates ln(Δ[**4a**]/Δt) versus ln[$(CuOTf)_2$●PhH] gave a straight line (R^2=0.9898), indicative of a 1st order dependence on [$(CuOTf)_2$●PhH] (see Figure S10).

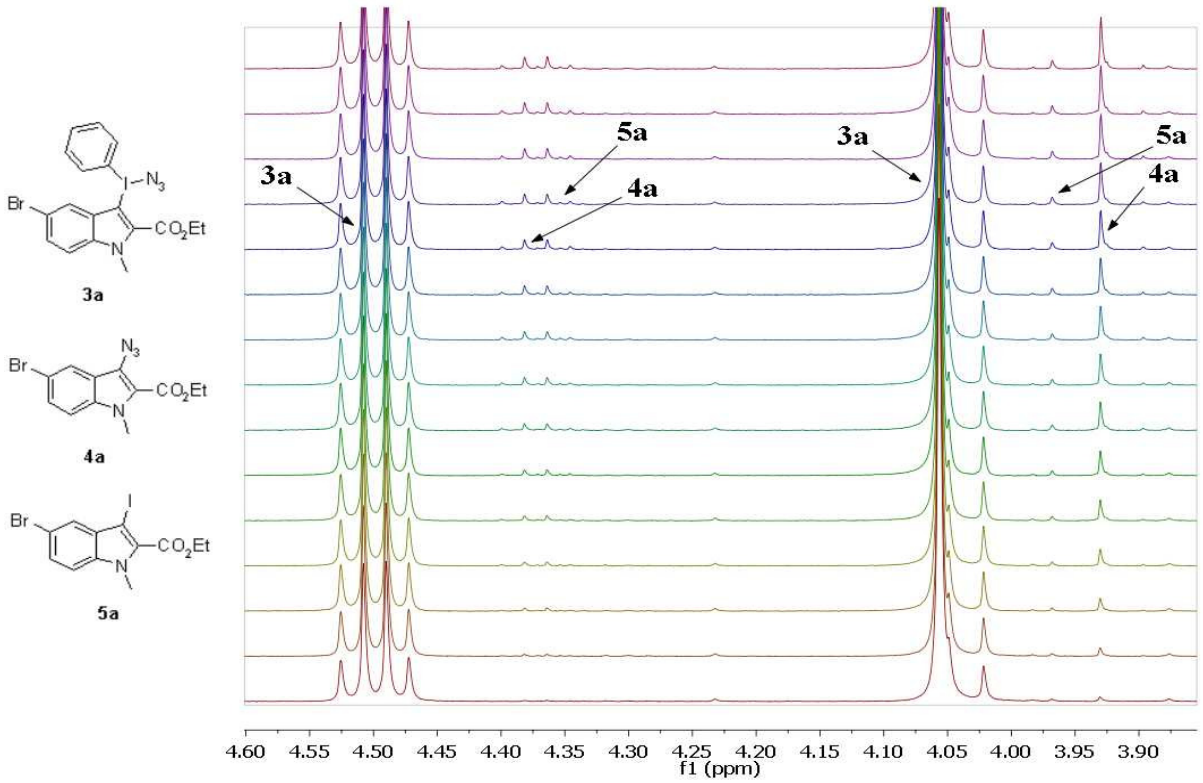


Figure S4. Catalyzed fragmentation ^{1}H-NMR experiment of **3a** with 0.25 mol% of $(CuOTf)_2$●PhH in DMSO-d_6

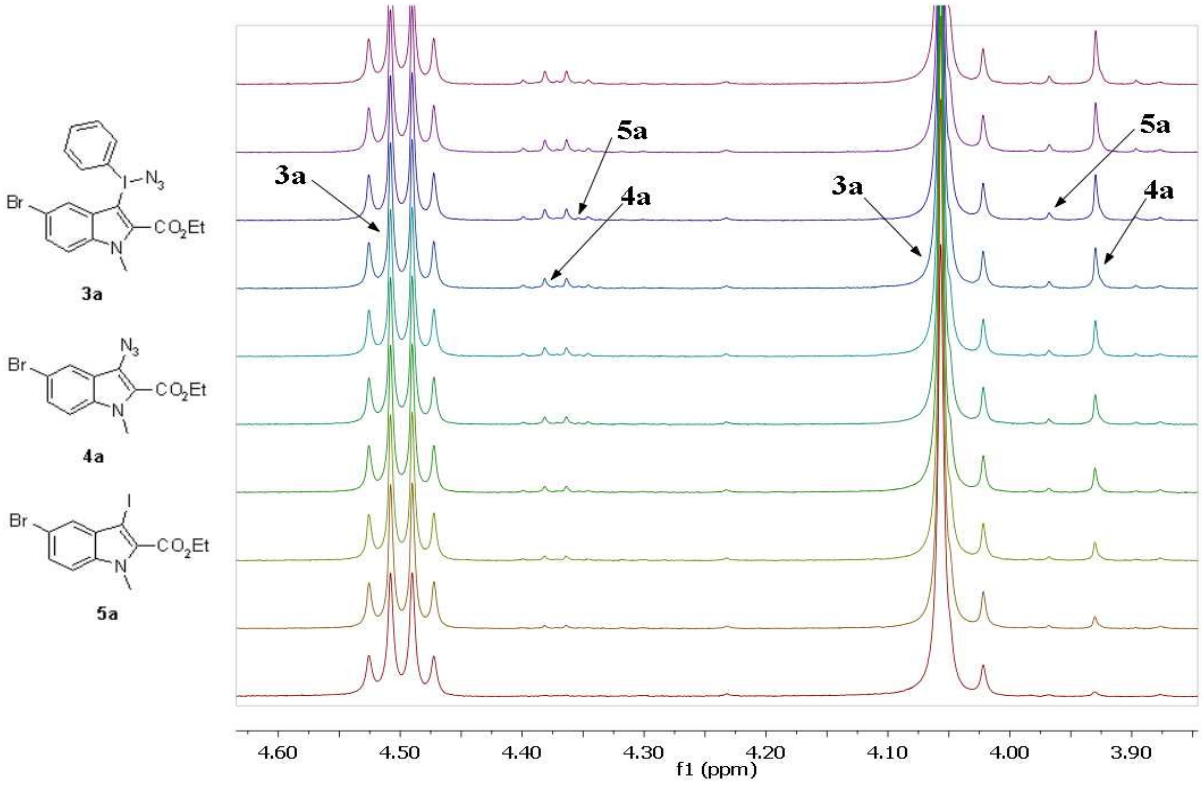


Figure S5. Catalyzed fragmentation ^{1}H-NMR experiment of **3a** with 0.50 mol% of $(CuOTf)_2$●PhH in DMSO-d_6

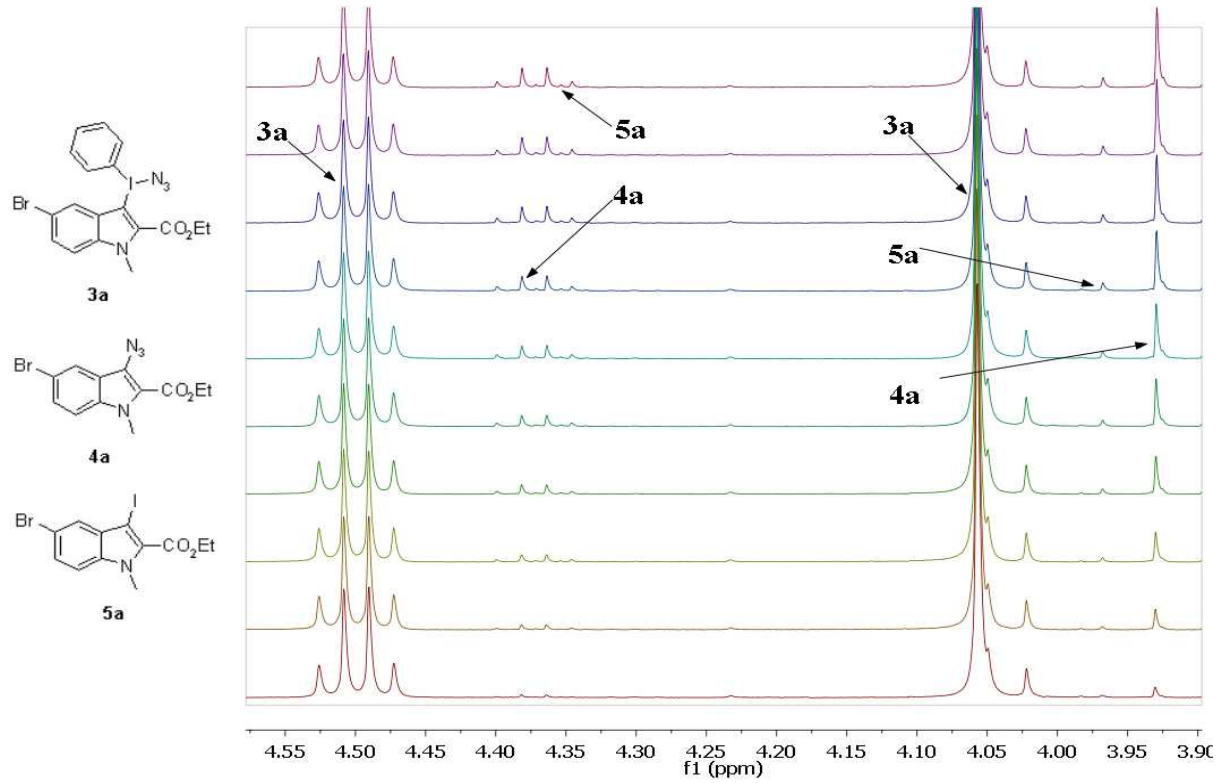


Figure S6. Catalyzed fragmentation ^{1}H-NMR experiment of **3a** with 1.00 mol% of $(CuOTf)_2$●PhH in DMSO-d_6

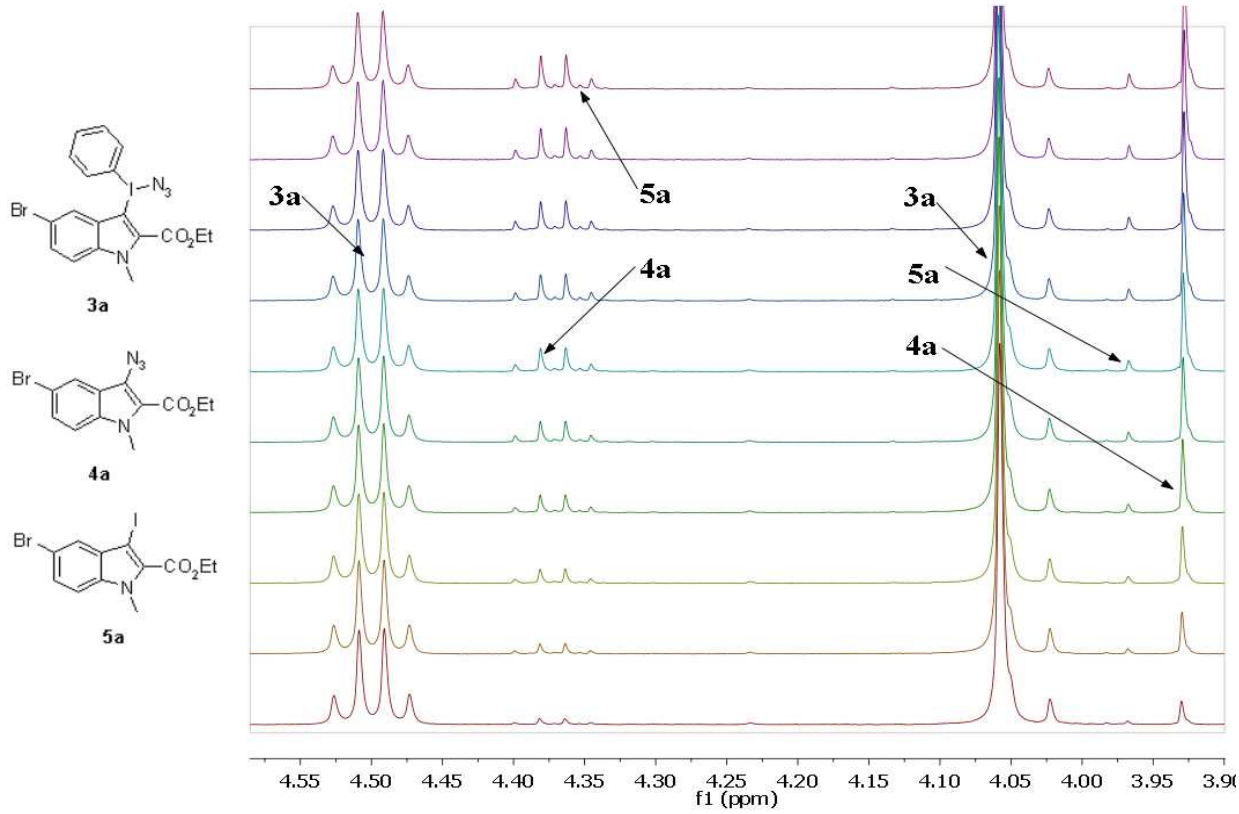


Figure S7. Catalyzed fragmentation ^{1}H-NMR experiment of **3a** with 3.00 mol% of $(CuOTf)_2$●PhH in DMSO-d_6

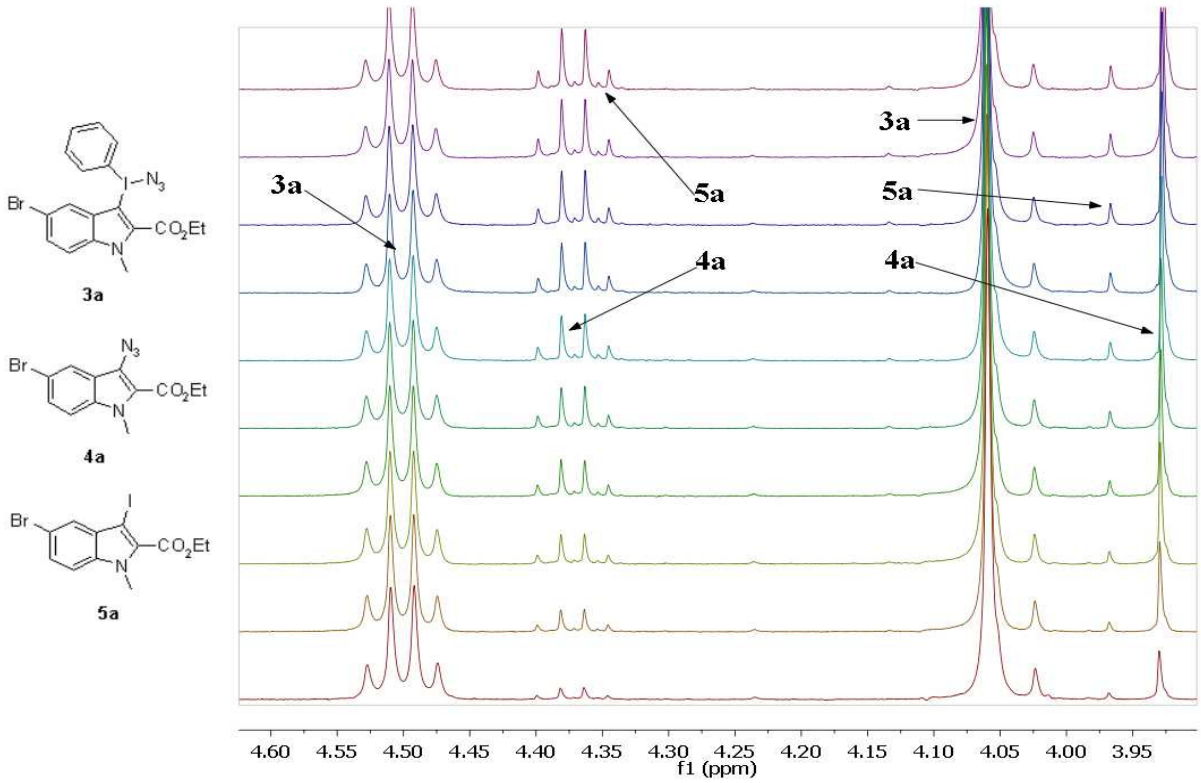


Figure S8. Catalyzed fragmentation ^{1}H-NMR experiment of **3a** with 5.00 mol% of $(CuOTf)_2$●PhH in DMSO-d_6

Table S2. Yields of **4a** in the $(CuOTf)_2$●PhH–catalyzed fragmentation of **3a**

time (s)	$(CuOTf)_2$●PhH, mol%				
	0.25	**0.50**	**1.00**	**3.00**	**5.00**
0	0	0	0	0	0
120	1.60	2.78	3.20	5.59	8.10
240	2.01	3.59	4.53	8.02	11.37
360	2.48	4.34	5.72	10.12	14.24
480	2.85	5.07	6.92	12.13	16.69
600	3.26	5.77	8.19	14.02	19.02
720	3.60	6.39	9.07	15.66	21.07
840	3.95	6.99	10.00	17.01	22.74
960	4.30	7.60	10.84	18.37	23.98
1080	4.62	8.12	11.52	19.64	25.06
1200	4.92	8.55	12.25	20.80	26.46

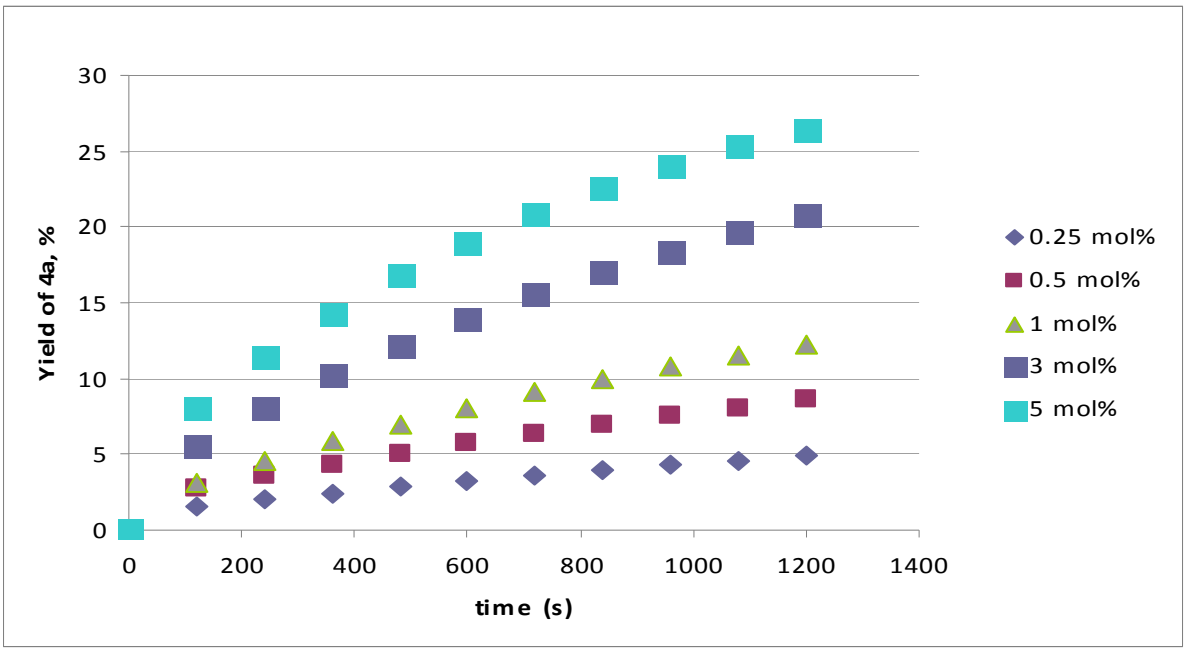


Figure S9. Kinetic profile of **3a** fragmentation at different concentrations of $(CuOTf)_2$●PhH in DMSO-d_6 at 23 °C

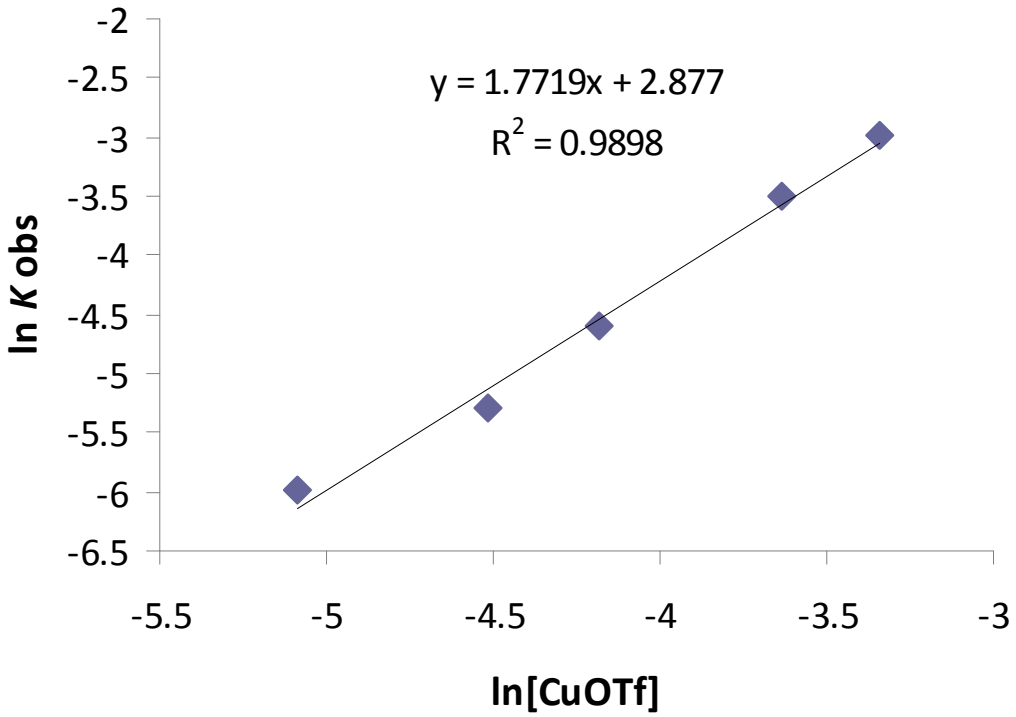


Figure S10. Plot of initial rates vs. concentration of $(CuOTf)_2$●PhH in DMSO-d_6 at 23 °C

Order of the reaction in azide anion

The order in azide anion was determined by studying the initial rates of the **3a** decomposition at 23 °C in DMSO-d_6 at different concentrations of the azide anion. Tetra-butilammonium azide (TBA–N_3) was used as the azide source.

The iodonium salt **3a** (13.18 mg, 0.025 mmol) and TBA–N_3 (0–3 equiv) were placed in an NMR tube and 100 μL of the $(CuOTf)_2$●PhH stock solution [prepared by dissolving $(CuOTf)_2$●PhH (2.52 mg, 0.005 mmol) in DMSO-d_6 (4 mL)] was added, followed with 900 μL of DMSO-d_6.

The amount of indolylazide **4a** was determined by integrating a peak at 3.93 ppm corresponding to the *N*-methyl group of **4a** (see Table S3). Kinetic curves for reactions at different concentrations of azide anion were constructed by *TableCurve* software and described by equation ($y = a + b \cdot x^c$); see Figure S15. To obtain the $k_{obs.}$, each equation ($y = a + b \cdot x^c$) was differentiated by time and evaluated at x=120 sec. A log plot of initial rate ln(Δ[**4a**]/Δt) versus ln[N_3^-] gave a straight line (R^2=0.9164), indicative of a 0th order dependence on [N_3^-]. k_{obs}=0.0465 mmol·mL·s^{-1} - 4.6504, presented in Figure S16.

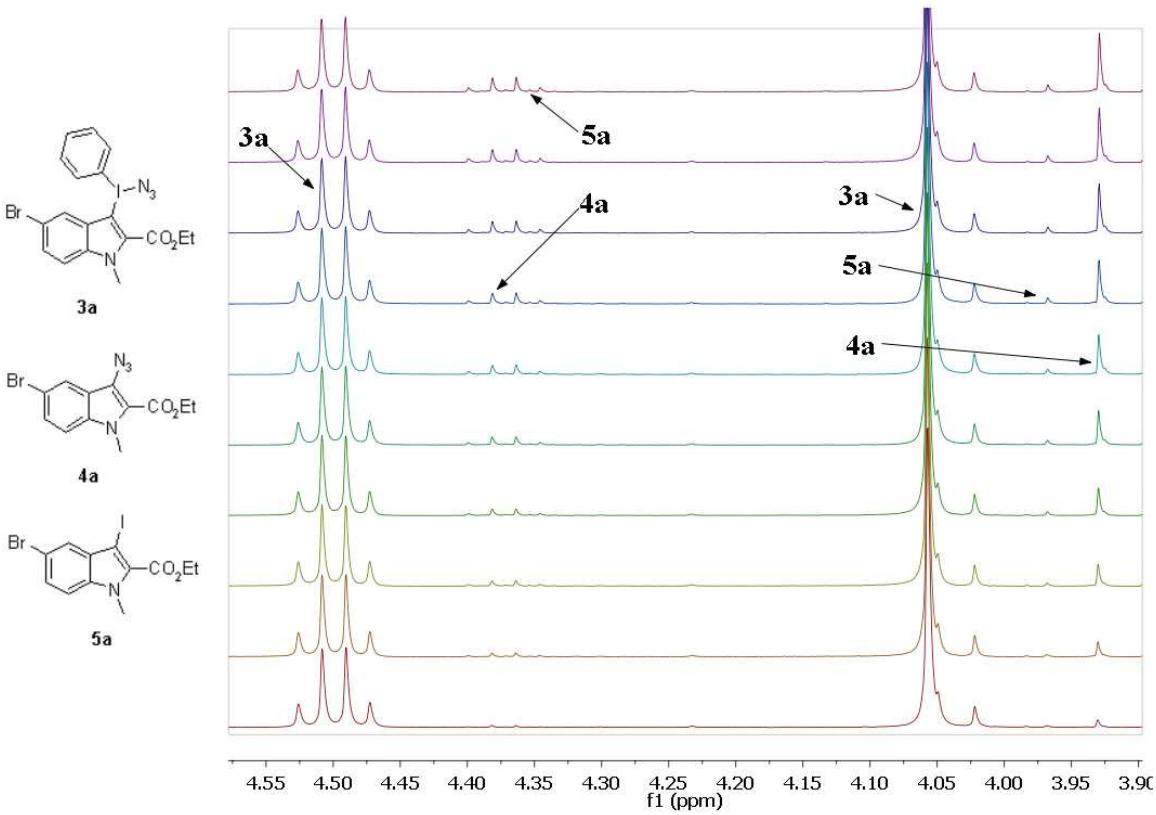


Figure S11. Cu–catalyzed fragmentation **3a** in DMSO-d_6 at 23 °C (1 mol% $(CuOTf)_2$●PhH)

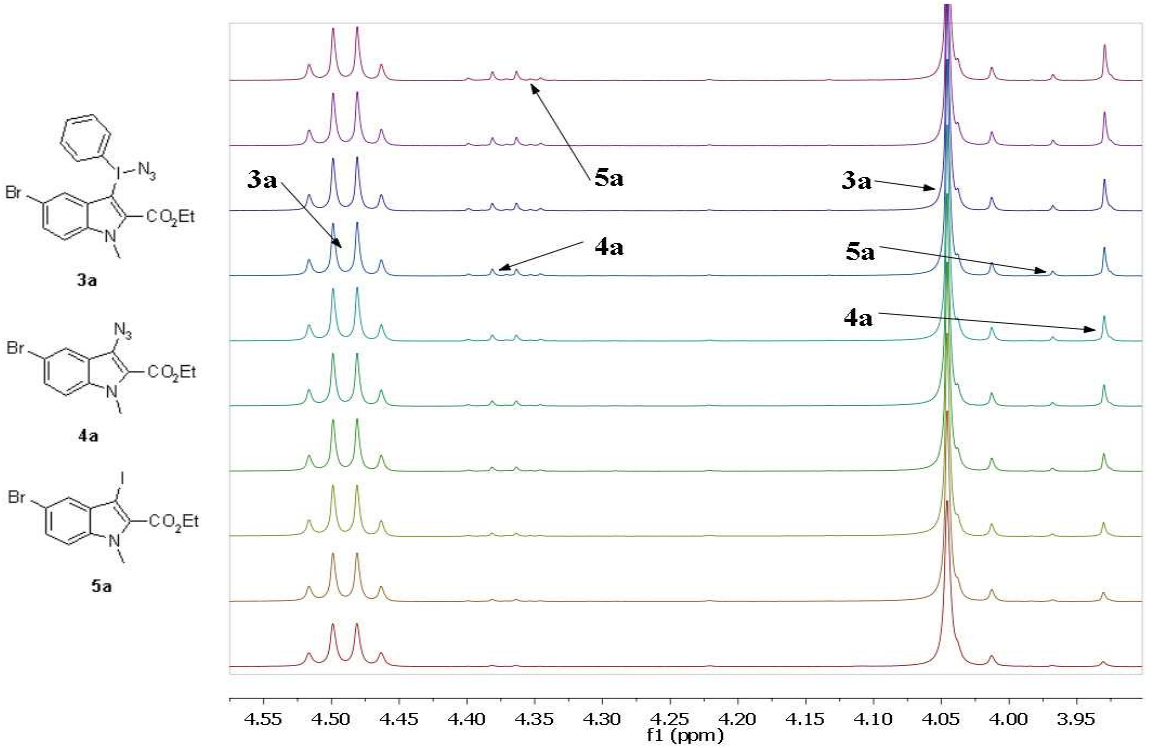


Figure S12. Cu–catalyzed fragmentation **3a** in DMSO-d_6 with 1 equiv of TBA–N_3 in DMSO-d_6 at 23 °C (1 mol% $(CuOTf)_2$●PhH))

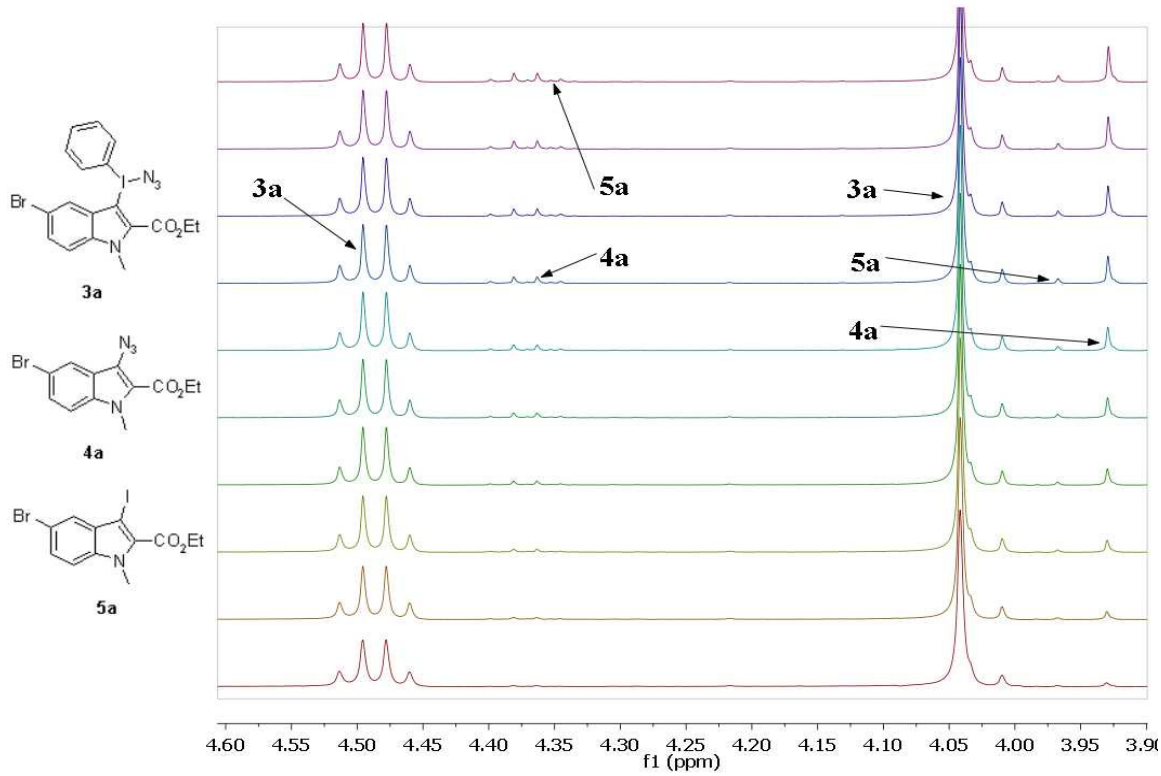


Figure S13. Cu–catalyzed fragmentation **3a** in DMSO-d_6 with 2 equiv of TBA–N_3 in DMSO-d_6 at 23 ºC ((1 mol% $(CuOTf)_2$●PhH))

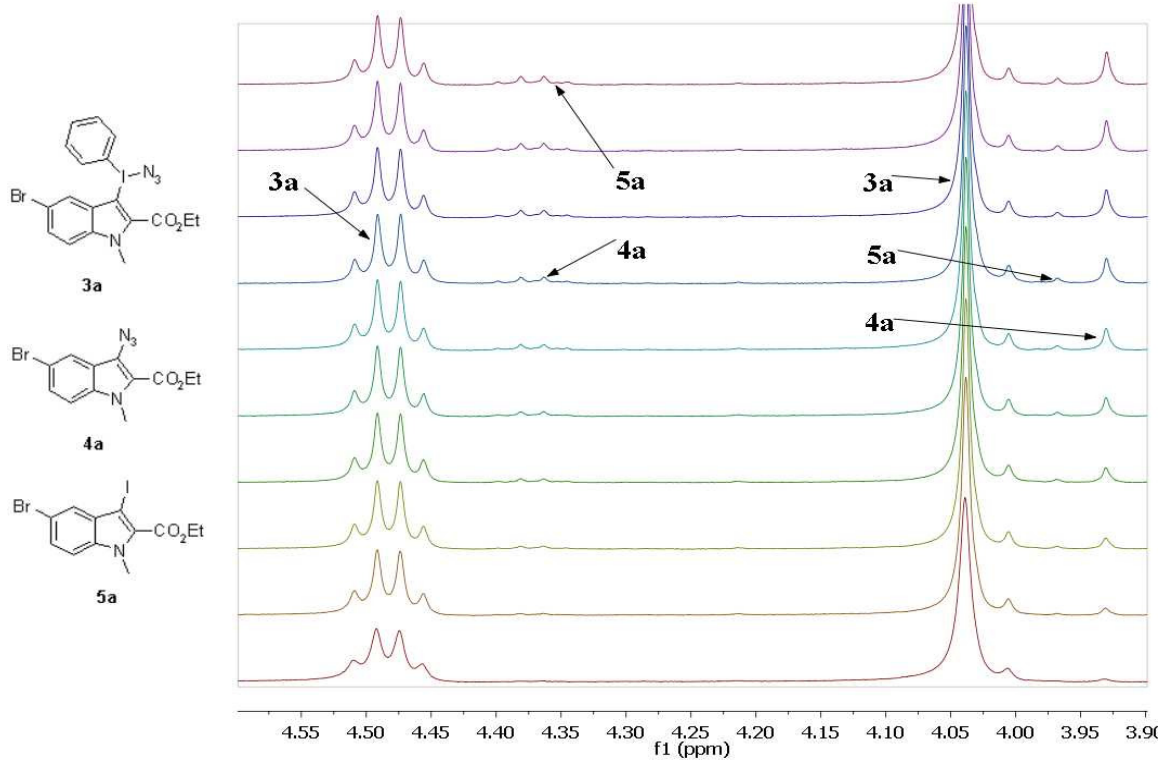


Figure S14. Cu–catalyzed fragmentation **3a** in DMSO-d_6 with 3 equiv of TBA–N_3 in DMSO-d_6 at 23 ºC ((1 mol% $(CuOTf)_2$●PhH))

Table S3. Yields of **4a** in the $(CuOTf)_2$●PhH–catalyzed fragmentation of **3a** with added TBA–N_3

time (s)	TBA–N_3, equiv			
	0	**1**	**2**	**3**
0	0	0	0	0
120	3.20	4.94	5.20	6.57
240	4.53	6.06	6.27	7.16
360	5.72	7.15	7.34	7.88
480	6.92	8.21	8.35	8.80
600	8.19	9.06	9.91	9.37
720	9.07	9.92	10.14	10.04
840	10.00	10.68	10.94	10.51
960	10.84	11.38	11.69	11.26
1080	11.52	12.07	12.39	11.81
1200	12.25	12.68	12.83	12.23

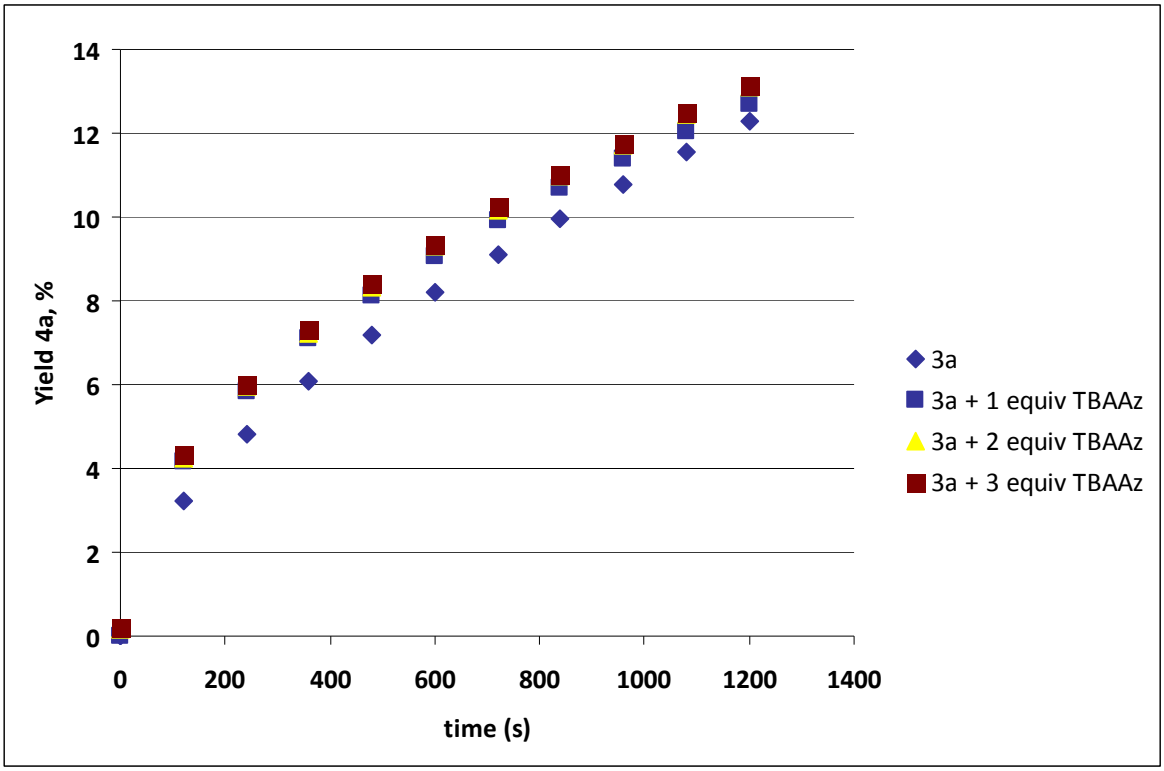


Figure S15. Kinetic profile of **3a** fragmentation at different concentrations of azide anion in DMSO-d_6 at 23 °C (1 mol% $(CuOTf)_2$●PhH))

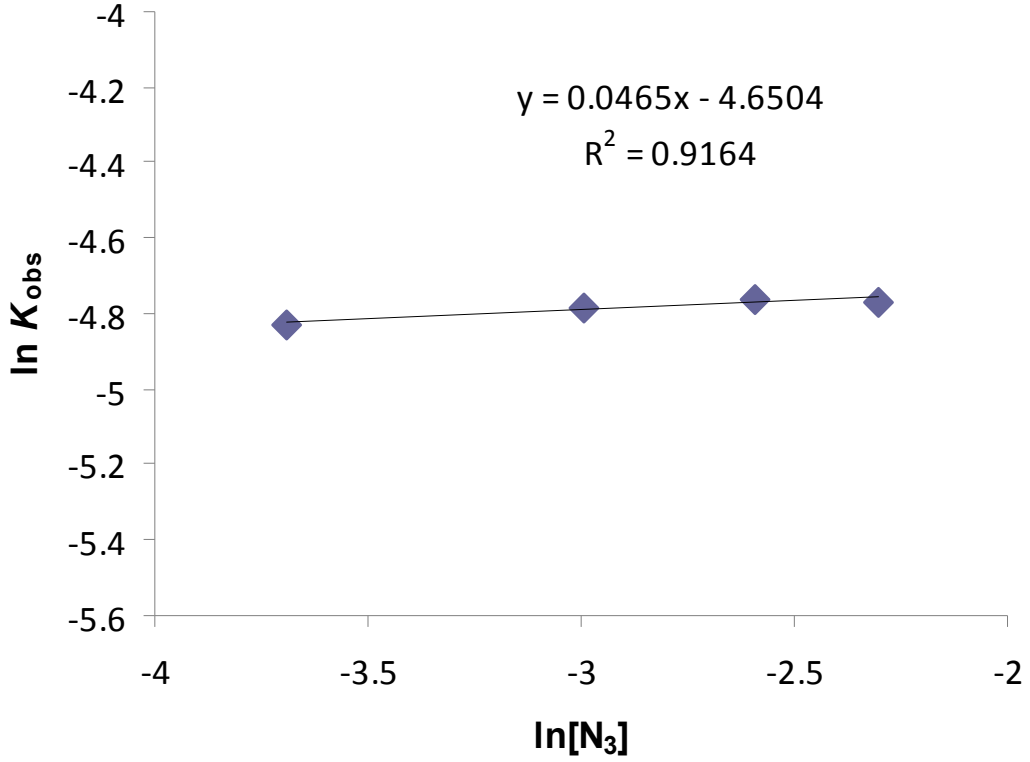


Figure S16. Plot of initial rates vs. concentration of azide anion in DMSO-d_6 at 23 °C (1 mol% $(CuOTf)_2$●PhH))

Cu-catalyzed fragmentation of 3a in the presence of neocuproin

Influence of neocuproine (2 equiv.) on $(CuOTf)_2$●PhH–catalyzed fragmentation of **3a** with was established by the following NMR experiments:

1. To the iodonium salt **3a** (13.18 mg, 0.025 mmol) in NMR tube was added 100 μL of the stock solution of $(CuOTf)_2$●PhH [prepared by dissolving $(CuOTf)_2$●PhH (2.52 mg, 0.005 mmol) in CH_2Cl_2-d_2 (4 mL)], followed with 900 μL of CD_2Cl_2.
2. To a mixture of the iodonium salt **3a** (13.18 mg, 0.025 mmol) and neocuproine (1.01 mg, 0.005 mmol) in NMR tube was added 100 μL of the stock solution of $(CuOTf)_2$●PhH [prepared by dissolving $(CuOTf)_2$●PhH (2.52 mg, 0.005 mmol) in CH_2Cl_2-d_2 (4 mL)], followed with 900 μL of CD_2Cl_2.

The amount of indolylazide **4a** was determined by integrating a peak at 3.97 ppm corresponding to the *N*-methyl group of **4a** (see Table S4).

Table S4. Yields of **4a** (%) in Cu–catalyzed fragmentation of **3a** with 1 mol% of $(CuOTf)_2$PhH with and witout neocuproine in CH_2Cl_2-d_2

time (s)	Yield of 4a, %	
	no cuproine	200 mol% cuproine
0	0	0
120	11.72	0.59
240	14.49	0.65
360	16.88	0.70
480	19.18	0.78
600	21.26	0.79
720	23.30	0.87
840	25.01	0.85
960	26.60	0.87
1080	28.23	0.89
1200	29.84	1.05

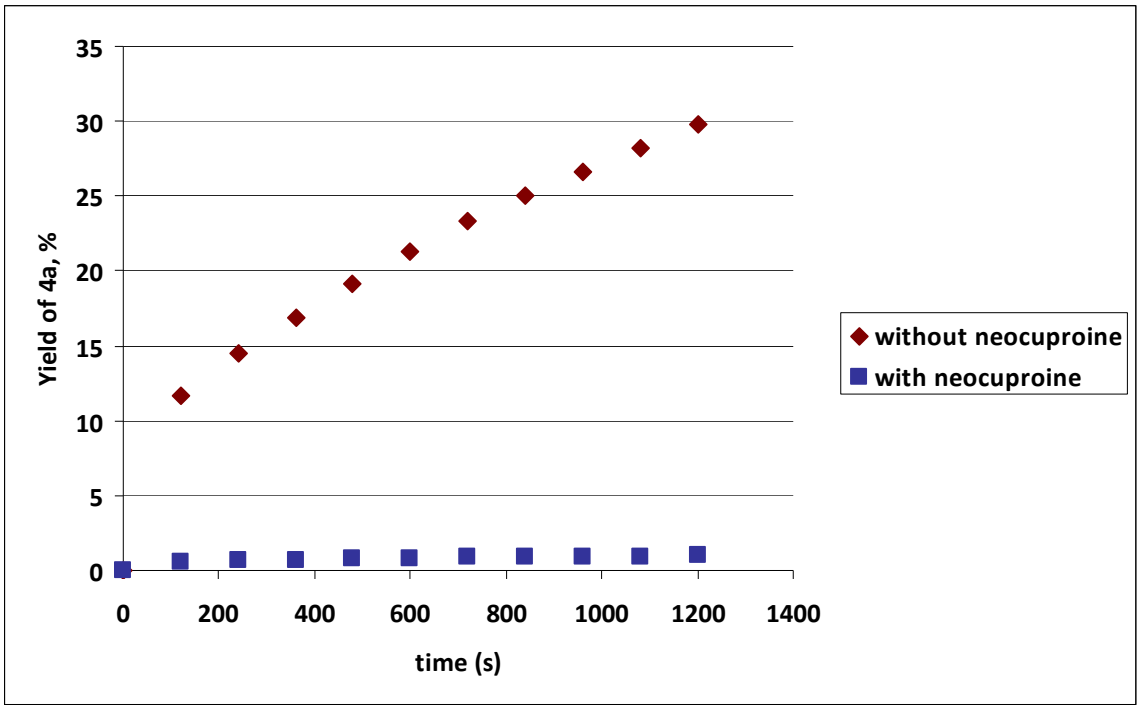
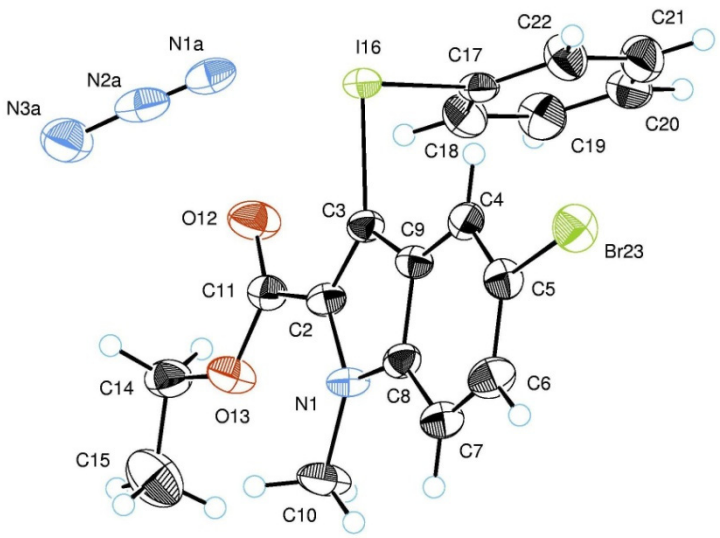


Figure S17. Kinetic profile Cu–catalyzed fragmentation of **3a** in CH_2Cl_2-d_2 with added neocuproine (20 mol%) and without neocuproine

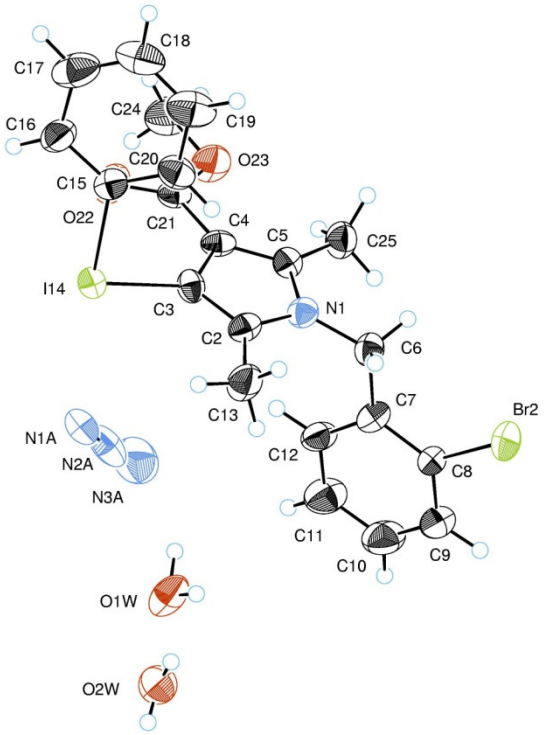
X-ray Crystallographic Analysis

X-ray structure, crystal data and structure refinements for 3a



Empirical formula	$C_{18}H_{16}BrINO_2$, C_4H_8O, N_3
Formula weight	599.25
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 10.1750(3) A alpha = 87.896(2) deg.
	b = 11.2802(4) A beta = 74.343(2) deg.
	c = 11.3973(4) A gamma = 67.681(2) deg.
Volume	1162.05(7) A^3
Z	2
Density (calculated)	1.713 Mg/m^3
Absorption coefficient	3.128 mm^-1
F(000)	592
Crystal size	0.15 x 0.11 x 0.10 mm
Two-theta range for data	57.0 deg.
Index ranges	0<=h<=13, -13<=k<=14, -14<=l<=14
Reflections collected	8720
Independent reflections	5767 [R(int) = 0.031]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4225 / 0 / 255
Goodness-of-fit on F^2	1.98
Final R indices [I>3sigma(I)]	R1 = 0.051, wR2 = 0.137
R indices (all data)	R1 = 0.078, wR2 = 0.194
Largest diff. peak and hole	1.92 and -1.93 e.A^-3

X-ray structure, crystal data and structure refinements for 3h



Empirical formula	$2(C_{21}H_{20}BrINO_2)$, $2(N_3)$, $3(H_2O)$
Formula weight	1188.47
Temperature	193(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 7.7822(3) A alpha = 92.675(2) deg
	b = 12.3633(5) A beta = 94.9141(14) deg
	c = 12.6194(6) A gamma = 97.142(2) deg
Volume	1198.29(9) A^3
Z	1
Density (calculated)	1.647 Mg/m^3
Absorption coefficient	3.034 mm^-1
F(000)	586
Crystal size	0.13 x 0.04 x 0.03 mm
Two-theta range for data	58.0 deg.
Index ranges	-10<=h<=10, -16<=k<=12, -17<=l<=17
Reflections collected	9109
Independent reflections	6144 [R(int) = 0.035]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4029 / 0 / 272
Goodness-of-fit on F^2	1.438
Final R indices [I>3sigma(I)]	R1 = 0.0791, wR2 = 0.1915
R indices (all data)	R1 = 0.1376, wR2 = 0.2510
Largest diff. peak and hole	1.402 and -1.390 e.A^-3

PIELIKUMS 8

Sokolovs, I.; Lubriks, D.; Suna, E. Copper-Catalyzed Intermolecular C-H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes. *J. Am. Chem. Soc.* **2014**, *136*, 6920–6928

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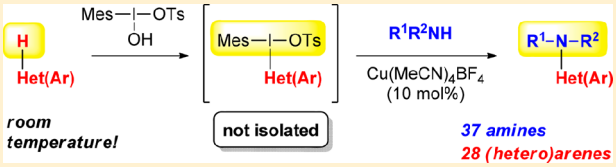
Copper-Catalyzed Intermolecular C–H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes

Igors Sokolovs, Dmitrijs Lubriks, and Edgars Suna*

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia

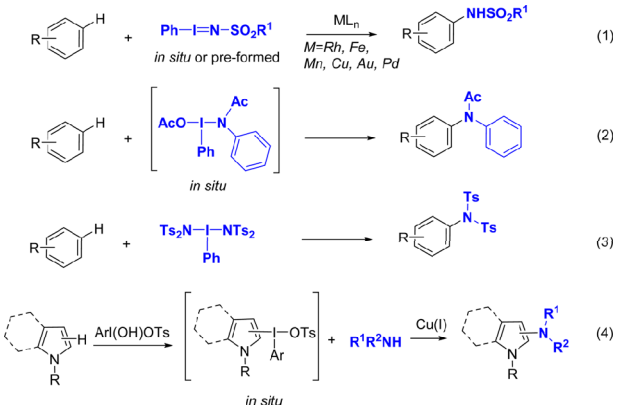
Supporting Information

ABSTRACT: A one-pot two-step method for intermolecular C–H amination of electron-rich heteroarenes and arenes has been developed. The approach is based on a room-temperature copper-catalyzed regioselective reaction of the in situ formed unsymmetrical (hetero)aryl-λ^3-iodanes with a wide range of primary and secondary aliphatic amines and anilines.



INTRODUCTION

Hypervalent iodine(III) species possessing an iodine–nitrogen bond are efficient reagents in oxidative C–H amination of nonprefunctionalized arenes and heteroarenes.[1] The most widely used are preformed or in situ generated sulfonylimino-λ^3-iodanes, which effect C–H to C–N bond transformations in the presence of transition metal catalyst (eq 1).[2] Phenyl-λ^3-



iodane (formed in situ from $PhI(OAc)_2$ and *N*-acetanilide) has been proposed as a precursor of acylnitrenium species in a transition metal-free C–H amination of arenes (eq 2).[3−5] Analogous phenyl-λ^3-iodanes possessing an iodine–nitrogen bond have also been suggested as plausible intermediates in an oxidative transfer of the phthalimide moiety to arene rings.[6,7] Recently, a well-defined bis-tosylimido-λ^3-iodane has been introduced by Muñiz for a metal-free oxidative amination of arenes and heteroarenes (eq 3).[8] All of the above-mentioned approaches, however, have a serious limitation: only amides, imides, and sulfonamides can be transferred to arenes or heteroarenes by hypervalent iodine(III) species. Simple amines are not compatible with these C–H amination conditions, as they are oxidized by monoaryl-λ^3-iodane reagents.[9] In contrast, amines are oxidatively stable toward diaryl-λ^3-iodanes, and these hypervalent iodine(III) species have been used for the *N*-arylation of amines.[10] Symmetrical diaryl-λ^3-iodanes are preferred for *N*-arylation because unsymmetrical diaryl-λ^3-iodanes usually form a mixture of *N*-arylation products.[10d,e]

We envisioned that a versatile method for C–H amination of (hetero)arenes with unprotected amines as the source of nitrogen could be developed, provided that the issue of regioselectivity of amine transfer to the desired aromatic ring of the unsymmetrical diaryl-λ^3-iodanes could be solved. Recently, we reported that a Cu(I) catalyst ensures complete regiocontrol in a reaction of azides with unsymmetrical diaryl-λ^3-iodanes.[11] During this study, it became evident that nucleophiles other than azide could be reacted regioselectively with a variety of unsymmetrical heteroaryl-λ^3-iodanes that are generated as intermediates using suitable ArI(OH)OTs reagent. Herein, we report a mild and versatile Cu(I)-catalyzed method for intermolecular C–H amination of electron-rich heterocycles (pyrroles, pyrrolopyridines, thienopyrroles, pyrrolopyrimidines, and uracil) as well as simple arenes, comprising a one-pot two-step room-temperature reaction between the (hetero)aryl-λ^3-iodanes formed in situ and a wide range of primary and secondary amines (eq 4). The reactivity pattern of the developed C–H amination approach is consistent with that of an electrophilic aromatic substitution (S_EAr) reaction. Because of the operational simplicity, mild reaction conditions, and wide substrate scope, our C–H amination approach provides a convenient way for C–H functionalization of heteroarenes,[12] a topic of high importance in medicinal and pharmaceutical chemistry given the drug-like properties of heteroarenes and abundance of heterocycles in drugs.

RESULTS AND DISCUSSION

At the outset of our investigation, we synthesized the indolyliodonium tosylate **2a** in a pure form from MesI(OH)-OTs[13] and indole **1a**. The structure of **2a** was confirmed by X-ray crystallographic analysis (Figure 1). λ^3-Iodane **2a** is stable in MeCN, DCM, and DMSO solutions at room temperature for

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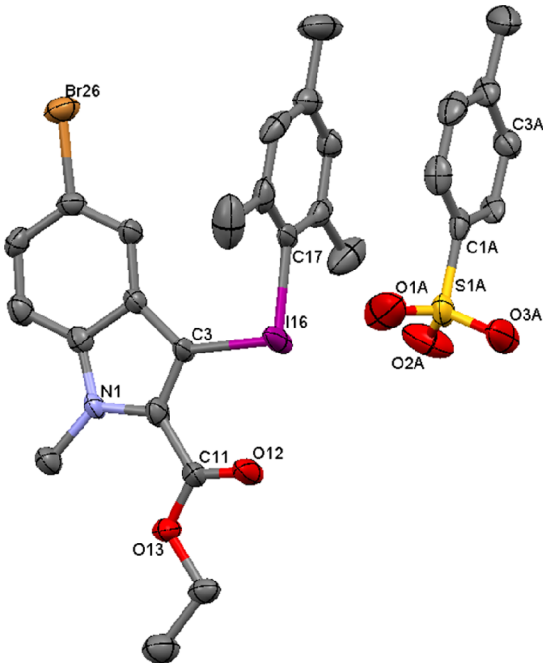


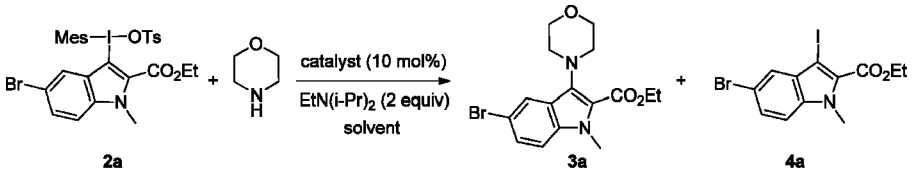
Figure 1. X-ray crystal structure of λ^3-iodane **2a** (ellipsoids at 50% probability) with hydrogen atoms omitted for clarity. Selected bond distances (Å) and angles (deg): I16–C3, 2.086(7); I16–C17, 2.108(8); I16–O12, 2.713(7); I–O1A, 3.088(9); I–O2A, 3.001(8); C3–I16–C17, 98.2(3). See the Supporting Information for details.

at least 72 h, but addition of morpholine and DIPEA to a DCM solution of **2a** brought about its slow transformation to iodoindole **4a** (entry 1, Table 1). The process was facilitated by using DMSO as solvent (entry 2). The conversion of **2a** to **4a** was highly selective, and only traces of indolylamine **3a** were observed. In striking contrast, addition of CuOTf (10 mol %) resulted in complete reversal of selectivity favoring the formation of the desired **3a**. Furthermore, the copper catalyst considerably decreased the reaction time (entry 3 vs entries 1–2, Table 1). Both Cu(I) and Cu(II) salts could be utilized; however, the Cu(I) species ensured faster reaction (entry 3 vs 4). Faster formation of **3a** helped to improve the **3a**:**4a** ratio by diminishing an impact of the competing noncatalyzed background formation of **4a** (entry 2). The determined initial rates of the noncatalyzed background reaction of **2a** with morpholine in DMSO (initial rate coefficient $k_{obs} = 1.98 \times 10^{-7}$ mmol mL^{-1} s^{-1}, DMSO-d_6, 25 °C) evidence that the background reaction delivers ca. 10% of **4a** within 90 min. By this time, the Cu(I)-catalyzed conversion of **2a** to **3a** is almost quantitative, so the faster is **3a** formation, the higher is **3a**:**4a** selectivity. Screening of various Cu(I) sources helped to identify the relatively stable $Cu(MeCN)_4BF_4$ as the most efficient catalyst (entry 5). λ^3-Iodane **2a′** containing a Ph ligand instead of the mesityl group could also be used at the expense of slightly diminished selectivity (entry 6). However, Pd(II), Ni(II), and Sc(III) salts were inefficient as catalysts (entries 7–9, Table 1).[14]

Indolylamine **3a** could also be synthesized in a sequential one-pot approach without isolation of the iodonium salt **2a**. Accordingly, $Cu(MeCN)_4BF_4$, morpholine, and EtN(*i*-Pr)$_2$ were added to the reaction mixture after the corresponding λ^3-iodane **2a** had been formed.[15] The one-pot sequential C–H amination approach afforded lower yields of **3a** as compared to the two-step synthesis (74% vs 85%), but avoided the isolation and handling of potentially unstable intermediate λ^3-iodanes. This advantage compensates for the decreased yields.

Various amines were subsequently examined in the Cu(I)-catalyzed two-step one-pot C–H amination of indole **1a** (Table 2). A wide variety of aliphatic secondary amines (entries 1–11), aliphatic primary amines (entries 12–26), primary and secondary aromatic amines (entries 27–35), as well as a heteroarylamine (entry 36) and ammonia (entry 37) could be employed. Importantly, the reaction conditions are compatible with alkene and alkyne moieties in the amine (entries 10, 22, 23).[16] *N*-Boc (entry 17), *N*-acetyl (entry 5), and *S*-trityl (entry 20) protecting groups, acetals (entry 21), ketals (entry 2), as well as various functional groups such as esters (entry 30), nitriles (entries 9,15), nitro (entry 31), and halides (entries 24, 25, 28) are all tolerated. Sterically hindered amines (entries 14,

Table 1. Reaction of λ^3-Iodane 2a with Morpholine



entry	catalyst (10 mol %)	solvent, time	conversion %[a,b]	**3a**:**4a** ratio, (yield %)[b,c]
1	none	CH_2Cl_2, 24 h	15	1:99 (8)
2	none	DMSO, 24 h	81	1:99 (67)
3	CuOTf·PhH	CH_2Cl_2–DMSO 4:1, 1.5 h	60	97:3 (46)
4	$Cu(OTf)_2$	CH_2Cl_2–DMSO 4:1, 1.5 h	22	93:7 (14)
5	$Cu(MeCN)_4BF_4$	CH_2Cl_2–DMSO 4:1, 1 h	92	97:3 (85)[d]
6[e]	$Cu(MeCN)_4BF_4$	CH_2Cl_2-DMSO 4:1, 1.5 h	93	89:11 (76)
7	$Pd(OCOCF_3)_2$	CH_2Cl_2–DMSO 4:1, 1.5 h	5	1:99 (3)
8	$Ni(OTf)_2$	CH_2Cl_2–DMSO 4:1, 1.5 h	5	1:99 (5)
9	$Sc(OTf)_3$	CH_2Cl_2–DMSO 4:1, 1.5 h	7	1:99 (5)

[a]Conditions: λ^3-iodane **2a** (1.0 equiv), morpholine (1.2 equiv), solvent (10 mL/1 mmol of **2a**), room temperature. [b]Determined by LC–MS assay. [c]Yield of the major product. [d]Isolated yield of >95% pure indole **3a**. [e]λ^3-Iodane **2a′** possessing Ph ligand instead of a mesityl group (Mes = Ph) was used.

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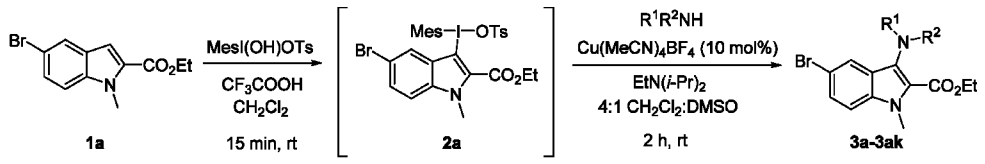
Table 2. Sequential One-Pot Synthesis of Indolylamines 3a–3ak[a]



Mes=2,4,6-trimethylphenyl

entry	R^1R^2NH	Yield (%)	entry	R^1R^2NH	Yield (%)	entry	R^1R^2NH	Yield (%)
1		**3a**, 74	14		**3n**, 76	26		**3z**, 79
2		**3b**, 66	15		**3o**, 63	27		**3aa**, 73
3		**3c**, 75	16		**3p**, 67	28		**3ab**, 74
4		**3d**, 71	17		**3q**, 73	29		**3ac**, 54
5		**3e**, 76	18		**3r** ,40	30		**3ad**, 69
6		**3f**, 76	19		**3s**, 75	31		**3ae**, 67
7		**3g**, 70	20		**3t**, 73	32		**3af**, 62
8		**3h**, 35[b]	21		**3u**, 80	33		**3ag**, 79
9		**3i**, 65	22		**3v**, 80	34		**3ah**, 76
10		**3j**, 67	23		**3w**, 71	35		**3ai**, 77
11		**3k**, 65	24		**3x**, 83	36		**3aj**, 65
12		**3l**, 71						
13		**3m**, 70	25		**3y**, 77	37		**3ak**, 71[c]

[a]Conditions: Indole **1a** (1.0 equiv), MesI(OH)OTs (1.1 equiv), CF_3COOH (1.2 equiv), CH_2Cl_2 (4 mL/1 mmol of **1a**), room temperature, 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), Cu(MeCN)$_4$BF$_4$ (0.1 equiv), 1:1 CH_2Cl_2:DMSO (4 mL/1 mmol of **1a**), room temperature, 2 h. [b]Reaction time for the formation of **3h** from λ^3-iodane: 18 h. [c]3 equiv of EtN(*i*-Pr)$_2$ was used.

33, 34) are also suitable as substrates.[17] Amines react chemoselectively in the presence of unprotected alcohol (entry 16), amide (entry 6), and sulfonamide moieties (entry 32), and monoamination with piperazine is also possible (entry 7). It should be noted that moderate yields were obtained for bi- and tridentate amines potentially capable of chelating the Cu(I) catalyst (entries 8, 18).

Next, the scope of substrates for the C–H amination was surveyed employing morpholine, cyclopropylmethylamine, and 4-bromoaniline as representative amines (Table 3). All heterocycles that react with MesI(OH)OTs and form iodonium salts that survive in solution are suitable as substrates, including 2-substituted indoles (entries 1–6),[18] pyrroles (7–14), thieno[3,2-*b*]pyrrole (entries 15, 16), pyrrolo[2,3-*b*]pyridines (entries 17, 18), pyrrolo[2,3-*d*]pyrimidine (entry 19), pyrazoles (entries 20–22), and *N*,*N*-dimethyluracil (entry 23). The formation of the intermediate iodonium salts was found to be sensitive to the electronic properties of heterocycle.[19] Thus, relatively electron-rich *N*-alkyl pyrroles (entries 7–10, 12–14) and pyrrolo[2,3-*b*]pyridine (entry 18) reacted rapidly and produced the intermediate iodonium salts within 5 min. In contrast, introduction of an electron-withdrawing *N*-acyl moiety in pyrrole (entry 11) increased the reaction time to 30 min. The formation of iodonium salts from less electron-rich heterocycles such as indoles (entries 1–6), pyrrolo[2,3-*b*]pyridine (entry 17), pyrrolo[2,3-*d*]pyrimidine (entry 19), pyrazoles (entries 20–22), and *N*,*N*-dimethyluracil (entry 23) was considerably slower. However, the reaction of these substrates with MesI(OH)OTs could be facilitated by addition of CF_3COOH (1.2 equiv). This did not work always, and pyrroles possessing several electron-withdrawing substituents such as *N*-tosyl-1*H*-pyrrole-2-carboxylic acid ethyl ester did not give substantial conversion to the corresponding iodonium salt under our standard conditions with added CF_3COOH. Furthermore, potential substrates such as *N*-methylbenzimidazole, benzo[*b*]-thiophene, and ethyl thiophene-2-carboxylate were also unreactive. Apparently, the latter heterocycles are insufficiently electron-rich to produce iodonium salts in the reaction with MesI(OH)OTs. On the other hand, we were especially pleased to find that electron-rich carbocyclic arenes undergo C–H amination as exemplified in Table 4. Surprisingly, even the simple substrates such as tetraline (entry 1) and *N*-Boc-*N*-methylaniline (entry 2) could be employed in the C–H amination reaction. The formation of the intermediate diaryl-λ^3-iodane from tetraline (entry 1) required prolonged time (18 h) apparently because of insufficiently electron-rich nature of tetraline. The presence of electron-releasing alkoxy groups facilitates considerably the formation of intermediate diaryl-λ^3-iodane (entries 3–5 vs entry 1). Further improvement of C–H amination yields was achieved for arenes containing two electron-releasing substituents (entries 6–9, Table 4). In general, the more electron-rich is (hetero)arene, the shorter are the times required to produce the intermediate diaryl-λ^3-iodane. However, transient λ^3-iodanes formed from electron-rich (hetero)arenes usually are unstable and are prone to undesired decomposition if the addition of Cu catalyst and/or

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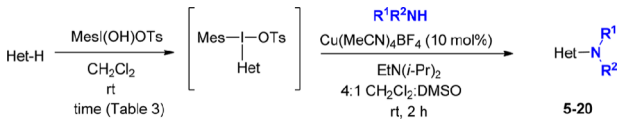
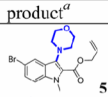
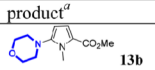
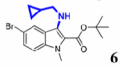
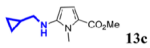
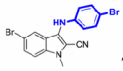
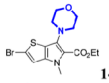
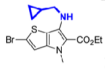
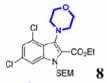
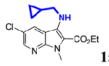
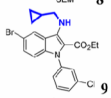
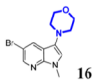
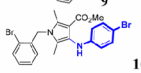
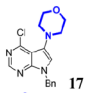
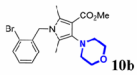
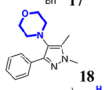
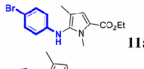
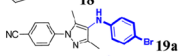
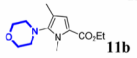
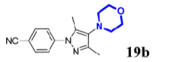
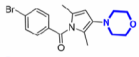
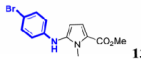
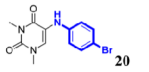
Table 3. C−H Amination of Heterocycles



entry	product[a]	time	yield (%)	entry	product[a]	time	yield (%)
1	 **5**	30 min[b]	69	13	 **13b**	5 min	71
2	 **6**	30 min[b]	79	14	 **13c**	5 min	65
3	 **7a**	18 h[b]	84	15	 **14b**	2 h	57
4	 **7b**	18 h[b]	77	16	 **14c**	2 h	62
5	 **8**	18 h[b]	50	17	 **15**	1 h[b]	78
6	 **9**	18 h[b]	72	18	 **16**	5 min[c]	62
7	 **10a**	5 min	70	19	 **17**	3 h[b]	60
8	 **10b**	5 min	62	20	 **18**	5 h[b]	52
9	 **11a**	5 min	60	21	 **19a**	24 h[b]	60
10	 **11b**	5 min	62	22	 **19b**	24 h[b]	62
11	 **12**	30 min	63				
12	 **13a**	5 min	91	23	 **20**	18 h[b]	65

[a]Conditions: Heteroarene (1.0 equiv), MesI(OH)OTs (1.1 equiv), CH_2Cl_2 (4 mL/1 mmol of the starting heteroarene), 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), Cu(MeCN)$_4$BF$_4$ (0.1 equiv), 2:1 CH_2Cl_2:DMSO (4 mL/1 mmol of the starting heteroarene), room temperature, 2 h. [b]In the presence of CF_3COOH (1.2 equiv). [c]λ^3-Iodane was formed at −20 °C.

amine is delayed. Therefore, it is important to establish the optimum conversion time of the starting (hetero)arene into λ^3-iodane.

The regioselectivity of the C−H amination is controlled at the stage of the formation of the intermediate iodonium salts. Although the regioselectivity is a result of the combined directing effects of substituents in heterocycles and arenes, in general, it is consistent with that of electrophilic aromatic substitution (S_EAr) reactions. Thus, λ^3-iodanes are formed at the β-position of indoles (entries 1−6, Table 3) and fused pyrroles (entries 15−19), at the α-position of pyrroles[20a] (entries 9, 10, 12−14), and at position 5 of uracil[20b] (entry 23), while 2,5-disubstituted pyrroles (entries 7, 8, 11) produce iodonium salts at the β-position. In the case of simple arenes, intermediate λ^3-iodanes are selectively formed in the *para*-position to the strongest electron-releasing substituent in the molecule, for example, alkyl moiety (entry 1, Table 4), *N*-Boc-*N*-methylamino group (entry 2), alkoxy (entry 4), and MeO groups (entries 3, 5−8).[21] Interestingly, C−H amination proceeds in *para*-position to the MeO group also in *N*-protected methoxyanilines (entries 9−11), substrates that possess two different electron-releasing substituents. The observed regioselectivity of C−H amination in *meta*-anisidines (entries 10, 11) might also be attributed to stabilization of intermediate λ^3-iodane by the adjacent *N*-Boc moiety. However, we regard such stabilization unlikely because *N*-Boc-*N*-methylaniline underwent C−H amination in the *para*-position, and not next to the aniline nitrogen (entry 2, Table 4). Notably, all of the other C−H amination products (Tables 3 and 4) were likewise obtained as pure regioisomers, and the formation of minor isomers was not observed within ^{1}H NMR detection limits.

The C−H amination conditions are compatible with the presence of *O*-allyl (entry 1, Table 3), *O*-*tert*-butyl (entry 2, Table 3), *O*-alkyl ester moieties (entries 5−10, 12−17, Table 3), as well as amides (entries 7, 8, Table 4) and *tert*-butyl carbamates (entries 2, 10, 11, Table 4). The successful C−H amination of substrates containing secondary amide (entry 7, Table 4) and carbamate (entry 10, Table 4) moieties is noteworthy, because structurally related *N*-acetanilides react with PhI(OAc)$_2$ and generate highly reactive acylnitrenium species.[3b,d] Bromine and chlorine substituents in the substrate

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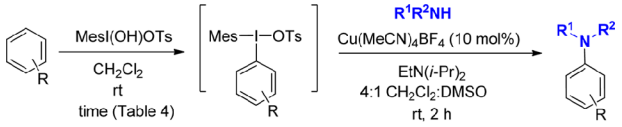
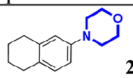
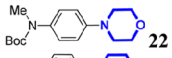
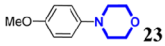
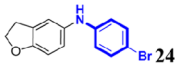
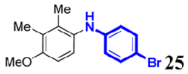
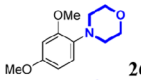
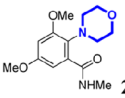
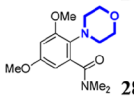
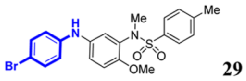
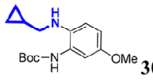
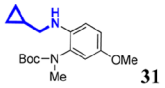
Table 4. C–H Amination of Arenes



21-31

entry	product[a]	time	yield (%)
1	 21	18 h[b]	41
2	 22	30 min[b]	30[c]
3	 23	30 min[b]	52
4	 24	30 min	49
5	 25	30 min[b]	56
6	 26	30 min[b]	61
7	 27	30 min[b]	71
8	 28	30 min[b]	74
9	 29	18 h[b]	60
10	 30	30 min	40
11	 31	60 min	50

[a]Conditions: Arene (1.0 equiv), MesI(OH)OTs (1.1 equiv), CH_2Cl_2 (4 mL/1 mmol of the starting arene), 15 min; then amine (1.2 equiv), EtN(*i*-Pr)$_2$ (2.0 equiv), Cu(MeCN)$_4$BF$_4$ (0.1 equiv), 2:1 CH_2Cl_2:DMSO (4 mL/1 mmol of the starting arene), room temperature, 2 h. [b]In the presence of CF_3COOH (1.2 equiv). [c]At 70% conversion.

as well as *N*-benzoyl, *N*-benzyl, *N*-tosyl, and *N*-SEM protecting groups are also tolerated (Tables 3 and 4).

Mechanistic Studies. Although both Cu(I) and Cu(II) salts can be employed as catalysts in the C–H amination reaction, the considerably faster formation of **3a** in the presence of Cu(I) species as compared to Cu(II) (entry 3 vs entry 4, Table 1) suggests that Cu(I) salts are the catalytically active species. The slow formation of **3a** in the Cu(II)-catalyzed reaction (entry 4, Table 1) could be ascribed to an in situ reduction of Cu(II) to active Cu(I) catalyst by amine.[22,23] To verify the catalytic efficiency of Cu(I) species, the Cu(OTf)$_2$-catalyzed C–H amination of **2a** was performed in the presence of 2 equiv of neocuproin, a highly specific chelating agent for Cu(I) ions. Neocuproin (2,9-dimethyl-1,10-phenanthroline) is a bidentate ligand that forms a stable bright orange-colored complex of formula Cu^{I}(neocuproin)$_2$,[24] thus acting as an inhibitor of Cu(I)-catalyzed reactions.[25] Complete inhibition of the Cu(OTf)$_2$-catalyzed formation of **3a** in the presence of neocuproin was observed, evidencing that the catalytically active species are indeed Cu(I) salts.

A radical inhibition test was performed to exclude the possibility of C–H amination of **2a** via a radical chain pathway. Accordingly, the addition of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT)[26] and TEMPO[27] (both in 10-fold excess with respect to Cu(I)) did not affect the rate of Cu(MeCN)$_4$BF$_4$-catalyzed conversion of **2a** to **3a** in CH_2Cl_2–DMSO = 4:1. These data strongly argue against the involvement of a radical chain process. Notably, the addition of radical scavengers considerably decelerated the background noncatalyzed reaction of λ^3-iodane **2a** with morpholine to produce **4a** (Table 1, entry 2). Thus, only 27% of **4a** was formed in the presence of TEMPO after 24 h at room temperature (at 31% conversion of **2a**), and 15% of **4a** (at 24% conversion) was observed after 12 h at room temperature with added BHT (both radical scavengers were added in equimolar amounts to the starting **2a**). Presumably, the noncatalyzed reaction of λ^3-iodane **2a** with morpholine proceeds through a radical chain pathway.

Kinetic studies were also carried out to establish the kinetic order of Cu(I)-catalyzed C–H amination of **2a** in each reaction component. Morpholine was employed both as a nucleophile and as a base, and (CuOTf)$_2$·PhH was used as a catalyst. The reactions were monitored by NMR spectroscopy, and the method of initial rates was used to determine rate coefficients. The Cu(I)-catalyzed conversion of **2a** to **3a** in DMSO-d_6 at 25 °C was found to be first-order in (CuOTf)$_2$·PhH (see Supporting Information, Figure S2), first-order in morpholine (see Supporting Information, Figure S3), and zeroth-order in λ^3-iodane **2a** (see Supporting Information, Figure S4). These data indicate that the Cu(I) catalyst and morpholine are both involved in the rate-limiting step of the catalytic cycle, whereas the subsequent reactions of λ^3-iodane **2a** are fast. It is likely that (CuOTf)$_2$·PhH and morpholine form a complex **I**, which exists in equilibrium with the bis-amine complex **II**. Assuming that **II** is a resting state of the catalyst,[28] dissociation of morpholine under equilibrium conditions would produce a catalytically active complex **I** (Scheme 1).

Several plausible pathways for Cu(MeCN)$_4$BF$_4$-catalyzed C–H amination of **2a** are consistent with the data above (Scheme 1). In pathway A, Cu(I)–amine complex **I** coordinates with the electron-rich indole moiety in the λ^3-iodane **2a**, forming a η^2-complex **III**. Subsequent substitution of tosylate by amine in the intermediate **III** and reductive elimination from the highly unstable λ^3-iodane **IV**[29] would lead to aminoheterocycle **3a**. The formation of η^2-coordinated species such as **III** and **IV** has been proposed in the transition state for the oxidative addition of aryl halides to Cu(I) complexes.[28a,30] π-Interaction between the Cu(I)–amine complex **I** and indole **2a** should increase electrophilicity of the heterocycle *ipso*-carbon in the putative intermediates **III** and **IV**, thus facilitating C–N bond forming reductive elimination from λ^3-iodane **IV**. However, other Lewis acids such as Pd(OCOCF$_3$)$_2$, Ni(OTf)$_2$, and Sc(OTf)$_3$ did not catalyze the formation of **3a** (Table 1, entries 7–9), so the involvement of η^2-coordination between Cu(I) species and the indole moiety in intermediates **III** or **IV** can be questioned.

In an alternative possibility, pathway B involves direct oxidative addition of the λ^3-iodane **2a** to Cu(I)–amine complex **I** to form the Cu(III) intermediate **V**.[31] For unsymmetrical diaryl-λ^3-iodanes, regioselectivity of the oxidative addition to Cu(I) species can be controlled by the use of a mesityl group as

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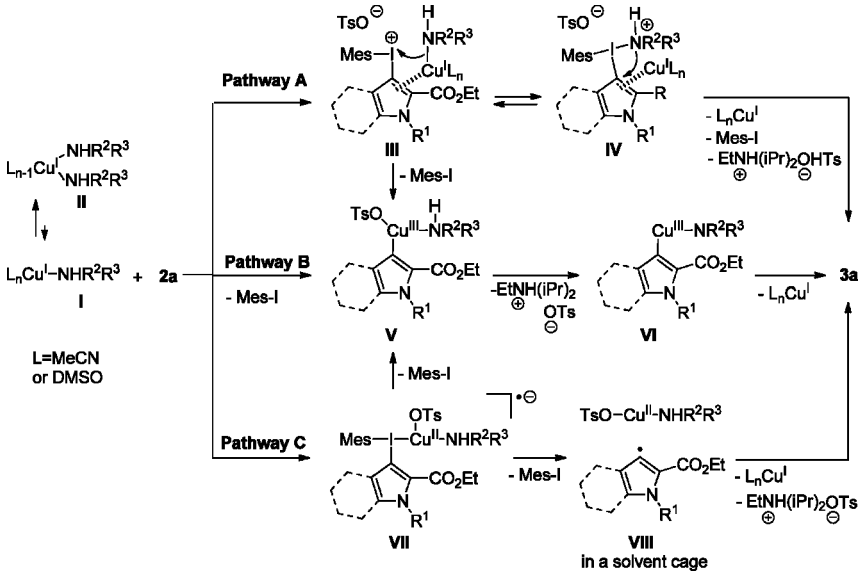
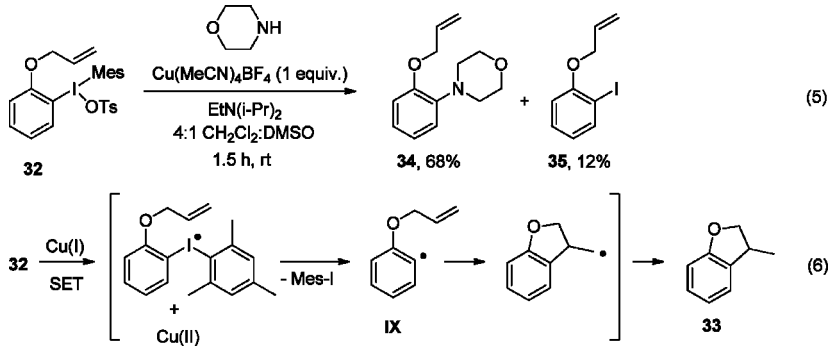
Scheme 1. Plausible Pathways for C–H Amination of Heteroarenes



Scheme 2. C–H Amination of λ^3-Iodane 32 Containing a Radical Probe



a nontransferable aryl ligand.[31c–f,32] The Cu(III) intermediate **V** undergoes N–H deprotonation of the Cu(III)-coordinated amine with $EtN(i\text{-}Pr)_2$.[33] Product-forming reductive elimination from the resulting Cu(III)–amide complex **VI** would afford **3a** and regenerate a catalytically active Cu(I) species.[34] However, the proposed transient Cu(III) complexes **V** or **VI** could not be detected, presumably because they undergo rapid C–N bond forming reductive elimination.[35] This behavior is expected because related, highly reactive Cu(III) species have only been observed in chelation-stabilized complexes based on stabilizing triazamacrocyclic ligands.[36]

As a third option, pathway C involves a Cu(I)/Cu(II) catalytic cycle, which starts with an inner-sphere single-electron transfer (SET) from Cu(I)-complex[22,25b,37] to the λ^3-iodane **2a**, generating an intimate radical anion–Cu(II) complex **VII**.[38] Experimental redox potentials versus SCE were determined by cyclic voltammetry for λ^3-iodane **2a** (E = −0.76 V) and for $Cu(MeCN)_4BF_4$ (E = +0.85 V),[39] and they support the feasibility of SET between Cu(I) catalyst and iodonium salt **2a**. The radical anion–Cu(II) complex **VII** might undergo fragmentation to a radical pair **VIII**, which couples with the amine moiety with a second SET that regenerates the Cu(I) species.[40] To test for the intermediacy of heteroaryl radicals in the Cu(I)-catalyzed C–H amination reaction, diaryl-λ^3-iodane **32** containing an *O*-allyl moiety as a radical clock probe was employed as substrate in the reaction with morpholine in the presence of equimolar and catalytic (10 mol %, not shown) amounts of $Cu(MeCN)_4BF_4$ (Scheme 2, eq 5). It has been demonstrated that the λ^3-iodane **32**-derived aryl radical **IX** undergoes extremely rapid 5-*exo*-*trig* cyclization (rate constant $k = 9.6 \times 10^9\ s^{-1}$) to furnish 3-methyl-2,3-dihydrobenzofurane **33** after abstraction of the hydrogen atom from the medium (Scheme 2, eq 6).[41] In our hands, *N*-substituted morpholine **34** was obtained as the major product, and no detectable amount of the cyclization product **33** was observed (Scheme 2, eq 5).[42] These data provide strong evidence that the Cu(I)-catalyzed C–H amination occurs without involvement of free heteroaryl radicals such as **VIII** (Scheme 1, pathway C). On the other hand, the putative radical anion–Cu(II) complex **VII** may undergo a radical recombination to furnish aryl–Cu(III) species **V**.[43] The subsequent steps would involve the same conversion from **V** to **VI** as in pathway B. Although we regard the latter scenario as the most probable, neither pathway A nor pathway C could be ruled out. Further mechanistic studies are necessary to fully elucidate the mechanism of the newly developed C–H amination approach.

■ CONCLUSIONS

In summary, a versatile method for an intermolecular C–H amination of electron-rich heteroarenes and arenes has been

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developed. The one-pot sequential two-step procedure comprises the in situ formation of unsymmetrical (hetero)-aryl-λ^3-iodanes followed by their Cu(I)-catalyzed reaction with a wide range of primary and secondary aliphatic amines and anilines. The Cu(I) catalyst ensures the desired selectivity in the reaction between the intermediate unsymmetrical λ^3-iodanes and amines. Initial mechanistic studies point toward a stepwise oxidative addition and involvement of single electron transfer from Cu(I) catalyst to unsymmetrical (hetero)aryl-λ^3-iodanes. The reaction proceeds at room temperature and tolerates a number of functional groups both in the amine and in the (hetero)arene. The regioselectivity of the C−H activation is typical for electrophilic aromatic substitution (S_EAr) reactions. Our C−H amination approach is an alternative and complementary method to transition metal-catalyzed direct intermolecular C_{sp2}−H amination of arenes,[44] which often requires the presence of a metalation-directing group in substrate[45] and employs imides, amides, sulfonamides, as well as organic azides or preactivated amino precursors such as *N*-chloroamines as sources of nitrogen.[46] In cases where the transition metal-catalyzed amination is not applicable, our method may be especially useful for late-stage amination of pharmaceutically relevant aromatics, and especially heterocycles.

EXPERIMENTAL SECTION

Ethyl 5-Bromo-1-methyl-3-({[(4-methylphenyl)sulfonyl]oxy}-(2,4,6-trimethylphenyl)-λ^3-iodanyl)-1*H*-indole-2-carboxylate (2a). To a solution of MesI(OH)OTs (2.39 g, 5.50 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added TsOH·H_2O (1.05 g, 5.50 mmol, 1.1 equiv), and the resulting suspension was stirred for 5 min at room temperature. Next, a solution of indole **1a** (1.41 g, 5.00 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added rapidly to the well-stirred suspension. The progress of the reaction was monitored by TLC (disappearance of the starting material spot, R_f = 0.55, 1:5 EtOAc/petroleum ether), and complete conversion of the starting **1a** was observed within 30 min. Solvent was concentrated to ca. 2/3 of the original volume, and Et_2O was added (50 mL). Formed precipitate was filtered, washed with Et_2O (100 mL), and dried in vacuo to afford **2a** as a white powder (3.30 g, 95% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f = 0.49. Pure material was obtained by crystallization from CH_2Cl_2/diethyl ether: mp 125 °C. dec IR (film, cm^{-1}): 1710 (C═O), 1206 (SO_2). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.79 (1H, d, J = 9.0 Hz), 7.61 (1H, dd, J = 9.0, 1.8 Hz), 7.48−7.43 (3H, m), 7.21−7.16 (2H, m), 7.10 (2H, d, J = 8.0 Hz), 4.45 (2H, q, J = 7.2 Hz), 4.08 (3H, s), 2.58 (6H, s), 2.28 (6H, s), 1.38 (3H, t, J = 7.2 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm): δ 159.4, 145.8, 142.9, 141.9, 137.5, 137.2, 131.8, 129.8, 128.1, 128.0, 125.5, 122.7, 121.7, 115.7, 115.1, 81.2, 62.8, 33.8, 26.1, 20.8, 20.4, 13.8. HRMS−ESI (m/z) calcd for $C_{21}H_{22}BrINO_2$ $[M - OTs]^+$ 525.9873, found 525.9861.

General Procedure for C−H Amination of Heterocycles and Arenes. To a solution of MesI(OH)OTs (239 mg, 0.55 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere was added a solution of heterocycle or arene (0.50 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL). For a less reactive substrate (see Tables 3 and 4), neat TFA (46 μL, 0.60 mmol, 1.2 equiv) was then added slowly (dropwise, within 2−3 min; too fast addition of TFA leads to the formation of side-products). The resulting solution (color range: pale yellow to brown) was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase 3:1 light petroleum ether/EtOAc; the intermediate λ^3-iodane does not migrate from the application point). Immediately upon full conversion of the starting heterocycle or arene (see Tables 3 and 4 for appropriate time), the reaction mixture was transferred via cannula to another flask, which contained preweighed solid $Cu(MeCN)_4BF_4$ (16 mg, 0.05 mmol, 10 mol %) and a magnetic stirbar, and the source flask was rinsed with CH_2Cl_2 (1 mL). To the resulting well-stirred suspension was immediately added a solution of amine or aniline (0.6 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (1 mL) (Important: Decomposition of the formed λ^3-iodane begins if the addition of Cu catalyst and/or amine is delayed!). Finally, neat DIPEA (174 μL, 1.00 mmol, 2 equiv) was added, followed by DMSO (1 mL). The resulting solution was stirred at room temperature under argon atmosphere, and the progress of the reaction was monitored by TLC (the intermediate λ^3-iodanes have R_f = 0.4−0.6; mobile phase 20:80:5 MeOH/CH_2Cl_2/AcOH). In most cases, the reaction was completed in 2 h. The solution was poured into 50 mL of water and 20 mL of saturated aqueous ammonia solution, extracted with CH_2Cl_2 (3 × 30 mL), and combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization data, ^{1}H and ^{13}C NMR spectra, X-ray crystallographic data for λ^3-iodane **2a** (CIF), cyclic voltammograms (CV), and details of the kinetic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Increased conversion of **2a** (ca. 30%) was observed at 60 °C using $Pd(OCOCF_3)_2$ as catalyst (compare with entry 7, Table 1). However, only trace amounts (∼1−2%) of 3-morpholino-indole **3a** were observed, and the major product was iodoindole **4a** (1:99 ratio of **3a**:**4a**). Furthermore, none of the products corresponding to C−O bond formation were detected in the reaction mixture. For a complete survey of optimization, see Table S1 (page S58) in the Supporting Information.
(15) We found that the formation of λ^3-iodane **2a** was facilitated by addition of CF_3COOH.
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(17) Sterically highly hindered amines such as diisopropylamine do not react.
(18) 2-Unsubstituted indoles as well as indoles possessing relatively electron-rich substituents such as 2-methyl or 2-phenyl groups form intermediate indolyl-λ^3-iodanes, which could be transformed into the corresponding indolyl-3-amines. However, the latter are unstable and undergo rapid oxidation under the C−H amination conditions. The low stability of indolyl-3-amines toward oxidation is well-known, see, for example: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 290−291. (b) Huang-Hsinmin; Mann, F. G. *J. Chem. Soc.* **1949**, 2903. (c) Bruni, P.; Colonna, M.; Greci, L. *Tetrahedron* **1971**, *27*, 5893. Consequently, the presence of stabilizing electron-withdrawing substituents at position 2 of indole is necessary to obtain stable indolyl-3-amines.
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Copper-Catalyzed Intermolecular C-H Amination of (Hetero)arenes via Transient Unsymmetrical λ^3-Iodanes

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CONTENTS

Materials and Methods

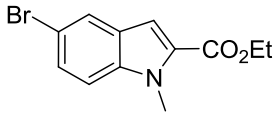
All reactions were carried out under argon atmosphere. Progress of reactions was monitored by thin-layer chromatography on Merck Kieselgel $60F_{254}$. Flash column chromatography was performed using Biotage SP1 Flash Purification System and Biotage KP-Sil 25+M or Biotage KP-Sil 12+M silica cartridges.

^{1}H and ^{13}C NMR spectra were recorded on Varian Inova 400 MHz NMR spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS or with the residual solvent peak as an internal reference. Melting points were uncorrected. Elemental analyses were performed using Carlo-Erba CHNS-0 EA1108 instrument. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

All reagents were obtained commercially and used as received.

Experimental Data

Synthesis of Heterocycles 1a, 5sm–12sm, 14sm–16sm, 18sm-20sm and Arene 22sm, 27sm-31sm



Ethyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (1a). Ethyl 5-bromo-1*H*-indole-2-carboxylate (2.00 g, 14.40 mmol) was converted to indole **1a** in accordance with literature procedure.[12] Purification of the crude product by column chromatography (Biotage Si 40+M) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a white solid (1.96 g, 93% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.55. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 91-92 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, dd, J = 1.8, 0.8 Hz), 7.41 (1H, dd, J = 8.9, 1.8 Hz), 7.27-7.24 (1H, m, overlapped with $CHCl_3$), 7.21 (1H, d, J = 0.8 Hz), 4.38 (2H, q, J = 7.1 Hz), 4.06 (3H, s), 1.41 (3H, t, J = 7.1 Hz).

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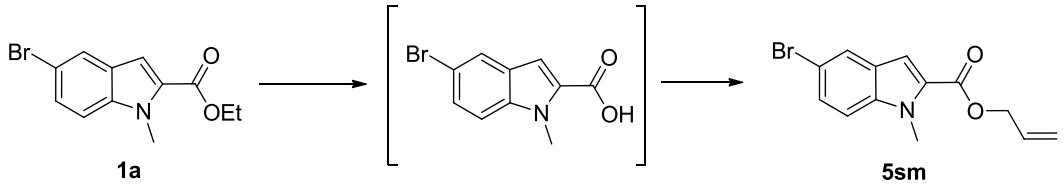
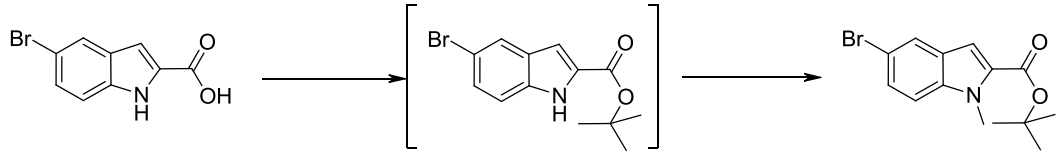
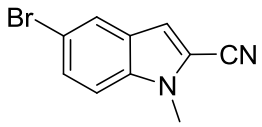


Prop-2-en-1-yl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (5sm). A mixture of ethyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate **1a** (5.00 g, 17.70 mmol, 1 equiv) and aqueous 2N NaOH (22 mL) was heated in dioxane (40 mL) at 80 °C for 2 h, cooled to room temperature and acidified to pH=3 with aqueous 2N HCl solution. The formed precipitate was filtered, washed with H_2O (100 mL) and dried *in vacuo*. Pale yellow powder (1.00 g, 3.94 mmol, 1 equiv) was dissolved in DMF (10 mL) and powdered K_2CO_3 (653 mg, 4.73 mmol, 1.2 equiv) was added, followed by allyl bromide (409 μL, 4.73 mmol, 1.2 equiv). After stirring for 12 h at room temperature volatiles were removed *in vacuo* and the brown semi-solid residue was partitioned between water (50 mL) and EtOAc (30 mL). Aqueous layer was extracted with EtOAc (2x30 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded **5sm** as a yellow powder (1.13 g, 97% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.56. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 111–112 °C. IR (film, cm^{-1}) 1715 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, d, *J*=1.8 Hz), 7.42 (1H, dd, *J*=9.0, 1.8 Hz), 7.27–7.23 (2H, m), 6.11–5.99 (1H, m), 5.47–5.39 (1H, m), 5.34–5.28 (1H, m), 4.85–4.80 (2H, m), 4.06 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.6, 138.3, 132.2, 128.7, 128.1, 127.5, 125.0, 118.6, 113.9, 111.9, 109.6, 65.4, 32.0. HRMS-ESI (m/z) calcd for $C_{13}H_{13}BrNO_2$ $[M+H]^+$ 294.0124, found 294.0133.

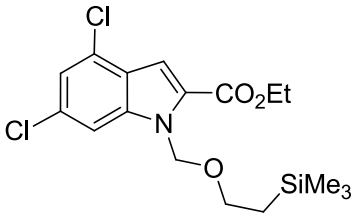


***tert*-Butyl 5-bromo-1-methyl-1*H*-indole-2-carboxylate (6sm).** *N*,*N*-Dimethylform-amide di-*tert*-butyl acetal (6.00 mL, 24.9 mmol, 6 equiv) was added dropwise to the refluxed suspension of ethyl 5-bromo-1*H*-indole-2-carboxylic acid (1.00 g, 4.17 mmol, 1 equiv) in anhydrous benzene (14 mL). After heating under reflux for 30 min and cooling to room temperature, volatiles were removed *in vacuo*. The yellow solid residue was treated with a mixture of Et_2O (10 mL) and hexane (30 mL), crystalline material was filtered and dried *in vacuo*. *tert*-Butyl 5-bromo-1*H*-indole-2-carboxylate (1.100 g, 3.71 mmol) was converted to indole **6sm** in accordance with literature procedure.[1] Purification of the crude product by column chromatography (Biotage M+25 column) using

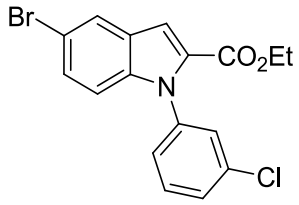
gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **6sm** as a white powder (1.06 g, 92% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.66. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 125-126 °C. IR (film, cm^{-1}) 1707 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.77 (1H, d, *J*=1.8 Hz), 7.39 (1H, dd, *J*=9.0, 1.8 Hz), 7.23 (1H, d, *J*=9.0 Hz), 7.13 (1H, s), 4.03 (3H, s), 1.61 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.4, 138.1, 130.5, 127.6, 127.4, 124.8, 113.7, 111.8, 109.0, 81.8, 31.9, 28.5. HRMS-ESI (m/z) calcd for $C_{14}H_{17}BrNO_2$ $[M+H]^+$ 310.0437, found 310.0437.



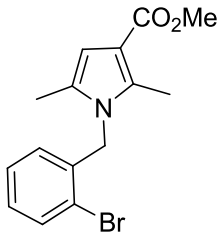
5-Bromo-1-methyl-1*H*-indole-2-carbonitrile (7sm). The same procedure was used as for **1a**. Accordingly, 5-bromo-1*H*-indole-2-carbonitrile (1.50 g, 6.78 mmol) was converted to **7sm**. Purification of the crude product by column chromatography (Biotage M+25) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **7sm** as a yellow solid (1.44 g, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 122-123 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 (1H, dd, *J*=1.8, 0.6 Hz), 7.48 (1H, dd, *J*=8.9, 1.8 Hz), 7.25-7.20 (1H, m), 7.07 (1H, d, *J*=0.8 Hz), 3.89 (3H, s).



Ethyl 4,6-dichloro-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole-2-carboxylate (8sm). The same procedure was used as for **1a**. Accordingly, 4,6-dichloro-1*H*-indole-2-carboxylate (500 mg, 1.94 mmol) was converted into **8sm**. Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **8sm** as a colorless solid (687 mg, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.56. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 58-59 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49–7.47 (1H, m), 7.37 (1H, d, *J*=0.8 Hz), 7.20 (1H, d, *J*=1.6 Hz), 5.96 (2H, s), 4.39 (2H, q, *J*=7.1 Hz), 3.53 (2H, dd, *J*=8.2, 8.2 Hz), 1.42 (3H, t, *J*=7.1 Hz), 0.88 (2H, dd, *J*=8.2, 8.2 Hz), –0.07 (9H, s).



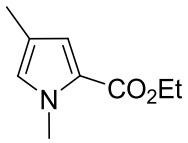
Ethyl 5-bromo-1-(3-chlorophenyl)-1*H*-indole-2-carboxylate (9sm). Ethyl 5-bromo-1*H*-indole-2-carboxylate (804 mg, 3.00 mmol) was converted into indole **9sm** in accordance with literature procedure.[13] Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded **9sm** as a colorless solid (1.10 g; 97% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.53. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 85-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.84 (1H, d, *J*=1.8 Hz), 7.48-7.40 (2H, m), 7.37-7.30 (3H, m), 7.23-7.19 (1H, m), 6.95 (1H, d, *J*=8.8 Hz), 4.22 (2H, q, *J*=7.0 Hz), 1.22 (3H, t, *J*=7.0 Hz).



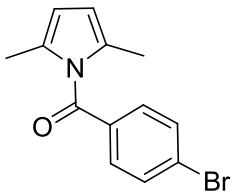
Methyl 1-(2-bromobenzyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (10sm). Methyl 2,5-dimethyl-1*H*-pyrrole-3-carboxylate (766 mg, 5.00 mmol) was converted into **10sm** in accordance

(13) Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem*. **2009**, *74*, 7195.

with literature procedure.[14] Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **10sm** as a yellow oil (1.48 g, 92% yield), which slowly crystallized when stored in a freezer; analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.31. Pure material was obtained by recrystallization from diethylether/petroleum ether: mp 95-96 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.58 (1H, dd, *J*=7.7, 1.4 Hz), 7.18 (1H, td, *J*=7.5, 1.4 Hz), 7.13 (1H, td, *J*=7.7, 1.9 Hz), 6.36 (1H, d, *J*=1.0 Hz), 6.25-6.21 (1H, m), 5.02 (2H, s), 3.80 (3H, s), 2.41 (3H, s), 2.09 (3H, s).

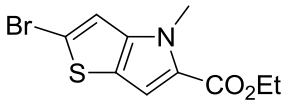


Ethyl 1,4-dimethyl-1*H*-pyrrole-2-carboxylate (11sm). The same procedure was used as for **10sm**. Accordingly, ethyl 4-methyl-1*H*-pyrrole-2-carboxylate (500 mg, 3.26 mmol) was converted into **11sm.** Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **11sm** as a yellow oil (472 mg, 87% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.59. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.68 (1H, d, *J*=2.0 Hz), 6.51–6.44 (1H, m), 4.18 (2H, q, *J*=7.1 Hz), 3.78 (3H, s), 1.98 (3H, s), 1.26 (3H, t, *J*=7.1 Hz).

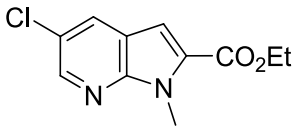


1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrole (12sm). 2,5-Dimethyl-1*H*-pyrrole (1.00 g, 10.51 mmol) was converted into 1-[(4-bromophenyl)carbonyl]-1*H*-pyrrole **12sm** in accordance with literature procedure.[4] Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **12sm** as a brown solid (1.90 g, 65% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.59. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 48-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64–7.60 (2H, m), 7.58–7.54 (2H, m), 5.88 (2H, s), 2.07 (6H, s).

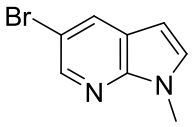
(14) Lubriks, D.; Sokolovs, I.; Suna, E. *Org. Lett.* **2011**, *13,* 4324.



Ethyl 2-bromo-4-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (14sm). The same procedure was used as for **1a**. Accordingly, 2-bromo-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (350 mg, 1.28 mmol) was converted to **14sm**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **14sm** as a colorless solid (330 mg, 89% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.42. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 86-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.08 (1H, s), 7.00 (1H, s), 4.32 (2H, q, *J*=7.1 Hz), 4.00 (3H, s), 1.37 (3H, t, *J*=7.1 Hz).



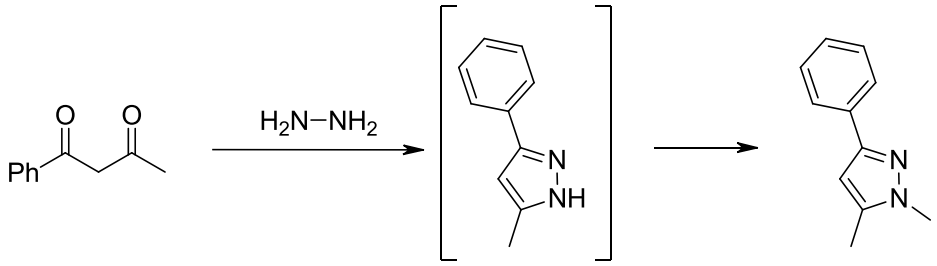
Ethyl 5-chloro-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (15sm). Ethyl 5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (674 mg, 3.00 mmol) was converted to **15sm** in accordance with literature procedure.[15] Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **15sm** as a yellow solid (544 mg, 76% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.54. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 89-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (1H, d, *J*=2.3 Hz), 7.93 (1H, d, *J*=2.3 Hz), 7.16 (1H, s), 4.40 (2H, q, *J*=7.1 Hz), 4.13 (3H, s), 1.42 (3H, t, *J*=7.1 Hz).



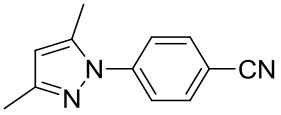
5-Bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (16sm). The same procedure was used as for **1a**. Accordingly, 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (500 mg, 2.54 mmol) was converted to **16sm**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **16sm** as a colorless solid (485 mg, 90% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 62-

([15]) Lubriks, D.; Sokolovs, I.; Suna, E. *J. Am. Chem. Soc.* **2012**, *134,* 15436.

63 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.35 (1H, d, *J*=2.1 Hz), 8.02 (1H, d, *J*=2.1 Hz), 7.19 (1H, d, *J*=3.5 Hz), 6.40 (1H, d, *J*=3.5 Hz), 3.87 (3H, s).



1,5-Dimethyl-3-phenyl-1*H*-pyrazole (18sm). 1-Phenyl-1,3-butanedione (2.00 g, 12.33 mmol) was converted to 1*H*-pyrazole in accordance with literature procedure.[16] The crude 1*H*-pyrazole was converted without purification to pyrazole **18sm** in accordance with literature procedure.[17] Column chromatography (Biotage M+40 column) using isocratic elution with 5% Et_2O/CH_2Cl_2 afforded **18sm** as a colorless solid (1.45 g; 68% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 37-38 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.77-7.73 (2H, m), 7.40-7.34 (2H, m), 7.30-7.25 (1H, m, overlapped with $CHCl_3$), 6.32 (1H, s), 3.82 (3H, s), 2.31 (3H, s).

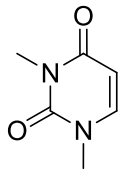


4-(3,5-Dimethyl-1*H*-pyrazol-1-yl)benzonitrile (19sm). 4-Hydrazinobenzonitrile hydrochloride (1.00 g, 5.90 mmol) was converted to pyrazole **19sm** in accordance with literature procedure.[18] Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **19sm** as a colorless solid (1.12 g, 96% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.19. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 100-101 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.76–7.71 (2H, m), 7.63–7.59 (2H, m), 6.05 (1H, s), 2.39 (3H, s), 2.29 (3H, s).

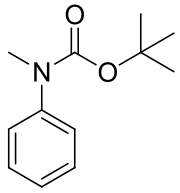
(16) Govindaswamy, P.; Mozharivskyj, Y.A.; Kollipara, M.R. *J. Organomet. Chem.*, **2004**, *689*, 3265.

(17) Del Giudice, M.R.; Mustazza, C.; Borioni, A.; Gatta, F.; Tayebati, K.; Amenta, F.; Tucci, P.; Pieretti, S. *Arch. Pharm.* **2003**, *336*, 143.

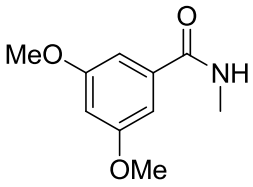
(18) Abdellatif, K.R.A.; Chowdhury, M.A.; Velázquez, C.A.; Huang, Z.; Dong, Y.; Das, D.; Yu, G.;Suresh, M.R.; Knaus, E.E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4544.



1,3-Dimethylpyrimidine-2,4(1*H*,3*H*)-dione (20sm). Pyrimidine-2,4(1*H*,3*H*)-dione (500 mg, 4.46 mmol) was converted to **20sm** in accordance with literature procedure.[19] Purification of the crude product by column chromatography (Biotage M+25 column) using isocratic elution with 10% MeOH/CH_2Cl_2 afforded product as a colorless solid (534 g; 85% yield); analytical TLC on silica gel, 1:10 MeOH/CH_2Cl_2, R_f=0.47. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.12 (1H, d, *J*=7.8 Hz), 5.73 (1H, d, *J*=7.8 Hz), 3.40 (3H, s), 3.34 (3H, s).



***tert*-Butyl methyl(phenyl)carbamate (22sm)**. *N*-Methylaniline (3.0 g, 28.0 mmol) was converted into **22sm** in accordance with literature procedure.[20] Purification of the crude product by column chromatography (Biotage Si 25+M column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **22sm** as a yellow oil (5.51 g, 95% yield); analytical TLC on silica gel, 1:10 EtOAc/petroleum ether, R_f=0.35. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35–7.29 (2H, m), 7.28–7.19 (2H, m), 7.18–7.13 (1H, m), 3.26 (3H, s), 1.45 (9H, s).



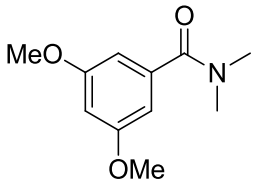
3,5-Dimethoxy-*N*-methylbenzamide (27sm).3,5-Dimethoxy-benzoic acid (1.0 g, 5.49 mmol) was converted into 3,5-dimethoxy-benzoyl chloride in accordance with literature procedure.[21] The crude acid chloride was dissolved in anhydrous DCM (10 mL) and the resulting solution was added dropwise to the solution of methylamine hydrochloride (389 mg, 5.76 mmol, 1.05 equiv) and triethylamine (2.29 mL, 16.47 mmol, 3 equiv) in anhydrous DCM (10 mL). After stirring for 12 h at room temperature, the reaction mixture washed with water (2x20 mL). Combined aqueous layers

(19) Hannon, S. J.; Kundu N. G.; Hertzberg R. P.; Bhatt R. S.; Heidelberger, C. *Tetrahedron Lett.* **1980**, *21*, 1105.

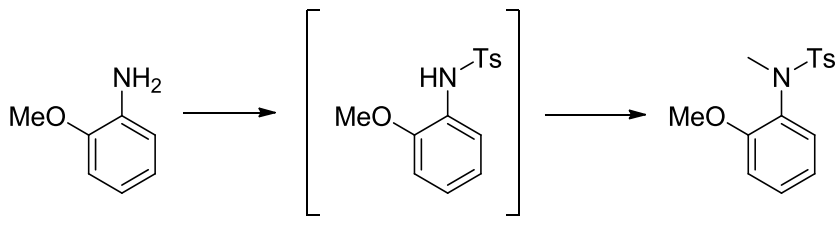
(20) Chankeshwara, S.V.; Chakraborti, A. K. *Tetrahedron Lett*. **2006**, *47*, 1087.

(21) Pickaert, G.; Ziessel, R.; Cesario, M. *J. Org. Chem.* **2004**, *69*, 5335.

were back-extracted with DCM (2x20 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 15% EtOAc/petroleum ether to 100% EtOAc afforded **27sm** as a colorless solid (883 mg, 82% yield); analytical TLC on silica gel, 1:10 MeOH/DCM, R_f=0.25. Pure material was obtained by crystallization from EtOAc/petroleum ether: mp 118-119 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 6.87 (2H, d, *J*=2.3 Hz), 6.56 (1H, dd, *J*=2.3, 2.3 Hz), 6.31–6.02 (1H, br s), 3.81 (6H, s), 2.99 (3H, d, *J*=4.9 Hz).



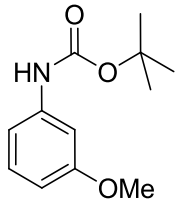
3,5-Dimethoxy-*N*,*N*-dimethylbenzamide (28sm). 3,5-Dimethoxy-benzoic acid (500 mg, 2.74 mmol) was converted into 3,5-dimethoxy-benzoyl chloride in accordance with literature procedure.[21] The crude acid chloride was dissolved in dry DCM (5 mL) and the resulting solution was added dropwise to the solution of dimethylamine (2M in THF, 2.06 mL, 4.11 mmol, 1.5 equiv) and TEA (571 µL, 4.11 mmol, 1.5 equiv) in anhydrous DCM (5 mL). After stirring for 12 h at room temperature the reaction mixture was diluted with DCM (20 mL) washed with water (2x30 mL). Combined aqueous layers were back-extracted with DCM (2x20 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage M+25 column) using gradient elution from 15% EtOAc/petroleum ether to 100% EtOAc afforded **28sm** as a colorless oil (500 mg, 87% yield); analytical TLC on silica gel, 1:10 MeOH/DCM, R_f=0.19. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 6.51 (2H, d, *J*=2.3 Hz), 6.46 (1H, dd, *J*=2.3, 2.3 Hz), 3.78 (6H, s), 3.11–3.04 (3H, br s), 3.01–2.92 (3H, br s).



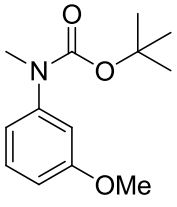
***N*-(2-Methoxyphenyl)-*N*,4-dimethylbenzenesulfonamide (29sm)**. *ortho*-Anisidine (916 µL, 8.12 mmol) was converted into *N*-(2-methoxyphenyl)-4-methyl-benzenesulfonamide in accordance with literature procedure.[22] The crude product was purified by crystallization from

(22) Bharathi, E. V.; Dastagiri; Kamal, A.; Reddy, J. S. *Tetrahedron Lett*. **2008**, *49*, 348.

diethylether/petroleum ether to provide *N*-(2-methoxyphenyl)-4-methyl-benzenesulfonamide as a white solid (1.80 g, 80% yield). *N*-(2-Methoxyphenyl)-4-methyl-benzenesulfonamide from above (956 mg, 3.45 mmol, 1 equiv) and Cs_2CO_3 (1.68 g, 5.17 mmol, 1.5 equiv) were mixed with anhydrous DMF (5 mL) and MeI (322 µL, 5.17 mmol, 1.5 equiv) was added. After stirring for 12 h at room temperature volatiles were removed *in vacuo* and the brown semi-solid residue was partitioned between water (50 mL) and EtOAc (30 mL). Aqueous layer was extracted with EtOAc (2x30 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by crystallization from diethylether/petroleum ether afforded **29sm** as a pink solid (794 mg, 79% yield), mp 102-103 °C dec. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7-54-7.47 (2H, m), 7.42-7.36 (2H, m), 7.31 (1H, ddd, *J*=8.3, 7.6, 1.7 Hz), 7.11 (1H, dd, J=7.8, 1.7 Hz), 6.98 (1H, dd, J=8.3, 1.2 Hz), 6.92 (1H, dt, J=7.6, 1.2 Hz), 3.41 (3H, s), 3.08 (3H, s) 2.40 (3H, s).



***tert*-Butyl 3-methoxyphenylcarbamate (30sm)**. 3-Methoxyaniline (500 mg, 4.06 mmol) was converted into **30sm** in accordance with literature procedure.[23] Purification of the crude product by column chromatography (Biotage Si 25+M column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **30sm** as a white solid (875 mg, 95% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 60-61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.17 (1H, dd, *J*=8.2, 8.2 Hz), 7.13-7.07 (1H, m), 6.88-6.79 (1H, m), 6.62-6.55 (1H, m), 6.48 (1H, s), 3.80 (3H, s), 1.52 (9H, s).



***tert*-Butyl (3-methoxyphenyl)methylcarbamate (31sm)**. An oven-dried flask was charged with **30sm** (440 mg, 1.97 mmol, 1 equiv), Cs_2CO_3 (964 mg, 2.96 mmol, 1.5 equiv), closed with septa and flushed with a stream of argon. Anhydrous DMF (5 mL) and MeI (184 µL, 2.96 mmol, 1.5

(23) Chankeshwara, S.V.; Chakraborti, A. K. *Tetrahedron Lett*. **2006**, *47*, 1087.

equiv) were added via syringe. After stirring for 12 h at room temperature, volatiles were removed *in vacuo* the brown semi-solid residue was partitioned between water (50 mL) and EtOAc (30 mL). Aqueous layer was extracted with EtOAc (2x30 mL), combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage Si 25+M column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **31sm** as yellow oil (449 mg, 96% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.55. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.22 (1H, dd, *J*=8.1, 8.1 Hz), 6.84–6.78 (2H, m), 6.75–6.70 (1H, m), 3.80 (3H, s), 3.25 (3H, s), 1.45 (9H, s).

Preparation of $Cu(MeCN)_4BF_4$ and $(CuOTf)_2$●PhH

$[Cu(MeCN)_4]^+BF_4^-$

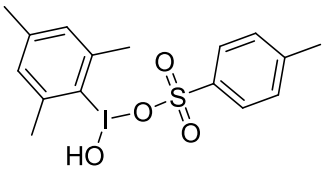
$[Cu(MeCN)_4]^+BF_4^-$ was synthesized in accordance with literature procedure.[24] To a slurry of blue $Cu(BF_4)_2$●$6H_2O$ (2.00 g, 5.79 mmol) suspended in dry MeCN (50 mL) was added copper powder (1.47 g, 23.17 mmol). The mixture was heated to reflux for 4 h under argon atmosphere and then filtered while still hot. As the pale filtrate cooled to –20 °C, a white solid crystallized out. The white solid was collected by filtration, washed with Et_2O (15 mL). Pure material was obtained by recrystallization from hot MeCN. Yield: 1.73 g (95%).

$(CuOTf)_2$●PhH

$(CuOTf)_2$●PhH was synthesized in accordance with literature procedure.[25] To a slurry of red Cu_2O (1.81 g, 12.65 mmol) in dry benzene (50 mL) was added trifluoromethanesulfonic anhydride (5.0 g, 17.7 mmol). The mixture was heated to reflux for 4 h and then filtered while still hot. As the yellow filtrate cooled to room temperature, a white solid crystallized out. The white solid was collected by filtration, washed with pentane (25 mL), and dried under vacuum. Yield: 2.78 g (75%).

([24]) Fortin, D.; Drouin, M.; Turcotte, M.; Harvey, P. D. *J. Am. Chem. Soc.* **1997**, *119*, 531; Kubas G. J. *Inorg. Synth.* **1979**, *19* , 90.
([25]) Bellott, B. J.; Girolami, G. S. *Organometallics* **2009,** *28,* 2046.

Preparation of MesI(OH)OTs



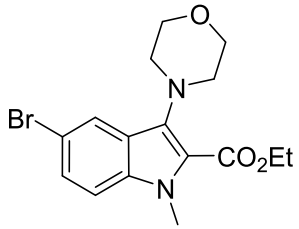
Hydroxy{[(4-methylphenyl)sulfonyl]oxy}(2,4,6-trimethylphenyl)-λ^3-iodane was synthesized in accordance with literature procedure.[26] To a solution of iodine (4.56 g, 18.0 mmol, 0.5 equiv) in DCM (120 mL) were added sequentially mesitylene (5.00 mL, 35.9 mmol), mCPBA (13.3 g, 54.0 mmol), and TsOH●H_2O (6.83 g, 35.9 mmol). The solution was stirred at room temperature for 12 h. The mixture was concentrated *in vacuo*, then Et_2O (150 mL) was added to the residue. The suspension was stirred at room temperature for 30 min. Precipitate was filtered off afforded the title compound (10.6 g, 68%) as a colorless solid: mp 105–106 °C dec. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.61–7.56 (2H, m), 7.26 (2H, s), 7.21-7.16 (2H, m), 2.71 (6H, s), 2.40 (3H, s), 2.36 (3H, s).

General Procedure for One-Pot Synthesis of Indolylamines 3a–3ak.

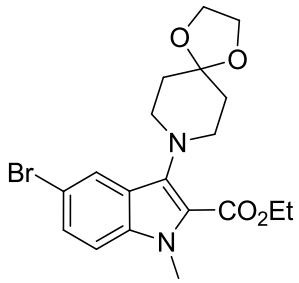
To a solution of MesI(OTs)OH (239 mg, 0.55 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (1 mL) under argon atmosphere was added a solution of indole **1a** (0.50 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL). For a less reactive substrates (see Table 3), neat TFA (46 μL, 0.60 mmol, 1.2 equiv) was added slowly (*dropwise, within 2-3 minutes; too fast addition of TFA leads to the formation of side-products*). The resulting solution (color range – pale yellow to brown) was stirred at room temperature under argon atmosphere and the progress of the reaction was monitored by TLC (disappearance of the starting material spot; mobile phase petroleum ether/EtOAc=3:1; the formed λ^3-iodane does not migrate from the application point). Immediately upon full conversion of the starting heterocycle or arene (see Table 3 for appropriate time), the reaction mixture was transferred via cannula to another flask which contained pre-weighed solid $Cu(MeCN)_4]^+BF_4^-$ (16 mg, 0.05 mmol, 10 mol%) and magnetic stir-bar, and the source flask was rinsed with CH_2Cl_2 (1 mL). To the resulting well-stirred suspension was immediately (!) added a solution of amine or aniline (0.6 mmol, 1.2 equiv) in anhydrous CH_2Cl_2 (1 mL) (*Important! Decomposition of the formed λ^3-iodane begins if the addition of Cu catalyst and/or amine is delayed*). Finally, neat DIPEA (174 μL 1.00 mmol, 2 equiv) was added, followed by DMSO (1 mL). The resulting solution was stirred at room temperature under argon atmosphere and the progress of the reaction was monitored by TLC (the intermediate λ^3-iodanes have R_f=0.4–0.6, 20:80:5 MeOH/CH_2Cl_2/AcOH). In the most cases the

([26]) Merritt, E. A.; Carneiro V. M. T.; Silva Jr, L. F.; Olofsson, B. *J. Org. Chem.* **2010**, *75*, 7416.

reaction was completed in 2 hours. The solution was poured into 50 mL of water and 20 mL of saturated aqueous ammonia solution, extracted with CH_2Cl_2 (3x30 mL), combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel.

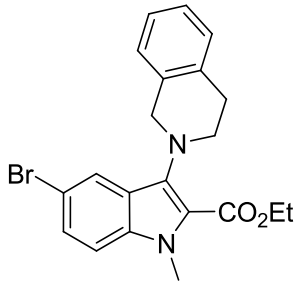


Ethyl 5-bromo-1-methyl-3-morpholin-4-yl-1*H*-indole-2-carboxylate (3a). Following the general procedure, indole **1a** (141 mg, 0.5 mmol) was converted into **3a**. Purification of the crude product by column chromatography (Biotage M+H) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (136 mg, 74% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.47. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 107-108 ^oC. IR (film, cm^{-1}) 1700 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97 (1H, d, *J*=1.8 Hz), 7.38 (1H, dd, *J*=9.0, 1.8 Hz), 7.20 (1H, d, *J*=9.0 Hz), 4.44 (2H, q, *J*=7.2 Hz), 3.89 (3H, s), 3.88-3.83 (4H, m), 3.30-3.24 (4H, m), 1.46 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.0, 136.0, 135.0, 128.1, 124.9, 123.9, 122.8, 112.9, 111.9, 68.1, 61.0, 52.7, 32.3, 14.7. HRMS-ESI (m/z) calcd for $C_{16}H_{20}BrN_2O_3$ $[M+H]^+$ 367.0652, found 367.0641.

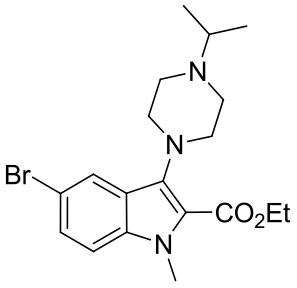


Ethyl 5-bromo-3-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-1-methyl-1*H*-indole-2-carboxylate (3b). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (140 mg, 66% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.43. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 101-102 ^oC. IR (film, cm^{-1}) 1700 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.98 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.18 (1H, d, *J*=9.0 Hz), 4.43 (2H, q, *J*=7.2 Hz), 4.02 (4H, s), 3.88 (3H,

s), 3.40-3.32 (4H, m), 1.92-1.84 (4H, m), 1.45 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.2, 136.0, 135.9, 128.0, 124.9, 124.2, 122.2, 112.6, 111.8, 107.5, 64.4, 61.0, 51.0, 36.2, 14.7. HRMS-ESI (m/z) calcd for $C_{19}H_{24}BrN_2O_4$ $[M+H]^+$ 423.0914, found 423.0913.

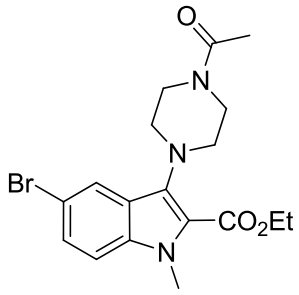


Ethyl 5-bromo-3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-1-methyl-1*H*-indole-2-carboxylate (3c). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3c**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (155 mg, 75% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.63. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 93-94 °C. IR (film, cm^{-1}) 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89 (1H, d, *J*=1.8 Hz), 7.39 (1H, dd, *J*=9.0, 1.8 Hz), 7.22 (1H, d, *J*=9.0 Hz), 7.20-7.13 (3H, m), 7.09-7.01 (1H, m), 4.45 (2H, s), 4.36 (2H, q, *J*=7.2 Hz), 3.93 (3H, s), 3.57 (2H, t, *J*=5.8 Hz), 3.02 (2H, t, *J*=5.8 Hz), 1.27 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.1, 136.0, 135.8, 135.4, 134.9, 129.2, 128.2, 126.2, 126.1, 125.7, 125.3, 123.8, 112.9, 111.8, 61.0, 54.6, 50.4, 32.3, 30.6, 14.4. HRMS-ESI (m/z) calcd for $C_{21}H_{22}BrN_2O_2$ $[M+H]^+$ 413.0859, found 413.0828.

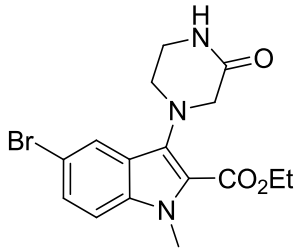


Ethyl 3-(4-(1-methylethyl)piperazin-1-yl)-5-bromo-1-methyl-1*H*-indole-2-carboxylate (3d). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3d**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a yellow oil (145 mg, 71% yield); analytical TLC on silica gel, 1:20 MeOH/CH_2Cl_2, R_f=0.76. IR (film, cm^{-1}) 1697 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.04 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.18 (1H, d, *J*=9.0 Hz), 4.43 (2H, q, *J*=7.2 Hz), 3.87 (3H, s), 3.39-3.30 (4H, m), 2.76 (1H, s,

J=6.5 Hz), 2.72-2.64 (4H, m), 1.44 (3H, t, *J*=7.2 Hz), 1.11 (6H, d, *J*=6.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.1, 136.1, 135.8, 127.9, 124.6, 124.5, 122.0, 112.6, 111.9, 60.9, 54.8, 53.1, 49.7, 32.3, 29.8, 18.7, 14.8. HRMS-ESI (m/z) calcd for $C_{19}H_{27}BrN_3O_2$ $[M+H]^+$ 408.1281, found 408.1279.

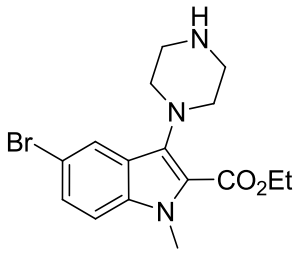


Ethyl 3-(4-acetylpiperazin-1-yl)-5-bromo-1-methyl-1*H*-indole-2-carboxylate (3e). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3e**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a yellow powder (155 mg, 76% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, R_f=0.16. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 157-158 °C. IR (film, cm^{-1}) 1696 (C=O), 1646 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.90 (1H, d, *J*=1.8 Hz), 7.38 (1H, dd, *J*=9.0, 1.8 Hz), 7.20 (1H, d, *J*=9.0 Hz), 4.42 (2H, q, *J*=7.2 Hz), 3.89 (3H, s), 3.81-3.73 (2H, m), 3.65-3.57 (2H, m), 3.30-3.18 (4H, m), 2.16 (3H, s), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.2, 161.8, 135.9, 134.6, 128.3, 124.9, 123.6, 122.9, 113.1, 112.0, 61.1, 52.4, 52.0, 47.6, 42.7, 32.4, 21.6, 14.7. HRMS-ESI (m/z) calcd for $C_{18}H_{23}BrN_3O_3$ $[M+H]^+$ 408.0917, found 408.0901.

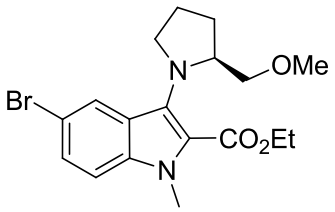


Ethyl 5-bromo-1-methyl-3-(3-oxopiperazin-1-yl)-1*H*-indole-2-carboxylate (3f). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3f**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a yellow powder (144 mg, 76% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, R_f=0.11. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 139-140 °C. IR (film, cm^{-1}) 3219 (NH), 1690 (C=O), 1669 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 (1H, d, *J*=1.4 Hz), 7.41 (1H, dd, *J*=8.8, 1.4 Hz), 7.23 (1H, d, *J*=8.8 Hz), 6.84-6.64 (1H, m), 4.43 (2H, q, *J*=7.2 Hz), 3.95 (2H, s), 3.93

(3H, s), 3.55-3.42 (4H, m), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 170.1, 161.6, 135.8, 132.6, 128.6, 125.1, 123.5, 123.1, 113.5, 112.0, 61.3, 55.7, 48.8, 42.8, 32.4, 14.6. HRMS-ESI (m/z) calcd for $C_{16}H_{19}BrN_3O_3$ $[M+H]^+$ 380.0604, found 380.0600.

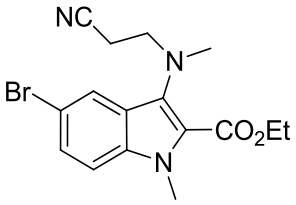


Ethyl 5-bromo-1-methyl-3-piperazin-1-yl-1*H*-indole-2-carboxylate (3g). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3g**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a yellow oil (128 mg, 70% yield); analytical TLC on silica gel, 1:20 MeOH/CH_2Cl_2, R_f=0.37. IR (film, cm^{-1}) 3300 (NH), 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=9.0, 1.8 Hz), 7.19 (1H, d, *J*=9.0 Hz), 4.44 (2H, q, *J*=7.2 Hz), 3.88 (3H, s), 3.33-3.23 (4H, m), 3.13-3.04 (4H, m), 3.03-2.95 (1H, m), 1.45 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.0, 136.0, 135.5, 128.1, 124.8, 124.0, 122.5, 112.8, 111.9, 61.0, 53.3, 46.7, 32.3, 14.8. HRMS-ESI (m/z) calcd for $C_{16}H_{21}BrN_3O_2$ $[M+H]^+$ 366.0812, found 366.0824.

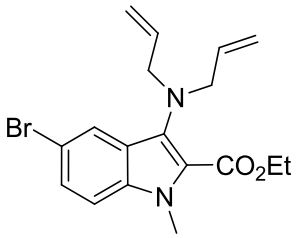


Ethyl 5-bromo-3-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]-1-methyl-1*H*-indole-2-carboxylate (3h). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3h**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 20% EtOAc/petroleum ether afforded product as a yellow powder (69 mg, 35% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 71-72 ^{o}C. IR (film, cm^{-1}) 1696 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.84 (1H, d, *J*=1.8 Hz), 7.38 (1H, dd, *J*=9.0, 1.8 Hz), 7.21 (1H, d, *J*=9.0 Hz), 4.47-4.36 (2H, m), 3.92 (3H, s), 3.86-3.79 (1H, m), 3.47-3.40 (1H, m), 3.24-3.14 (6H, m), 2.26-2.16 (1H, m), 2.03-1.87 (3H, m), 1.44-1.39 (3H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.1, 136.1, 132.4, 128.2, 126.9, 124.5, 123.5, 113.0, 111.8,

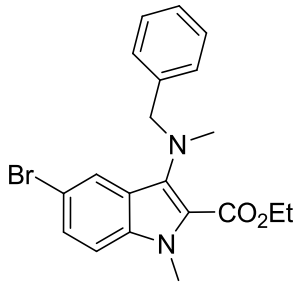
76.6, 61.8, 60.8, 59.1, 54.4, 32.3, 30.1, 25.2, 14.6. HRMS-ESI (m/z) calcd for $C_{18}H_{24}BrN_2O_3$ $[M+H]^+$ 395.0965, found 395.0982.



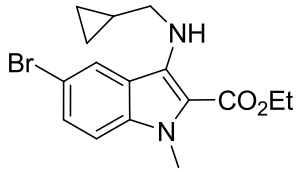
Ethyl 5-bromo-3-[(2-cyanoethyl)(methyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3i). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3i**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (118 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.34. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 72-73 °C. IR (film, cm^{-1}) 2247 (C≡N), 1704 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89 (1H, d, *J*=1.8 Hz), 7.41 (1H, dd, *J*=9.0, 1.8 Hz), 7.22 (1H, d, *J*=9.0 Hz), 4.45 (2H, q, *J*=7.2 Hz), 3.92 (3H, s), 3.50 (2H, d, *J*=7.0 Hz), 2.97 (3H, s), 2.47 (2H, d, *J*=7.0 Hz), 1.45 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.7, 135.8, 133.5, 128.5, 126.0, 124.3, 123.1, 119.1, 113.6, 112.0, 61.2, 52.7, 42.8, 32.4, 17.8, 14.6. HRMS-ESI (m/z) calcd for $C_{16}H_{19}BrN_3O_2$ $[M+H]^+$ 364.0655, found 364.0665.



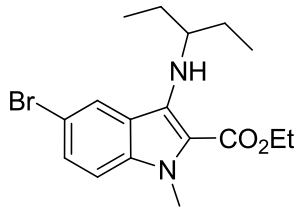
Ethyl 5-bromo-3-(diprop-2-en-1-ylamino)-1-methyl-1*H*-indole-2-carboxylate (3j). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3j**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (126 mg, 67% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.69. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 54-55 °C. IR (film, cm^{-1}) 1707 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=9.0, 1.8 Hz), 7.19 (1H, d, *J*=9.0 Hz), 5.91-5.75 (2H, m), 5.18-5.09 (2H, m), 5.07-4.99 (2H, m), 4.43 (2H, q, *J*=7.2 Hz), 3.90 (3H, s), 3.80 (4H, m), 1.45 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.1, 136.4, 135.9, 134.3, 128.1, 126.8, 124.1, 123.8, 116.6, 113.0, 111.8, 60.9, 57.1, 32.4, 14.6. HRMS-ESI (m/z) calcd for $C_{18}H_{22}BrN_2O_2$ $[M+H]^+$ 377.0859, found 377.0862.



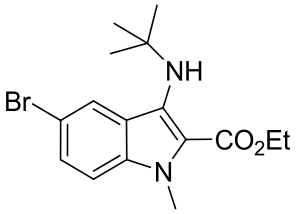
Ethyl 3-[benzyl(methyl)amino]-5-bromo-1-methyl-1*H*-indole-2-carboxylate (3k). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3k**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow oil (130 mg, 65% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.47. IR (film, cm^{-1}) 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.96-7.91 (1H, m), 7.44-7.36 (3H, m), 7.36-7.30 (2H, m), 7.27-7.24 (1H, m), 7.20 (1H, d, *J*=9.0 Hz), 4.45 (2H, q, *J*=7.1 Hz), 4.37 (2H, s), 3.91 (3H, s), 2.85 (3H, s), 1.45 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.2, 139.9, 136.7, 136.0, 128.5, 128.4, 128.2, 127.1, 125.6, 123.8, 122.9, 112.8, 111.8, 61.2, 61.0, 41.9, 32.3, 14.6. HRMS-ESI (m/z) calcd for $C_{20}H_{22}BrN_2O_2$ $[M+H]^+$ 401.0859, found 401.0855.



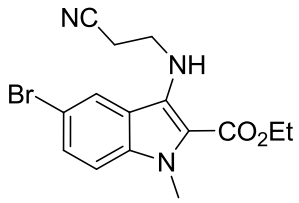
Ethyl 5-bromo-3-[(cyclopropylmethyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3l). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3l**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow powder (125 mg, 71% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.47. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 62-63 °C. IR (film, cm^{-1}) 3355 (NH), 1690 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.09 (1H, d, *J*=9.0 Hz), 6.29-6.05 (1H, m), 4.40 (2H, q, *J*=7.2 Hz), 3.83 (3H, s), 3.41 (2H, d, *J*=6.9 Hz), 1.43 (3H, t, *J*=7.2 Hz), 1.21-1.07 (1H, m), 0.61-0.53 (2H, m), 0.34-0.24 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.3, 138.8, 137.8, 129.2, 125.2, 119.7, 111.7, 110.8, 110.7, 60.1, 52.0, 32.5, 14.7, 12.0, 3.5. HRMS-ESI (m/z) calcd for $C_{16}H_{20}BrN_2O_2$ $[M+H]^+$ 351.0703, found 351.0733.



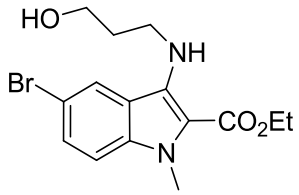
Ethyl 5-bromo-3-[(1-ethylpropyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3m). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3m**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 20% EtOAc/petroleum ether afforded product as a yellow powder (129 mg, 70% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.56. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 93-94 ^{o}C. IR (film, cm^{-1}) 3322 (NH), 1653 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=9.0, 1.8 Hz), 7.10 (1H, d, *J*=9.0 Hz), 6.15-5.88 (1H, m), 4.39 (2H, q, *J*=7.2 Hz), 3.83 (3H, s), 3.75-3.64 (1H, m), 1.67-1.54 (4H, m), 1.42 (3H, t, *J*=7.2 Hz), 0.97 (6H, t, *J*=7.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.4, 138.8, 138.0, 129.2, 125.1, 119.5, 111.8, 111.2, 110.7, 60.1, 58.0, 32.6, 27.9, 14.7, 10.1. HRMS-ESI (m/z) calcd for $C_{17}H_{24}BrN_2O_2$ $[M+H]^+$ 367.1049, found 367.1049.



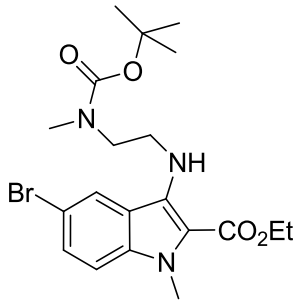
Ethyl 5-bromo-3-(*tert*-butylamino)-1-methyl-1*H*-indole-2-carboxylate (3n). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3n**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 20% EtOAc/petroleum ether afforded product as a yellow powder (134 mg, 76% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.45. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 54-55 ^{o}C. IR (film, cm^{-1}) 3328 (NH), 1696 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=9.0, 1.8 Hz), 7.16 (1H, d, *J*=9.0 Hz), 4.95-4.70 (1H, br s), 4.41 (2H, q, *J*=7.2 Hz), 3.90 (3H, s), 1.45 (3H, t, *J*=7.2 Hz), 1.25 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.0, 137.0, 132.8, 128.5, 125.4, 125.4, 120.7, 112.5, 111.6, 60.7, 54.7, 32.5, 30.6, 14.6. HRMS-ESI (m/z) calcd for $C_{16}H_{22}BrN_2O_2$ $[M+H]^+$ 353.0859, found 353.0862.



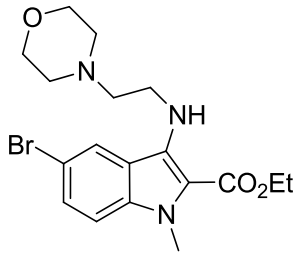
Ethyl 5-bromo-3-[(2-cyanoethyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3o). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3o**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 15% EtOAc/petroleum ether to 75% EtOAc/petroleum ether afforded product as a yellow powder (110 mg, 63% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.26. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 62-63 °C. IR (film, cm^{-1}) 3340 (NH), 1691 (C=O), 2247 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81 (1H, d, *J*=1.8 Hz), 7.40 (1H, dd, *J*=9.0, 1.8 Hz), 7.16 (1H, d, *J*=9.0 Hz), 6.19-6.03 (1H, m), 4.43 (2H, q, *J*=7.2 Hz), 3.88 (3H, s), 3.83-3.76 (2H, m), 2.61 (2H, d, *J*=6.6 Hz), 1.44 (3H, q, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.0, 137.3, 134.9, 129.3, 123.6, 119.7, 118.0, 113.7, 112.2, 111.8, 60.8, 43.1, 32.6, 19.4, 14.6. HRMS-ESI (m/z) calcd for $C_{15}H_{17}BrN_3O_2$ $[M+H]^+$ 350.0499, found 350.0502.



Ethyl 5-bromo-3-[(3-hydroxypropyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3p). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3p**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (119 mg, 67% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.30. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 77-78 °C. IR (film, cm^{-1}) 3421 (OH), 3356 (NH), 1660 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.98 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.09 (1H, d, *J*=1.8 Hz), 6.50-5.50 (1H, m), 4.39 (2H, q, *J*=7.2 Hz), 3.84 (2H, t, *J*=6.0 Hz), 3.82 (3H, s), 3.67 (2H, d, *J*=6.0 Hz), 2.27-1.67 (1H, m), 1.93 (2H, quintet, *J*=6.0 Hz), 1.41 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.4, 138.6, 137.7, 129.6, 125.0, 119.7, 111.8, 111.2, 110.9, 61.0, 60.2, 44.3, 33.3, 32.6, 14.7. HRMS-ESI (m/z) calcd for $C_{15}H_{20}BrN_2O_3$ $[M+H]^+$ 355.0652, found 355.0663.

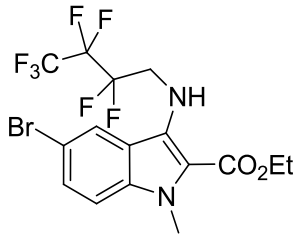


Ethyl 5-bromo-3-(2-[(tert-butoxycarbonyl)(methyl)amino]ethylamino)-1-methyl-1*H*-indole-2-carboxylate (3q). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3q**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow powder (166 mg, 73% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.38. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 102-103 ^{o}C. IR (film, cm^{-1}) 3341 (NH), 1694 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05-7.86 (1H, m), 7.37 (1H, dd, *J*=9.0, 1.6 Hz), 7.11 (1H, d, *J*=9.0 Hz), 6.32-6.09 (1H, m), 4.39 (2H, q, *J*=7.2 Hz), 3.84 (3H, s), 3.75-3.62 (2H, m), 3.56-3.39 (2H, m), 2.90 (3H, s), 1.51-1.34 (9H, m), 1.41 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.3, 138.0, 137.7, 129.2, 124.9, 124.6, 119.4, 111.9, 111.0, 79.8, 60.2, 49.5, 44.9, 32.6, 28.5, 14.7. HRMS-ESI (m/z) calcd for $C_{20}H_{29}BrN_3O_4$ $[M+H]^+$ 454.1336, found 454.1338.

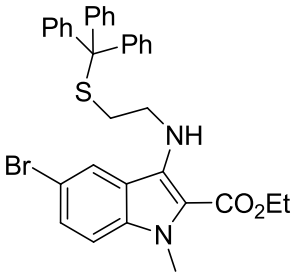


Ethyl 5-bromo-1-methyl-3-[(2-morpholin-4-ylethyl)amino]-1*H*-indole-2-carboxylate (3r). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3r**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 75% EtOAc/petroleum ether afforded product as a yellow powder (82 mg, 40% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.10. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 96-97 ^{o}C . IR (film, cm^{-1}) 3347 (NH), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.10 (1H, d, *J*=9.0 Hz), 6.62-6.09 (1H, m), 4.41 (2H, q, *J*=7.2 Hz), 3.84 (3H, s), 3.77-3.71 (4H, m), 3.67 (2H, d, *J*=6.2 Hz), 2.67 (2H, d, *J*=6.2 Hz), 2.56-2.43 (4H, m), 1.44 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 138.3, 137.8, 129.1,

125.1, 119.7, 111.8, 110.8, 110.8, 67.1, 60.1, 58.2, 53.6, 43.5, 32.5, 14.8. HRMS-ESI (m/z) calcd for $C_{18}H_{25}BrN_3O_3$ $[M+H]^+$ 410.1074, found 410.1084.

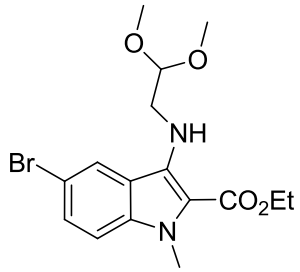


Ethyl 5-bromo-3-[(2,2,3,3,4,4,4-heptafluorobutyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3s). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3s**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow powder (180 mg, 75% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.48. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 57-58 °C. IR (film, cm^{-1}) 3344 (NH), 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (1H, d, *J*=1.8 Hz), 7.41 (1H, dd, *J*=9.0, 1.8 Hz), 7.17 (1H, d, *J*=9.0 Hz), 6.15 (1H, t, *J*=7.4 Hz), 4.43 (2H, q, *J*=7.2 Hz), 4.09 (2H, dt, *J*=15.4, 7.4 Hz), 3.89 (3H, s), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.9, 137.2, 135.1, 129.3, 123.3, 119.5, 114.0, 112.2, 112.0, 110.2, 60.8, 47.1, 32.5, 14.5. HRMS-ESI (m/z) calcd for $C_{16}H_{15}BrF_7N_2O_2$ $[M+H]^+$ 479.0200, found 479.0198.

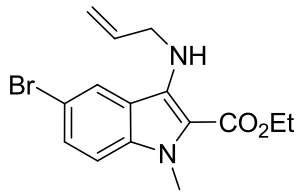


Ethyl 5-bromo-1-methyl-3-[2-(tritylsulfanyl)ethyl]amino-1*H*-indole-2-carboxylate (3t). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3t**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded product as a yellow powder (219 mg, 73% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.38. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 131-132 °C. IR (film, cm^{-1}) 3346 (NH), 1689 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74 (1H, d, *J*=1.8 Hz), 7.45-7.40 (6H, m), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.29-7.23 (6H, m), 7.22-7.15 (3H, m), 7.10 (1H, d, *J*=9.0 Hz), 6.11-5.95 (1H, m), 4.36 (2H, q, *J*=7.2 Hz), 3.84 (3H, s), 3.40-3.30 (2H, m), 2.48 (2H, t, *J*=7.0 Hz), 1.38 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 144.8, 137.7,

137.2, 129.7, 129.1, 128.0, 126.8, 124.8, 119.6, 111.8, 111.0, 66.9, 60.3, 45.7, 32.9, 32.5, 14.7. HRMS-ESI (m/z) calcd for $C_{33}H_{32}BrN_2O_2S$ $[M+H]^+$ 599.1362, found 599.1344.

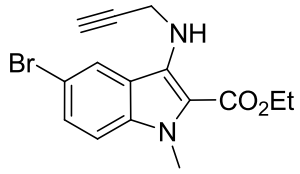


Ethyl 5-bromo-3-[(2,2-dimethoxyethyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3u). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3u**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (154 mg, 80% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.29. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 50-51 ^oC. IR (film, cm^{-1}) 3362 (NH), 1690 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (1H, d, *J*=1.8 Hz), 7.37 (1H, dd, *J*=9.0, 1.8 Hz), 7.12 (1H, d, *J*=9.0 Hz), 6.21-5.96 (1H, m), 4.60 (1H, t, *J*=5.6 Hz), 4.40 (2H, q, *J*=7.2 Hz), 3.85 (3H, s), 3.65 (2H, d, *J*=5.6 Hz), 3.43 (6H, s), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 137.7, 137.4, 129.1, 124.7, 119.7, 111.8, 111.8, 111.1, 103.0, 60.3, 53.9, 48.4, 32.4, 14.6. HRMS-ESI (m/z) calcd for $C_{16}H_{22}BrN_2O_4$ $[M+H]^+$ 385.0757, found 385.0777.

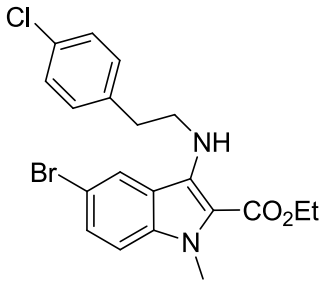


Ethyl 5-bromo-1-methyl-3-(prop-2-en-1-ylamino)-1*H*-indole-2-carboxylate (3v). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3v**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 20% EtOAc/petroleum ether afforded product as a yellow powder (143 mg, 80% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.46. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 56-57 ^oC. IR (film, cm^{-1}) 3356 (NH), 1706 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.92 (1H, d, *J*=1.8 Hz), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.10 (1H, d, *J*=9.0 Hz), 6.29-6.13 (1H, m), 6.03 (1H, ddt, *J*=17.2, 10.3, 5.2 Hz), 5.34 (1H, dd, *J*=17.2, 1.6 Hz), 5.19 (1H, dd, *J*=10.3, 1.6 Hz), 4.40 (2H, q, *J*=7.2 Hz), 4.16 (2H, d, *J*=5.2 Hz), 3.83 (3H, s), 1.42 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.4, 138.5,

137.8, 135.9, 129.2, 125.1, 119.4, 116.3, 111.8, 111.1, 110.9, 60.2, 49.1, 32.6, 14.7. HRMS-ESI (m/z) calcd for $C_{15}H_{18}BrN_2O_2$ $[M+H]^+$ 337.0546, found 337.0574.

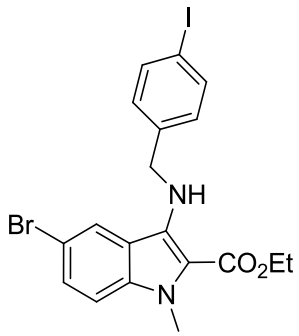


Ethyl 5-bromo-1-methyl-3-(prop-2-yn-1-ylamino)-1*H*-indole-2-carboxylate (3w). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3w**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (119 mg, 71% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.38. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 101-102 °C. IR (film, cm^{-1}) 3293 (NH), 1705 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.96 (1H, d, *J*=1.8 Hz), 7.39 (1H, dd, *J*=9.0, 1.8 Hz), 7.14 (1H, d, *J*=9.0 Hz), 6.21-6.00 (1H, m), 4.41 (2H, q, *J*=7.2 Hz), 4.27-4.20 (2H, m), 3.87 (3H, s), 2.26 (1H, t, *J*=2.4 Hz), 1.43 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 137.4, 136.3, 129.2, 124.5, 119.9, 113.2, 111.9, 111.5, 81.4, 72.4, 60.5, 36.9, 32.5, 14.6. HRMS-ESI (m/z) calcd for $C_{15}H_{16}BrN_2O_2$ $[M+H]^+$ 335.0390, found 335.0423.

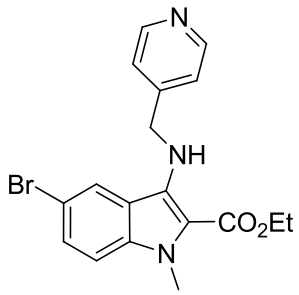


Ethyl 5-bromo-3-[2-(4-chlorophenyl)ethyl]amino-1-methyl-1*H*-indole-2-carboxylate (3x). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3x**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded product as a yellow powder (181 mg, 83% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.45. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 112-113 °C. IR (film, cm^{-1}) 3346 (NH), 1685 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93 (1H, d, *J*=1.6 Hz), 7.38 (1H, dd, *J*=9.0, 1.6 Hz), 7.30-7.26 (2H, m), 7.18-7.14 (2H, m), 7.12 (1H, d, *J*=9.0 Hz), 6.19-5.92 (1H, m), 4.31 (2H, q, *J*=7.1 Hz), 3.84 (3H, s), 3.78 (2H, d, *J*=7.0 Hz), 2.92 (2H, d, *J*=7.0 Hz), 1.32 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.2, 137.8, 137.7,

137.7, 132.4, 130.3, 129.2, 128.8, 124.8, 119.6, 111.9, 111.4, 111.0, 60.2, 47.9, 36.5, 32.6, 14.6. HRMS-ESI (m/z) calcd for $C_{20}H_{21}BrClN_2O_2$ $[M+H]^+$ 435.0469, found 435.0523.

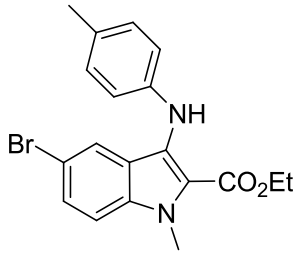


Ethyl 5-bromo-3-[(4-iodobenzyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3y). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3y**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (197 mg, 77% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 128-129 °C. IR (film, cm^{-1}) 3362 (NH), 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.84 (1H, d, *J*=1.8 Hz), 7.71-7.61 (2H, m), 7.36 (1H, dd, *J*=9.0, 1.8 Hz), 7.14-7.09 (3H, m), 6.73-6.04 (1H, m), 4.66-4.63 (2H, m), 4.37 (2H, q, *J*=7.2 Hz), 3.84 (3H, s), 1.36 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.3, 139.7, 138.5, 137.9, 137.9, 137.6, 130.9, 129.4, 129.3, 124.8, 119.4, 111.9, 111.7, 111.1, 92.8, 60.3, 50.5, 32.6, 14.6. HRMS-ESI (m/z) calcd for $C_{19}H_{19}BrIN_2O_2$ $[M+H]^+$ 512.9669, found 512.9672.

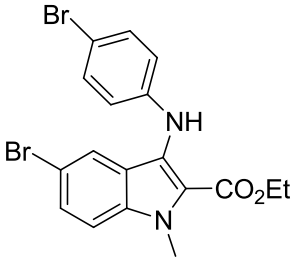


Ethyl 5-bromo-1-methyl-3-[(pyridin-4-ylmethyl)amino]-1*H*-indole-2-carboxylate (3z). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3z**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded product as a brown powder (153 mg, 79% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.22. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 99-100 °C. IR (film, cm^{-1}) 3347 (NH), 1691 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56 (2H, d,

J=4.8 Hz), 7.74 (1H, d, *J*=1.8 Hz), 7.35 (1H, dd, *J*=9.0, 1.8 Hz), 7.31 (2H, d, *J*=4.8 Hz), 7.11 (1H, d, *J*=9.0 Hz), 6.58 (1H, t, *J*=6.6 Hz), 4.72 (2H, d, *J*=6.6 Hz), 4.39 (2H, q, *J*=7.2 Hz), 3.85 (3H, s), 1.39 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.4, 150.3, 149.2, 137.7, 137.5, 129.3, 124.4, 122.1, 119.2, 112.0, 111.8, 111.2, 60.4, 49.7, 32.6, 14.6. HRMS-ESI (m/z) calcd for $C_{18}H_{19}BrN_3O_2$ $[M+H]^+$ 388.0655, found 388.0665.

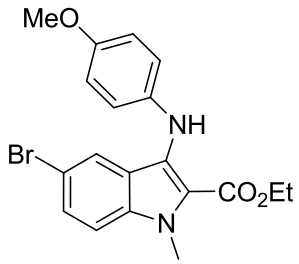


Ethyl 5-bromo-1-methyl-3-[(4-methylphenyl)amino]-1*H*-indole-2-carboxylate (3aa). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3aa**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded product as a yellow powder (141 mg, 73% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 109-110 °C. IR (film, cm^{-1}) 3345 (NH), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.51 (1H, d, *J*=1.8 Hz), 7.43-7.36 (2H, m), 7.19 (1H, d, *J*=9.0 Hz), 7.09-7.03 (2H, m), 6.91-6.85 (2H, m), 4.40 (2H, q, *J*=7.2 Hz), 3.94 (3H, s), 2.32 (3H, s), 1.42 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.9, 141.3, 137.1, 130.9, 130.6, 129.8, 129.1, 125.1, 121.0, 118.4, 115.9, 111.9, 111.6, 60.8, 32.5, 20.8, 14.6. HRMS-ESI (m/z) calcd for $C_{19}H_{20}BrN_2O_2$ $[M+H]^+$ 387.0703, found 387.0703.

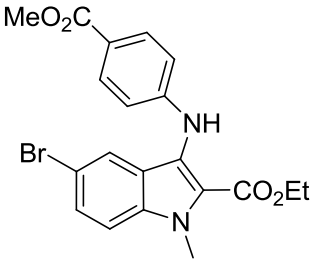


Ethyl 5-bromo-3-[(4-bromophenyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3ab). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ab**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (167 mg, 74% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.37. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 179-180 °C. IR (film, cm^{-1}) 3346 (NH), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.54-7.49 (1H, m), 7.44-7.40 (1H,

m), 7.35-7.30 (2H, m), 7.29-7.27 (1H, m), 7.22 (1H, d, *J*=9.0 Hz), 6.83-6.77 (2H, m), 4.41 (2H, q, *J*=7.2 Hz), 3.96 (3H, s), 1.41 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.7, 143.3, 136.9, 132.1, 129.2, 128.5, 124.6, 121.3, 118.9, 117.2, 113.0, 112.3, 112.1, 61.0, 32.6, 14.5. HRMS-ESI (m/z) calcd for $C_{18}H_{17}Br_2N_2O_2$ $[M+H]^+$ 450.9651, found 450.9645.

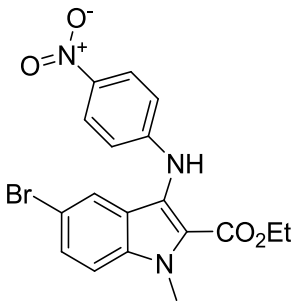


Ethyl 5-bromo-3-[(4-methoxyphenyl)amino]-1-methyl-1*H*-indole-2-carboxylate (3ac). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ac**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (110 mg, 54% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.37. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 112-113 °C. IR (film, cm^{-1}) 3405 (NH), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.46 (1H, s), 7.39-7.35 (2H, m), 7.19-7.14 (1H, m), 7.00-6.96 (2H, m), 6.87-6.82 (2H, m), 4.41 (2H, q, *J*=7.2 Hz), 3.92 (3H, s), 3.81 (3H, s), 1.42 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 155.4, 137.4, 136.8, 132.2, 129.2, 125.1, 121.4, 120.3, 114.7, 114.6, 111.8, 111.3, 60.7, 55.8, 32.6, 14.6. HRMS-ESI (m/z) calcd for $C_{19}H_{20}BrN_2O_3$ $[M+H]^+$ 403.0652, found 403.0647.

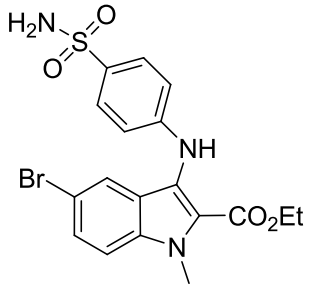


Ethyl 5-bromo-3-[4-(methoxycarbonyl)phenyl]amino-1-methyl-1*H*-indole-2-carboxylate (3ad). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ad**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a yellow powder (149 mg, 69% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.28. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 126-127 °C. IR (film, cm^{-1}) 3362 (NH), 1707 (C=O), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95-7.87 (2H, m), 7.58 (1H, d, *J*=1.8 Hz), 7.44 (1H, dd, *J*=9.0, 1.8 Hz), 7.32 (1H, s), 7.25 (1H, d,

J=9.0 Hz), 6.89-6.81 (2H, m), 4.40 (2H, q, *J*=7.2 Hz), 3.98 (3H, s), 3.87 (3H, s), 1.39 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 167.2, 162.4, 148.7, 136.6, 131.4, 129.2, 126.4, 124.4, 121.9, 121.5, 118.5, 115.2, 112.7, 112.2, 61.1, 51.9, 32.5, 14.5. HRMS-ESI (m/z) calcd for $C_{20}H_{20}BrN_2O_4$ $[M+H]^+$ 431.0601, found 431.0593.

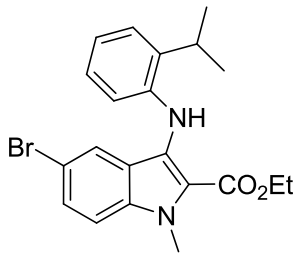


Ethyl 5-bromo-1-methyl-3-[(4-nitrophenyl)amino]-1*H*-indole-2-carboxylate (3ae). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ae**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded product as a orange powder (140 mg, 67% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.23. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 137-138 °C. IR (film, cm^{-1}) 3356 (NH), 1707 (C=O), 1598 (N=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17-8.07 (2H, m), 7.56 (1H, d, *J*=1.8 Hz), 7.47 (1H, dd, *J*=9.0, 1.8 Hz), 7.38 (1H, s), 7.30 (1H, d, *J*=9.0 Hz), 6.85-6.79 (2H, m), 4.41 (2H, q, *J*=7.2 Hz), 4.01 (3H, s), 1.39 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.0, 150.5, 140.4, 136.4, 129.4, 126.2, 124.4, 123.8, 122.1, 119.7, 114.5, 113.4, 112.4, 61.4, 32.6, 14.5. HRMS-ESI (m/z) calcd for $C_{18}H_{17}BrN_3O_4$ $[M+H]^+$ 418.0397, found 418.0394.

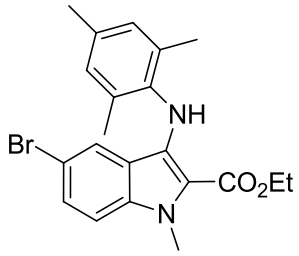


Ethyl 5-bromo-1-methyl-3-[(4-sulfamoylphenyl)amino]-1*H*-indole-2-carboxylate (3af). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into indole **3af**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2 afforded product as a yellow powder (140 mg, 62% yield); analytical TLC on silica gel, 1:10 MeOH/CH_2Cl_2, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 157-158 °C. IR (film, cm^{-1}) 3413 (NH), 1708 (C=O), 1304 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.31-8.26

(1H, m), 7.65 (1H, d, *J*=9.0 Hz), 7.59-7.54 (2H, m), 7.53 (1H, d, *J*=1.8 Hz), 7.49 (1H, dd, *J*=9.0, 1.8 Hz), 7.01 (2H, s), 6.78-6.71 (2H, m), 4.20 (2H, q, *J*=7.2 Hz), 3.99 (3H, s), 1.12 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 160.9, 149.5, 135.9, 132.5, 128.1, 127.2, 123.5, 122.7, 122.2, 121.9, 113.6, 112.8, 112.3, 64.9, 60.5, 32.2, 13.8. HRMS-ESI (m/z) calcd for $C_{18}H_{19}BrN_3O_4S$ $[M+H]^+$ 452.0274, found 452.0276.

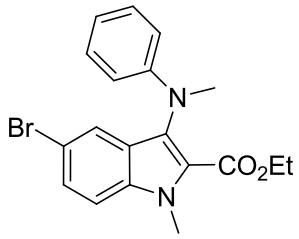


Ethyl 5-bromo-1-methyl-3-[2-(1-methylethyl)phenyl]amino-1*H*-indole-2-carboxylate (3ag). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ag**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (164 mg, 79% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.50. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 96-97 ^{o}C. IR (film, cm^{-1}) 3340 (NH), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.51 (1H, s), 7.38 (1H, dd, *J*=9.0, 1.8 Hz), 7.33 (1H, dd, *J*=7.0, 2.0 Hz), 7.29 (1H, d, *J*=1.8 Hz), 7.18 (1H, d, *J*=9.0 Hz), 7.06 (2H, ddd, *J*=7.0, 2.0, 2.0 Hz), 6.96 (1H, dd, *J*=7.0, 2.0 Hz), 4.43 (2H, q, *J*=7.2 Hz), 3.94 (3H, s), 3.35 (1H, q, *J*=6.8 Hz), 1.42 (3H, t, *J*=7.2 Hz), 1.35 (6H, d, *J*=6.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 140.3, 139.1, 137.4, 131.9, 129.2, 126.3, 125.8, 125.2, 122.8, 120.3, 119.8, 115.0, 111.8, 111.4, 110.2, 60.7, 32.6, 28.0, 23.0, 14.7. HRMS-ESI (m/z) calcd for $C_{21}H_{24}BrN_2O_2$ $[M+H]^+$ 415.1016, found 415.1007.

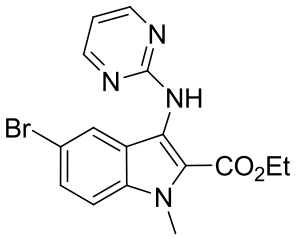


Ethyl 5-bromo-1-methyl-3-[(2,4,6-trimethylphenyl)amino]-1*H*-indole-2-carboxylate (3ah). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ah**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded product as a yellow powder (158 mg, 76% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether,

R_f=0.51. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 161-162 °C. IR (film, cm^{-1}) 3325 (NH), 1654 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.53 (1H, s), 7.27 (1H, dd, *J*=9.0, 1.8 Hz), 7.05 (1H, d, *J*=9.0 Hz), 7.00-6.94 (2H, m), 6.54 (1H, d, *J*=1.8 Hz), 4.46 (2H, q, *J*=7.2 Hz), 3.88 (3H, s), 2.36 (3H, s), 2.18 (6H, s), 1.45 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.6, 137.8, 137.6, 137.0, 136.7, 136.0, 129.4, 129.2, 124.3, 118.7, 111.4, 110.6, 109.3, 60.1, 32.6, 21.2, 18.5, 14.8. HRMS-ESI (m/z) calcd for $C_{21}H_{24}BrN_2O_2$ $[M+H]^+$ 415.1016, found 415.1045.

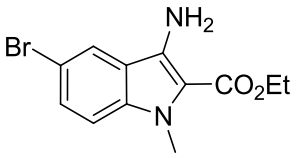


Ethyl 5-bromo-1-methyl-3-[methyl(phenyl)amino]-1*H*-indole-2-carboxylate (3ai). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ai**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% EtOAc/petroleum ether to 20% EtOAc/petroleum ether afforded product as a yellow oil (149 mg, 77% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.50. IR (film, cm^{-1}) 1705 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (1H, d, *J*=1.8 Hz), 7.44 (1H, dd, *J*=8.8, 1.8 Hz), 7.31 (1H, d, *J*=8.8 Hz), 7.14 (2H, dd, *J*=8.2, 7.4 Hz), 6.70 (1H, dd, *J*=7.4, 7.4 Hz), 6.57 (2H, d, *J*=8.2 Hz), 4.16 (2H, q, *J*=7.2 Hz), 4.05 (3H, s), 3.31 (3H, s), 1.08 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.5, 149.6, 136.3, 129.7, 128.9, 128.7, 125.7, 124.8, 122.9, 116.9, 114.1, 112.5, 112.0, 60.9, 39.8, 32.3, 14.1. HRMS-ESI (m/z) calcd for $C_{19}H_{20}BrN_2O_2$ $[M+H]^+$ 387.0703, found 387.0702.



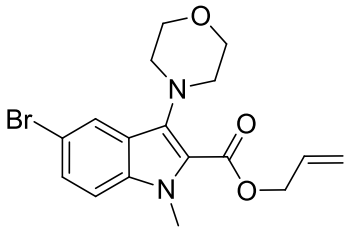
Ethyl 5-bromo-1-methyl-3-(pyrimidin-2-ylamino)-1*H*-indole-2-carboxylate (3aj). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ak**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 15% EtOAc/petroleum ether to 75% EtOAc/petroleum ether afforded product as a yellow powder (122 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.15. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 160-161 °C. IR (film, cm^{-1})

2981 (NH), 1705 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (2H, d, *J*=4.8 Hz), 8.07 (1H, s), 7.93-7.84 (1H, m), 7.42 (1H, d, *J*=9.0 Hz), 7.22 (1H, d, *J*=9.0 Hz), 6.72 (1H, dd, *J*=4.8, 4.8 Hz), 4.40 (2H, q, *J*=7.2 Hz), 3.98 (3H, s), 1.37 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.1, 160.9, 158.4, 136.6, 128.9, 126.0, 123.5, 122.9, 119.1, 112.9, 112.8, 111.9, 61.1, 32.4, 14.4. HRMS-ESI (m/z) calcd for $C_{16}H_{16}BrN_4O_2$ $[M+H]^+$ 375.0451, found 375.0433.



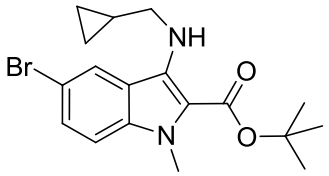
Ethyl 3-amino-5-bromo-1-methyl-1*H*-indole-2-carboxylate (3ak). Following the general procedure, indole **1a** (141 mg, 0.50 mmol) was converted into **3ak**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded product as a yellow powder (105 mg, 71% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, Rf=0.46. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 107-108 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.66 (1H, d, *J*=1.8 Hz), 7.38 (1H, dd, *J*=8.9, 1.8 Hz), 7.09 (1H, d, *J*=8.9 Hz), 4.88-4.69 (2H, br s), 4.41 (2H, q, *J*=7.2 Hz), 3.85 (3H, s), 1.43 (3H, t, *J*=7.2 Hz).

Experimental Procedures for C-H amination of Heterocycles 5sm–20sm and Arenes 21sm–31sm.

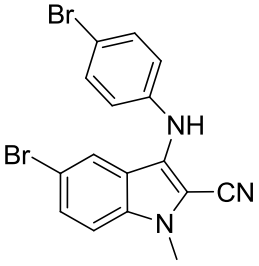


Prop-2-en-1-yl 5-bromo-1-methyl-3-morpholin-4-yl-1*H*-indole-2-carboxylate (5). Following the general procedure, indole **5sm** (147 mg, 0.50 mmol) was converted into **5**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 40% EtOAc/petroleum ether afforded **5** as a yellow powder (131 mg, 69% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.39. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 68-69 ^{o}C. IR (film, cm^{-1}) 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.98 (1H, d, *J*=1.8 Hz), 7.39 (1H, dd, *J*=9.0, 1.8 Hz), 7.21 (1H, d, *J*=9.0 Hz), 6.16-6.01 (1H, m), 5.50-5.40 (1H, m), 5.37-5.30 (1H, m), 4.90-4.84 (2H, m), 3.89 (3H, s), 3.86-3.81 (4H, m), 3.31-3.25 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ

161.6, 136.1, 135.5, 132.2, 128.3, 124.7, 124.0, 122.2, 119.4, 112.9, 112.0, 68.0, 65.8, 52.9, 32.4. HRMS-ESI (m/z) calcd for $C_{17}H_{20}BrN_2O_3$ $[M+H]^+$ 379.0652, found 379.0643.

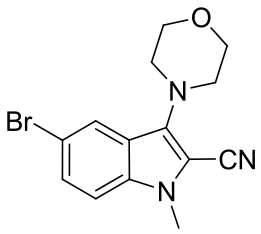


***tert*-Butyl 5-bromo-3-[(cyclopropylmethyl)amino]-1-methyl-1*H*-indole-2-carboxylate (6).** Following the general procedure, indole **6sm** (155 mg, 0.50 mmol) was converted into **6**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **6** as a yellow powder (150 mg, 79% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.64. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 62-63 ^oC. IR (film, cm^{-1}) 3353 (NH), 1685 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.93 (1H, d, *J*=1.8 Hz), 7.34 (1H, dd, *J*=9.0, 1.8 Hz), 7.09 (1H, d, *J*=9.0 Hz), 6.41-5.49 (1H, m), 3.83 (3H, s), 3.39 (2H, d, *J*=7.0 Hz), 1.64 (9H, s), 1.18-1.07 (1H, m), 0.61-0.52 (2H, m), 0.34-0.25 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.7, 137.8, 137.5, 128.8, 125.0, 119.9, 112.1, 111.7, 110.7, 81.5, 52.2, 32.5, 28.8, 12.0, 3.6. HRMS-ESI (m/z) calcd for $C_{18}H_{24}BrN_2O_2$ $[M+H]^+$ 379.1016, found 379.1015.

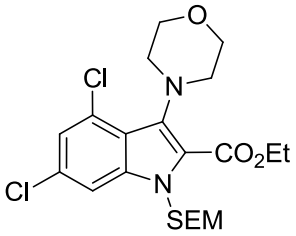


5-Bromo-3-[(4-bromophenyl)amino]-1-methyl-1*H*-indole-2-carbonitrile (7a). Following the general procedure, indole **7sm** (118 mg, 0.50 mmol) was converted into **7a**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **7a** as a white powder (170 mg, 84% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.44. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 145-146 ^oC. IR (film, cm^{-1}) 3343 (NH), 2212 (C≡N); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.55 (1H, d, *J*=1.8 Hz), 7.49 (1H, dd, *J*=9.0, 1.8 Hz), 7.35-7.30 (2H, m), 7.23 (1H, d, *J*=9.0 Hz), 6.72-6.67 (2H, m), 5.69 (1H, s), 3.85 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 143.3, 136.1, 132.3, 129.8, 127.9, 123.2, 122.9,

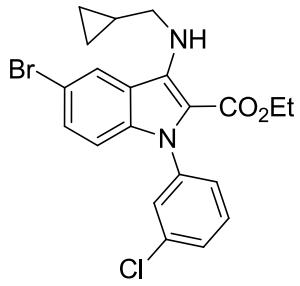
117.1, 114.1, 112.6, 112.5, 112.1, 105.1, 31.9. HRMS-ESI (m/z) calcd for $C_{16}H_{12}Br_2N_3$ $[M+H]^+$ 403.9392, found 403.9401.



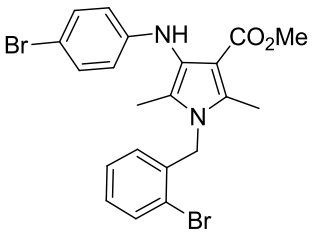
5-Bromo-1-methyl-3-morpholin-4-yl-1*H*-indole-2-carbonitrile (7b). Following the general procedure, indole **7sm** (118 mg, 0.50 mmol) was converted into **7b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **7b** as a yellow powder (123 mg, 77% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 166-167 ºC. IR (film, cm^{-1}) 2207 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.82-7.72 (1H, m), 7.50-7.38 (1H, m), 7.14 (1H, d, *J*=8.8 Hz), 3.94-3.85 (4H, m), 3.75 (3H, s), 3.44-3.32 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 139.3, 136.2, 129.5, 123.3, 122.3, 114.6, 113.3, 111.8, 100.4, 67.2, 52.5, 31.3. HRMS-ESI (m/z) calcd for $C_{14}H_{15}BrN_3O$ $[M+H]^+$ 320.0393, found 320.0386.



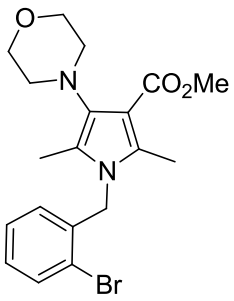
Ethyl 4,6-dichloro-3-morpholino-1-[2-(trimethylsilyl)ethoxy]methyl-1*H*-indole-2-carboxylate (8). Following the general procedure, indole **8sm** (194 mg, 0.50 mmol) was converted into indole **8**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **8** as a colorless oil (118 mg, 50% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.64. IR (film, cm^{-1}) 1707 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41-7.36 (1H, m), 7.17-7.11 (1H, m), 5.68 (2H, s), 4.47 (2H, q, *J*=7.2 Hz), 3.89-3.76 (4H, m), 3.45 (2H, t, *J*=8.0 Hz), 3.41-2.85 (4H, m), 1.46 (3H, t, *J*=7.2 Hz), 0.85 (2H, t, *J*=8.0 Hz), -0.07 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.2, 138.3, 135.0, 131.0, 128.0, 125.1, 123.1, 120.8, 109.8, 73.5, 67.6, 66.2, 61.8, 51.7, 17.9, 14.7, 1.4. HRMS-ESI (m/z) calcd for $C_{21}H_{31}Cl_2N_2O_4Si$ $[M+H]^+$ 473.1425, found 473.1444.



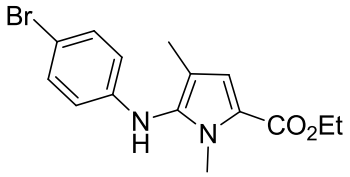
Ethyl 5-bromo-1-(3-chlorophenyl)-3-[(cyclopropylmethyl)amino]-1*H*-indole-2-carboxylate (9). Following the general procedure, indole **9sm** (189 mg, 0.50 mmol) was converted into **9**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **9** as a yellow powder (161 mg, 72% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.68. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 80-81 ^{o}C. IR (film, cm^{-1}) 3347 (NH), 1698 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02 (1H, d, *J*=1.8 Hz), 7.41-7.34 (2H, m), 7.31 (1H, dd, *J*=9.0, 1.8 Hz), 7.26-7.24 (1H, m), 7.18-7.12 (1H, m), 6.89 (1H, d, *J*=9.0 Hz), 6.59-6.41 (1H, m), 4.11 (2H, q, *J*=7.2 Hz), 3.51 (2H, d, *J*=6.8 Hz), 1.24-1.15 (1H, m), 1.00 (3H, t, *J*=7.2 Hz), 0.65-0.57 (2H, m), 0.38-0.30 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 162.8, 141.0, 140.8, 138.8, 134.4, 130.1, 129.8, 128.4, 127.6, 126.2, 125.3, 120.6, 113.0, 112.2, 110.6, 59.8, 51.4, 14.0, 12.0, 3.6. HRMS-ESI (m/z) calcd for $C_{21}H_{21}BrClN_2O_2$ $[M+H]^+$ 447.0469, found 447.0455.



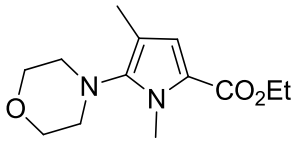
Methyl 1-(2-bromobenzyl)-4-[(4-bromophenyl)amino]-2,5-dimethyl-1*H*-pyrrole-3-carboxylate (10a). Following the general procedure, pyrrole **10sm** (161 mg, 0.50 mmol) was converted into **10a**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded **10a** as a yellow oil (172 mg, 70% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.44. IR (film, cm^{-1}) 3374 (NH), 1696 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.60 (1H, d, *J*=8.0 Hz), 7.25-7.20 (3H, m), 7.20-7.15 (1H, m), 6.57-6.48 (2H, m), 6.31 (1H, d, *J*=8.0 Hz), 6.09 (1H, s), 5.07 (2H, s), 3.75 (3H, s), 2.41 (3H, s), 1.93 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 166.1, 146.8, 136.0, 134.0, 132.9, 131.9, 129.3, 128.3, 126.5, 123.6, 122.3, 121.7, 116.1, 110.1, 106.6, 50.9, 47.7, 11.6, 10.0. HRMS-ESI (m/z) calcd for $C_{21}H_{21}Br_2N_2N_2O_2$ $[M+H]^+$ 490.9964, found 490.9950.



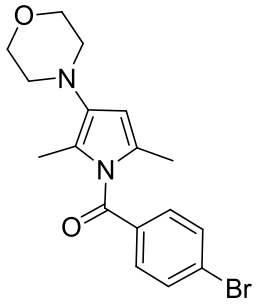
Methyl 1-(2-bromobenzyl)-2,5-dimethyl-4-morpholin-4-yl-1*H*-pyrrole-3-carboxylate (10b). Following the general procedure, pyrrole **10sm** (161 mg, 0.50 mmol) was converted into **10b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **10b** as a yellow powder (126 mg, 62% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.25. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 99-100 °C. IR (film, cm^{-1}) 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.57 (1H, dd, *J*=7.8, 1.4 Hz), 7.19 (1H, ddd, *J*=7.8, 7.4, 1.4 Hz), 7.13 (1H, ddd, *J*=7.8, 7.4, 1.4 Hz), 6.23 (1H, d, *J*=7.4 Hz), 5.00 (2H, s), 3.85 (3H, s), 3.79-3.75 (4H, m), 3.09-3.02 (4H, m), 2.34 (3H, s), 2.07 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 166.3, 136.3, 134.0, 132.9, 132.8, 129.1, 128.2, 126.7, 124.7, 121.6, 108.7, 68.5, 51.9, 50.8, 47.7, 11.4, 9.0. HRMS-ESI (m/z) calcd for $C_{19}H_{24}BrN_2O_3$ $[M+H]^+$ 407.0965, found 407.0956.



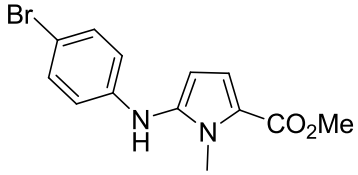
Ethyl 5-[(4-bromophenyl)amino]-1,4-dimethyl-1*H*-pyrrole-2-carboxylate (11a). Following the general procedure, pyrrole **11sm** (84 mg, 0.50 mmol) was converted into **11a**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded **11a** as a yellow oil (101 mg, 60% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.48 (**product is unstable!**). IR (film, cm^{-1}) 3345 (NH), 1702 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25-7.21 (2H, m), 6.82 (1H, s), 6.42-6.37 (2H, m), 5.27 (1H, s), 4.27 (2H, q, *J*=7.1 Hz), 3.67 (3H, s), 1.89 (3H, s), 1.34 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.4, 145.2, 132.6, 132.3, 119.3, 117.3, 115.1, 114.3, 111.0, 59.8, 31.7, 14.6, 10.5. HRMS-ESI (m/z) calcd for $C_{15}H_{18}BrN_2O_2$ $[M+H]^+$ 337.0546, found 337.0547.



Ethyl 1,4-dimethyl-5-morpholin-4-yl-1*H*-pyrrole-2-carboxylate (11b). Following the general procedure, pyrrole **11sm** (84 mg, 0.50 mmol) was converted into **11b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **11b** as a yellow oil (78 mg, 62% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.40 (**product is unstable!**). IR (film, cm^{-1}) 1692 (C=O) ; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.67 (1H, s), 4.24 (2H, q, *J*=7.1 Hz), 3.82-3.77 (4H, m), 3.76 (3H, s), 3.17-2.96 (4H, m), 2.12 (3H, s), 1.31 (3H, t, *J*=7.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.4, 142.7, 130.2, 128.9, 118.3, 117.4, 111.5, 67.8, 59.6, 51.0, 31.2, 14.6, 12.0. HRMS-ESI (m/z) calcd for $C_{12}H_{21}N_2O_3$ $[M+H]^+$ 253.1547, found 253.1543.

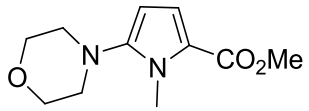


4-{1-[(4-Bromophenyl)carbonyl]-2,5-dimethyl-1*H*-pyrrol-3-yl}morpholine (12). Following the general procedure, pyrrole **12sm** (139 mg, 0.50 mmol) was converted into **12**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **12** as a orange powder (114 mg, 63% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 92-93 ^{o}C. IR (film, cm^{-1}) 1690 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63-7.58 (2H, m), 7.58-7.52 (2H, m), 5.91 (1H, s), 3.83-3.76 (4H, m), 2.89-2.81 (4H, m), 2.09 (3H, s), 1.94 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.7, 137.9, 134.8, 132.1, 131.7, 128.8, 128.2, 119.3, 105.0, 67.4, 53.3, 15.1, 12.5. HRMS-ESI (m/z) calcd for $C_{17}H_{20}BrN_2O_2$ $[M+H]^+$ 363.0703, found 363.0704.

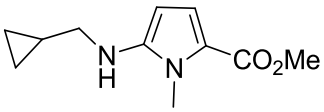


Methyl 5-[(4-bromophenyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (13a). Following the general procedure, methyl 1-methyl-1*H*-pyrrole-2-carboxylate (70 mg, 0.50 mmol) was converted

into **13a**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **13a** as a white powder (141 mg, 91% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 97-98 °C. IR (film, cm^{-1}) 3379 (NH), 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26-7.21 (2H, m), 6.76 (1H, d, *J*=2.0 Hz), 6.68 (1H, d, *J*=2.0 Hz), 6.67-6.63 (2H, m), 5.12 (1H, s), 3.90 (3H, s), 3.81 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.5, 146.0, 132.0, 125.3, 123.6, 121.2, 115.4, 113.2, 110.0, 51.3, 36.9. HRMS-ESI (m/z) calcd for $C_{13}H_{14}BrN_2O_2$ $[M+H]^+$ 309.0233, found 309.0230.

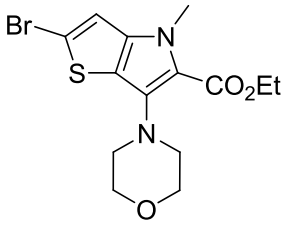


Methyl 1-methyl-5-morpholin-4-yl-1*H*-pyrrole-2-carboxylate (13b). Following the general procedure, methyl 1-methyl-1*H*-pyrrole-2-carboxylate (70 mg, 0.50 mmol) was converted into **13b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **13b** as a white powder (80 mg, 71% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.36. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 68-69 °C. IR (film, cm^{-1}) 1703 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.54 (1H, d, *J*=2.2 Hz), 6.33 (1H, d, *J*=2.2 Hz), 3.85 (3H, s), 3.83-3.79 (4H, m), 3.78 (3H, s), 2.92-2.87 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.7, 138.9, 120.7, 115.7, 105.7, 66.7, 51.2, 51.1, 36.7. HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_3$ $[M+H]^+$ 225.1234, found 225.1245.

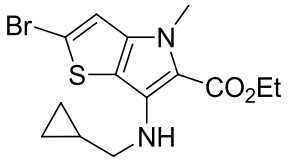


Methyl 5-[(cyclopropylmethyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (13c). Following the general procedure, methyl 1-methyl-1H-pyrrole-2-carboxylate (70 mg, 0.50 mmol) was converted into **13c**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded **13c** as a yellow oil (68 mg, 65% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.20. IR (film, cm^{-1}) 3362 (NH), 1700 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.44 (1H, d, *J*=2.2 Hz), 6.28 (1H, d, *J*=2.2 Hz), 3.82 (3H, s), 3.77 (3H, s), 3.02-2.83 (1H, m), 2.79 (2H, d, *J*=6.8 Hz), 1.12-1.02 (1H, m), 0.54-0.47 (2H, m), 0.21-0.13 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm)

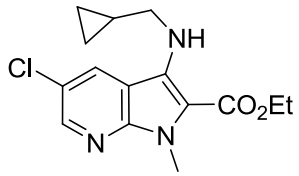
δ 161.7, 135.1, 120.3, 115.5, 105.9, 52.7, 51.0, 36.5, 11.3, 3.5. HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ 209.1285, found 209.1289.



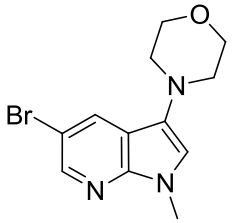
Ethyl 2-bromo-4-methyl-6-morpholin-4-yl-4*H*-thieno[3,2-b]pyrrole-5-carboxyla–te (14b). Following the general procedure, thieno[3,2-*b*]pyrrole **14sm** (144 mg, 0.50 mmol) was converted into **14b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **14b** as a yellow powder (107 mg, 57% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.28. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 97-98 °C. IR (film, cm^{-1}) 1681 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.94 (1H, s), 4.35 (2H, q, *J*=7.1 Hz), 3.88-3.84 (4H, m), 3.88 (3H, s), 3.23-3.19 (4H, m), 1.39 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.3, 142.1, 139.3, 117.1, 116.3, 113.8, 67.2, 60.3, 53.3, 35.9, 14.6. HRMS-ESI (m/z) calcd for $C_{14}H_{17}BrN_2O_3S$ $[M+H]^+$ 373.0216, found 373.0222.



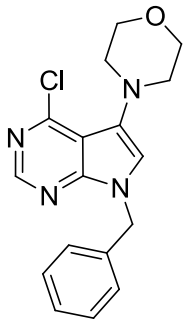
Ethyl 2-bromo-6-[(cyclopropylmethyl)amino]-4-methyl-4*H*-thieno[3,2-b]pyrrole-5-carboxylate (14c). Following the general procedure, thieno[3,2-*b*]pyrrole **14sm** (144 mg, 0.50 mmol) was converted into **14c**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **14c** as a yellow oil (111 mg, 62% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.60. IR (film, cm^{-1}) 3385 (NH), 1684 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 6.87 (1H, s), 6.01-5.71 (1H, m), 4.34 (2H, q, *J*=7.1 Hz), 3.78 (3H, s), 3.19 (2H, dd, *J*=6.2, 6.2 Hz), 1.39 (3H, t, *J*=7.1 Hz), 1.14-1.06 (1H, m), 0.56-0.50 (2H, m), 0.27-0.23 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.1, 143.6, 139.8, 117.5, 114.0, 108.7, 108.4, 59.6, 50.9, 35.2, 14.8, 12.0, 3.4. HRMS-ESI (m/z) calcd for $C_{14}H_{18}BrN_2O_2S$ $[M+H]^+$ 357.0267, found 357.0264.



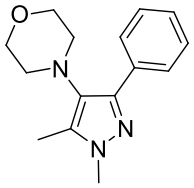
Ethyl 5-chloro-3-[(cyclopropylmethyl)amino]-1-methyl-1*H*-pyrrolo[2,3-b]pyridine-2-carboxylate (15). Following the general procedure, 1*H*-pyrrolo[2,3-b]pyridine **15sm** (119 mg, 0.50 mmol) was converted into **15**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **15** as a yellow powder (120 mg, 78% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.46. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 82-83 °C. IR (film, cm^{-1}) 3362 (NH), 1667 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.32 (1H, d, *J*=2.3 Hz), 8.06 (1H, d, *J*=2.3 Hz), 6.42-6.27 (1H, m), 4.40 (2H, q, *J*=7.2 Hz), 3.95 (3H, s), 3.40 (2H, d, *J*=6.4 Hz), 1.43 (3H, t, *J*=7.2 Hz), 1.19-1.09 (1H, m), 0.63-0.54 (2H, m), 0.34-0.25 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 163.5, 146.7, 146.2, 137.1, 130.4, 121.3, 111.1, 109.6, 60.3, 51.3, 31.1, 14.6, 11.8, 3.6. HRMS-ESI (m/z) calcd for $C_{15}H_{19}ClN_3O_2$ $[M+H]^+$ 308.1160, found 308.1155.



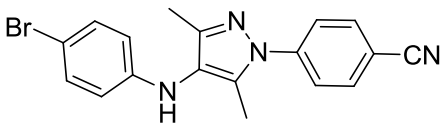
5-Bromo-1-methyl-3-morpholin-4-yl-1*H*-pyrrolo[2,3-b]pyridine (16). Following the general procedure, 5-bromo-1-methyl-1*H*-pyrrolo[2,3-b]pyridine **16sm** (106 mg, 0.50 mmol) was converted into **16**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 75% EtOAc/petroleum ether afforded **16** as a pink oil (92 mg, 62% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.26. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, d, *J*=2.2 Hz), 8.01 (1H, d, *J*=2.2 Hz), 6.68 (1H, s), 3.92-3.87 (4H, m), 3.79 (3H, s), 3.04-2.99 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 145.1, 143.9, 129.4, 129.0, 116.4, 116.0, 110.3, 67.0, 52.9, 31.2. HRMS-ESI (m/z) calcd for $C_{12}H_{15}BrN_3O$ $[M+H]^+$ 296.0393, found 296.0405.



7-Benzyl-4-chloro-5-morpholin-4-yl-7*H*-pyrrolo[2,3-d]pyrimidine (17). Following the general procedure, 7-benzyl-4-chloro-7*H*-pyrrolo[2,3-d]pyrimidine (122 mg, 0.50 mmol) was converted into **17**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded **17** as a pink oil (99 mg, 60% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.16 (**product is unstable!**). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (1H, s), 7.34-7.29 (3H, m), 7.24-7.20 (2H, m), 6.96 (1H, m), 5.36 (2H, s), 3.90-3.85 (4H, m), 3.73-3.68 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 159.7, 151.6, 150.8, 136.6, 129.0, 128.2, 127.9, 122.7, 103.9, 103.3, 67.1, 50.3, 48.2. HRMS-ESI (m/z) calcd for $C_{17}H_{18}ClN_4O$ $[M+H]^+$ 329.1164, found 329.1161.

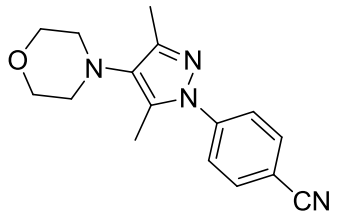


4-(1,5-Dimethyl-3-phenyl-1*H*-pyrazol-4-yl)morpholine (18). Following the general procedure, pyrazole **18sm** (86 mg, 0.50 mmol) was converted into **18**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **18** as a pink powder (67 mg, 52% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.26. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 125-126 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.97-7.87 (2H, m), 7.42-7.33 (2H, m), 7.32-7.27 (1H, m), 3.80-3.74 (7H, m), 3.05-2.99 (4H, m), 2.34 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 145.0, 134.7, 134.1, 129.7, 128.2, 127.6, 127.3, 68.0, 52.3, 36.7, 10.7. Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33 Found: C, 69.62; H, 7.53; N, 16.21.

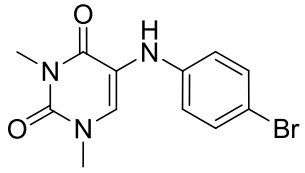


4-{4-[(4-Bromophenyl)amino]-3,5-dimethyl-1*H*-pyrazol-1-yl}benzonitrile (19a). Following the general procedure, pyrazole **19sm** (99 mg, 0.50 mmol) was converted into **19a**. Purification of the

crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **19a** as a white powder (110 mg, 60% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 123-124 °C. IR (film, cm^{-1}) 3369 (NH), 2228 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81-7.74 (2H, m), 7.70-7.64 (2H, m), 7.29-7.26 (2H, m), 6.52-6.46 (2H, m), 5.00 (1H, s), 2.30 (3H, s), 2.17 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 149.0, 146.1, 143.6, 136.9, 133.4, 132.2, 123.5, 121.9, 118.5, 114.7, 110.3, 110.1, 11.5, 11.3. HRMS-ESI (m/z) calcd for $C_{18}H_{16}BrN_4$ $[M+H]^+$ 367.0553, found 367.0550.

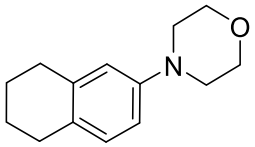


4-(3,5-Dimethyl-4-morpholin-4-yl-1*H*-pyrazol-1-yl)benzonitrile (19b). Following the general procedure, pyrazole **19sm** (99 mg, 0.50 mmol) was converted into **19b**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 45% EtOAc/petroleum ether afforded **19b** as a white powder (88 mg, 62% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.33. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 132-133 °C. IR (film, cm^{-1}) 2227 (C≡N); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74-7.68 (2H, m), 7.61-7.55 (2H, m), 3.83-3.75 (4H, m), 3.05-2.97 (4H, m), 2.35 (3H, s), 2.33 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 147.3, 143.7, 134.9, 133.2, 133.0, 123.6, 118.5, 109.9, 68.0, 52.3, 13.4, 11.3. HRMS-ESI (m/z) calcd for $C_{16}H_{19}N_4O$ $[M+H]^+$ 283.1553, found 283.1547.

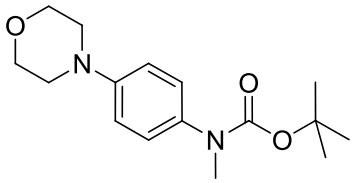


5-[(4-Bromophenyl)amino]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (20). Following the general procedure, pyrimidine-2,4(1*H*,3*H*)-dione **20sm** (70 mg, 0.50 mmol) was converted into **20**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 10% EtOAc/petroleum ether to 70% EtOAc/petroleum ether afforded **20** as a brown powder (101 mg, 65% yield); analytical TLC on silica gel, 1:1 EtOAc/petroleum ether, R_f=0.51. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 213-214 °C. IR (film, cm^{-1}) 3338 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39-7.33 (2H, m), 7.05

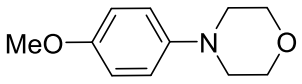
(1H, s), 6.86-6.80 (2H, m), 5.85 (1H, s), 3.42 (3H, s), 3.41 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 161.2, 150.1, 141.8, 132.5, 124.4, 118.9, 118.5, 113.4, 37.3, 28.7. HRMS-ESI (m/z) calcd for $C_{12}H_{13}BrN_3O_2$ $[M+H]^+$ 310.0186, found 310.0171.



4-(5,6,7,8-Tetrahydronaphthalen-2-yl)morpholine (21). Following the general procedure, 1,2,3,4-tetrahydronaphthalene (68 μL, 0.50 mmol) was converted into **21**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **21** as a pale yellow oil (45 mg, 41% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.56. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.99 (1H, d, J=8.4 Hz), 6.72 (1H, dd, J=8.4, 2.6 Hz), 6.64 (1H, d, J=2.6 Hz), 3.90–3.83 (4H, m), 3.15-3.07 (4H, m), 2.78–2.67 (4H, m), 1.83-1.75 (4H, m).

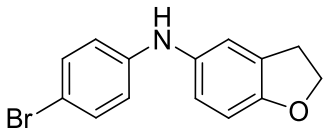


***tert*-Butyl methyl(4-morpholin-4-ylphenyl)carbamate (22).** Following the general procedure, **22sm** (104 mg, 0.50 mmol) was converted into **22**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **22** as a gray powder (44 mg, 30% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.28. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 109-110 ºC. IR (film, cm^{-1}) 1697 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.16–7.08 (2H, m), 6.87–6.83 (2H, m), 3.87–3.83 (4H, m), 3.21 (3H, s), 3.15–3.11 (4H, m), 1.43 (9H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.3, 149.1, 136.5, 126.6, 115.9, 80.1, 67.0, 49.7, 39.7, 28.5. HRMS-ESI (m/z) calcd for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ 293.1860, found 293.1867.

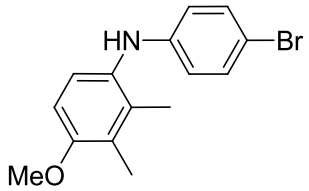


4-(4-Methoxyphenyl)morpholine (23). Following the general procedure, anisole (54 μL, 0.50 mmol) was converted into **23**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **23** as a white powder (50 mg, 52% yield); analytical TLC on silica

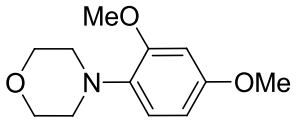
gel, 1:3 EtOAc/petroleum ether, R_f=0.40. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 70-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.92-6.83 (4H, m), 3.88-3.84 (4H, m), 3.77 (3H, s), 3.07-3.03 (4H, m).



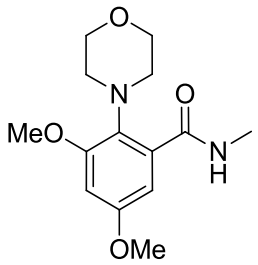
***N*-(4-Bromophenyl)-2,3-dihydro-1-benzofuran-5-amine (24).** Following the general procedure, 2,3-dihydro-benzofuran (60 mg, 0.50 mmol) was converted into **24**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 25% EtOAc/petroleum ether afforded **24** as a brown oil (71 mg, 49% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.68. IR (film, cm^{-1}) 3398 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29-7.24 (2H, m, overlapped with $CHCl_3$), 7.01-6.98 (1H, m), 6.86 (1H, dd, *J*=8.4, 2.3 Hz), 6.75-6.70 (3H, m), 5.42 (1H, s), 4.58 (2H, t, *J*=8.7 Hz), 3.19 (2H, t, *J*=8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 156.6, 145.2, 134.9, 132.1, 128.3, 122.3, 119.6, 116.8, 110.8, 109.8, 71.5, 30.1. HRMS-ESI (m/z) calcd for $C_{14}H_{13}BrNO$ $[M+H]^+$ 290.0175, found 290.0170.



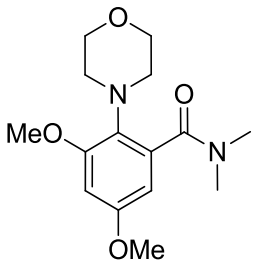
***N*-(4-Bromophenyl)-4-methoxy-2,3-dimethylaniline (25).** Following the general procedure, 4-methoxy-2,3-dimethylaniline (68 mg, 69 μL, 0.50 mmol) was converted into **25**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 35% EtOAc/petroleum ether afforded **25** as a white powder (85 mg, 56% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.50. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 105-106 °C. IR (film, cm^{-1}) 3372 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26-7.21 (2H, m), 7.01 (1H, d, *J*=8.6 Hz), 6.73 (1H, d, *J*=8.6 Hz), 6.52-6.47 (2H, m), 5.25 (1H, s), 3.84 (3H, s), 2.21 (3H, s), 2.14 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.4, 146.4, 134.5, 132.6, 132.0, 126.5, 123.6, 115.8, 109.9, 108.6, 55.9, 14.6, 12.5. Anal. Calcd for $C_{15}H_{16}BrNO$: C, 58.84; H, 5.27; N, 4.57 Found: C, 58.72; H, 5.19; N, 4.47.



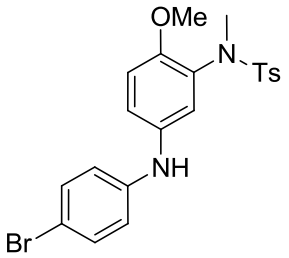
4-(2,4-Dimethoxyphenyl)morpholine (26). Following the general procedure, 1,3-dimethoxybenzene (69 mg, 65 μL, 0.50 mmol) was converted into **26**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **26** as a white powder (68 mg, 61% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.55. Pure material was obtained by crystallization from diethylether/petroleum ether: mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.85 (1H, d, *J*=8.6 Hz), 6.49 (1H, d, *J*=2.6 Hz), 6.43 (1H, dd, *J*=8.6, 2.6 Hz), 3.90–3.86 (4H, m), 3.84 (3H, s), 3.78 (3H, s), 3.01–2.96 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 156.4, 153.5, 135.1, 118.5, 103.5, 100.1, 67.4, 55.6, 55.6, 51.8. HRMS-ESI (m/z) calcd for $C_{12}H_{18}NO_3$ $[M+H]^+$ 224.1281, found 224.1285.



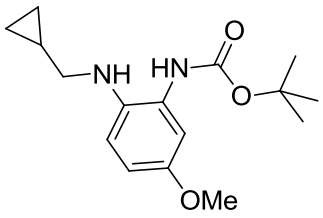
3,5-Dimethoxy-*N*-methyl-2-morpholin-4-ylbenzamide (27). Following the general procedure, **27sm** (98 mg, 0.50 mmol) was converted into **27**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 15% EtOAc/DCM to 100% EtOAc afforded **27** as a pale yellow solid (100 mg, 71% yield); analytical TLC on silica gel, 1:10 MeOH/DCM, R_f=0.24. Pure material was obtained by crystallization from diethylether/cyclohexane: mp 123–124 °C. IR (film, cm^{-1}) 3151 (NH), 1652 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.88–9.81 (1H, m), 6.89 (1H, d, *J*=2.8 Hz), 6.67 (1H, d, *J*=2.8 Hz), 3.82 (3H, s), 3.75 (3H, s), 3.67–3.62 (4H, m), 3.12-2.93 (4H, m), 2.82 (3H, d, *J*=4.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 166.5, 159.2, 157.6, 134.5, 130.3, 104.4, 101.7, 67.2, 55.8, 55.4, 49.9, 25.6. HRMS-ESI (m/z) calcd for $C_{14}H_{21}N_2O_4$ $[M+H]^+$ 281.1496, found 281.1487.



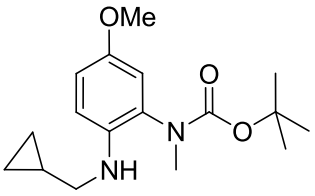
3,5-Dimethoxy-*N*,*N*-dimethyl-2-morpholin-4-ylbenzamide (28). Following the general procedure, **28sm** (105 mg, 0.50 mmol) was converted into **28**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 15% EtOAc/DCM to 100% EtOAc afforded **28** as a pale yellow solid (110 mg, 74% yield); analytical TLC on silica gel, 1:10 MeOH/DCM, R_f=0.19. Pure material was obtained by crystallization from diethylether/cyclohexane: mp 107–108 °C. IR (film, cm^{-1}) 1640 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.55 (1H, d, *J*=2.8 Hz), 6.24 (1H, d, *J*=2.8 Hz), 3.79 (3H, s), 3.73 (3H, s), 3.56-3.49 (4H, m), 3.09-2.99 (2H, m), 2.97 (3H, s), 2.87-2.79 (2H, m), 2.72 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 169.3, 158.6, 158.0, 138.9, 128.5, 101.7, 99.7, 67.3, 55.5, 55.4, 50.8, 37.9, 33.7. HRMS-ESI (m/z) calcd for $C_{15}H_{23}N_2O_4$ $[M+H]^+$ 295.1652, found 295.1647.



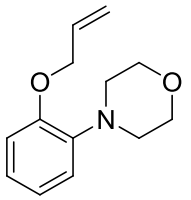
***N*-{5-[(4-Bromophenyl)amino]-2-methoxyphenyl}-*N*,4-dimethyl-benzenesulfon–amide (29).** Following the general procedure, **29sm** (146 mg, 0.50 mmol) was converted into **29**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 15% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **29** as a pink solid (138 mg, 60% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.52. Pure material was obtained by crystallization from diethylether/cyclohexane: mp 187–188 °C. IR (film, cm^{-1}) 3402 (NH), 1330 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.62–7.57 (2H, m), 7.31–7.27 (2H, m), 7.26–7.23 (2H, m), 7.06 (1H, d, *J*=2.8 Hz), 7.01 (1H, dd, *J*=8.8, 2.8 Hz), 6.81–6.76 (2H, m), 6.73 (1H, d, *J*=8.8 Hz), 5.54 (1H, s), 3.41 (3H, s), 3.19 (3H, s), 2.42 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 152.2, 143.6, 143.0, 136.7, 135.4, 132.3, 129.9, 129.2, 127.8, 124.1, 121.2, 117.7, 112.6, 111.8, 55.4, 38.0, 21.6. HRMS-ESI (m/z) calcd for $C_{21}H_{22}BrN_2O_3S$ $[M+H]^+$ 461.0529, found 461.0556.



***tert*-Butyl 2-[(cyclopropylmethyl)amino]-5-methoxyphenylcarbamate (30).** Following the general procedure, **30sm** (112 mg, 0.50 mmol) was converted into **30**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether afforded **30** as a white powder (58 mg, 40% yield); analytical TLC on silica gel, 1:3 EtOAc/petroleum ether, R_f=0.38. Pure material was obtained by crystallization from diethylether/cyclohexane: mp 118–119 °C dec. IR (film, cm^{-1}) 3327 (NH), 1715 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.15–6.96 (1H, m), 6.64 (1H, dd, *J*=8.3, 2.1 Hz), 6.48 (1H, d, *J*=8.3 Hz), 6.35–6.19 (1H, m), 4.20–4.06 (1H, m), 3.86 (3H, s), 2.93 (2H, d, *J*=7.0 Hz), 1.50 (9H, s), 1.16–1.07 (1H, m), 0.57–0.51 (2H, m), 0.25–0.20 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 153.4, 147.1, 135.0, 128.4, 112.0, 110.0, 103.0, 80.1, 55.7, 49.3, 28.6, 11.1, 3.7. HRMS-ESI (m/z) calcd for $C_{16}H_{25}N_2O_3$ $[M+H]^+$ 277.1911, found 277.1921.

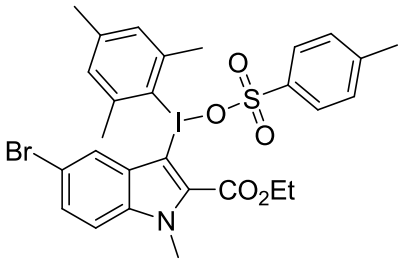


***tert*-Butyl {2-[(cyclopropylmethyl)amino]-5-methoxyphenyl}methylcarbamate (31).** Following the general procedure, **31sm** (119 mg, 0.50 mmol) was converted into **31**. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from 0% EtOAc/petroleum ether to 30% EtOAc/petroleum ether afforded **31** as a brown oil (75 mg, 50% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.56. IR (film, cm^{-1}) 3210 (NH), 1645 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.70–6.61 (2H, m), 6.48 (1H, d, *J*=8.3 Hz), 4.47–4.02 (1H, br s), 3.84 (3H, s), 3.20 (3H, s), 2.95 (2H, d, *J*=7.0 Hz), 1.43 (9H, s), 1.17–1.08 (1H, m), 0.58–0.52 (2H, m), 0.27–0.21 (2H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.5, 146.5, 136.6, 133.4, 118.4, 109.2, 108.4, 79.7, 55.6, 49.0, 38.1, 28.6, 11.0, 3.6. HRMS-ESI (m/z) calcd for $C_{17}H_{27}N_2O_3$ $[M+H]^+$ 307.2016, found 307.2009.



4-[2-(Prop-2-en-1-yloxy)phenyl]morpholine (34). An oven-dried flask was charged with phenyliodonium tosylate **32** (275 mg, 0.50 mmol), $Cu(MeCN)_4BF_4$ (157 mg, 0.50 mmol, 1 equiv) and flushed with argon. Anhydrous CH_2Cl_2 (4 mL) was added, followed by morpholine (72 μL, 0.60 mmol, 1.2 equiv), DIPEA (174 μL, 1.00 mmol, 2 equiv) and DMSO (1 mL). The resulting solution was stirred at room temperature under argon atmosphere and the progress of the reaction was monitored by TLC (disappearance of spot of λ^3-iodane **32**, R_f=0.45, 20:80:5 MeOH/CH_2Cl_2/AcOH). Full conversion of reaction was observed in 90 min. The solution was poured into water (50 mL) and saturated aqueous ammonia solution (20 mL), and extracted with CH_2Cl_2 (3x30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (Biotage M+12 column) using gradient elution from petroleum ether to 10% EtOAc/petroleum ether afforded product as a colorless oil (75 mg, 68% yield); analytical TLC on silica gel, 1:5 EtOAc/petroleum ether, R_f=0.38. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.01-6.93 (3H, m), 6.90-6.85 (1H, m), 6.09 (1H, ddt, *J*=17.4, 10.6, 5.0 Hz), 5.43 (1H, dq, *J*=17.4, 1.6 Hz), 5.28 (1H, dq, *J*=10.6, 1.6 Hz), 4.59 (2H, dt, *J*=5.0, 1.6 Hz) 3.91-3.87 (4H, m), 3.12-3.08 (4H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 151.3, 141.6, 133.5, 123.1, 121.6, 118.3, 117.1, 113.3, 69.1, 67.4, 51.3. HRMS-ESI (m/z) calcd for $C_{13}H_{18}NO_2$ $[M+H]^+$ 220.1332, found 220.1315.

Experimental for Synthesis of Indolyliodonium Tosylates 2a

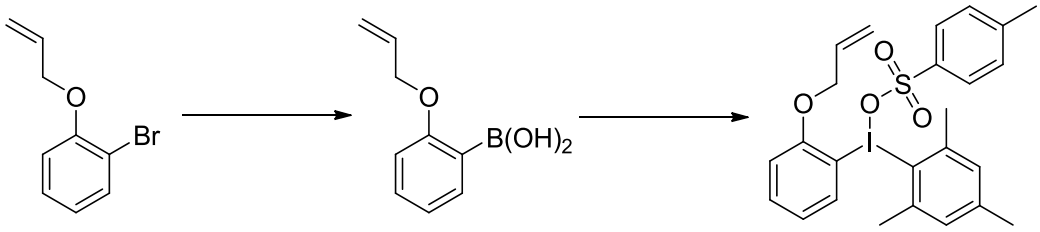


General Procedure.

Ethyl 5-bromo-1-methyl-3-({[(4-methylphenyl)sulfonyl]oxy}(2,4,6-trimethylphe–nyl)-λ^3-iodanyl)-1*H*-indole-2-carboxylate (2a). To a solution of MesI(OH)OTs (2.39 g, 5.50 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added TsOH●H_2O (1.05 g, 5.50 mmol, 1.1 equiv) and the resulting suspension was stirred for 5 min at room temperature. Then, a solution of indole **1a** (1.41 g, 5.00

mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added rapidly to the well-stirred suspension. The progress of the reaction was monitored by TLC (disappearance of the starting material spot, R_f=0.55, 1:5 EtOAc/petroleum ether) and complete conversion of the starting **1a** was observed within 30 min. Solvent was concentrated to ca. 2/3 of the original volume and Et_2O was added (50 mL). Formed precipitate was filtered, washed with Et_2O (100 mL) and dried *in vacuo* to afford **2a** as a white powder (3.30 g, 95% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f=0.49. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 125 °C dec. IR (film, cm^{-1}) 1710 (C=O), 1206 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.79 (1H, d, *J*=9.0 Hz), 7.61 (1H, dd, *J*=9.0, 1.8 Hz), 7.48-7.43 (3H, m), 7.21-7.16 (2H, m), 7.10 (2H, d, *J*=8.0 Hz), 4.45 (2H, q, *J*=7.2 Hz), 4.08 (3H, s), 2.58 (6H, s), 2.28 (6H, s), 1.38 (3H, t, *J*=7.2 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6, ppm) δ 159.4, 145.8, 142.9, 141.9, 137.5, 137.2, 131.8, 129.8, 128.1, 128.0, 125.5, 122.7, 121.7, 115.7, 115.1, 81.2, 62.8, 33.8, 26.1, 20.8, 20.4, 13.8. HRMS-ESI (m/z) calcd for $C_{21}H_{22}BrINO_2$ $[M\text{-}OTs]^+$ 525.9873, found 525.9861.

Experimental for Synthesis of Phenyliodonium Tosylate 32



{[(4-Methylphenyl)sulfonyl]oxy}[2-(prop-2-en-1-yloxy)phenyl](2,4,6-trimethyl–phenyl)-λ^3-iodane (32). 1-Allyloxy-2-bromobenzene (2.30 g, 10.79 mmol) was converted to boronic acid in accordance with literature procedure.[27] The boronic acid (400 mg, 2.25 mmol) was then converted to the iodonium salt **32** in accordance with literature procedure.[28] After drying *in vacuo* **32** was obtained as a white powder (943 mg, 76% yield); analytical TLC on silica gel, 20:80:5 MeOH/CH_2Cl_2/AcOH, R_f=0.45. Pure material was obtained by crystallization from CH_2Cl_2/diethylether: mp 170-171 °C dec. IR (film, cm^{-1}) 1193 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.14 (1H, dd, *J*=8.0, 1.6 Hz), 7.60 (1H, ddd, *J*=8.4, 7.4, 1.6 Hz), 7.48-7.43 (2H, m), 7.26 (1H, dd, *J*=8.4, 1.2 Hz), 7.15 (2H, s), 7.12-7.08 (2H, m), 7.06 (1H, ddd, *J*=8.0, 7.4, 1.2 Hz), 5.94-5.84 (1H, m), 5.29-5.26 (1H, m), 5.25-5.22 (1H, m), 4.75-4.72 (2H, m), 2.58 (6H, s), 2.28 (3H, s), 2.27 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, ppm) δ 155.6, 143.9, 142.9, 139.1, 133.1, 131.5, 131.2,

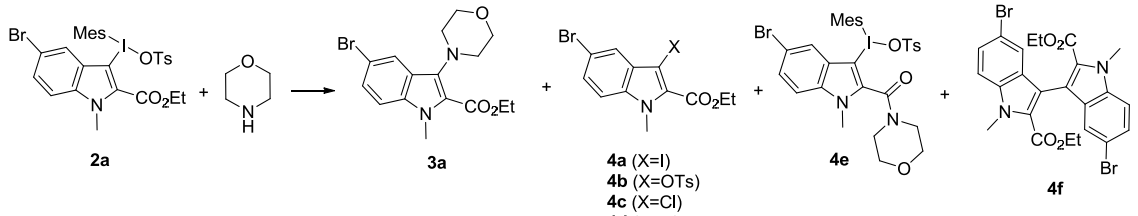
([27]) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1673.

([28]) Chen, D.-W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804.

130.1, 128.4, 126.0, 124.3, 120.0, 113.7, 101.9, 70.8, 27.2, 21.4, 21.2. HRMS-ESI (m/z) calcd for $C_{18}H_{20}IO$ $[M\text{-}OTs]^+$ 379.0553, found 379.0567.

Optimization of Reaction of λ^3-Iodane 2a with Morpholine

Table S1. Complete survey of optimization experiments for the reaction of λ^3-iodane **2a** with morpholine



entry	catalyst (10 mol%)	base (equiv.)	solvent	time (h)	conversion %[a,b]	**3a**:**4a** ratio, (yield %)[b,c]	other products (%)[b]
1	none	DIPEA (2.0)	MeCN	24	11	1:99 (6)	**2a** (88), **4e** (5)
2	none	DIPEA (2.0)	CH_2Cl_2	24	15	1:99 (8)	**2a** (85), **4e** (6)
3	none	DIPEA (2.0)	DMSO	24	81	1:99 (67)	**2a** (19), **4e** (6)
4	none	DIPEA (2.0)	MeCN-DMSO 1:1	24	78	1:99 (60)	**2a** (22), **4e** (8)
5	CuOTf□•PhH	DIPEA (2.0)	CH_2Cl_2	1.5	30	84:16 (10)	**4b** (9), **4f** (7)
6	CuOTf□•PhH	DIPEA (2.0)	DMSO	1.5	60	96:4 (53)	**2a** (37)
7	CuOTf□•PhH	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	60	97:3 (46)	**4a** (3), **4b** (3)
8	CuOTf□•PhH	DIPEA (2.0)	MeCN-DMSO 1:1	1.5	80	98:2 (72)	**2a** (17)
9	CuI	DIPEA (2.0)	MeCN-DMSO 1:1	1.5	90	83:17 (71)	**2a** (7)
10	CuCl	DIPEA (2.0)	MeCN-DMSO 1:1	1.5	85	84:16 (66)	**4c** (10), **2a** (12)
11	$CuOCOCF_3$	DIPEA (2.0)	MeCN-DMSO 1:1	1.5	87	97:3 (82)[d]	**2a** (10)
12	$Cu(MeCN)_4BF_4$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1	92	97:3 (85)[d]	**2a** (5)
13	$Cu(OTf)_2$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	22	93:7 (14)	**2a** (75)
14	$Cu(OTf)_2$	DIPEA (2.0)	CH_2Cl_2	1.5	14	82:18 (9)	**4b** (2), **2** (85)
15	$Cu(OTf)_2$	DIPEA (2.0)	MeCN-DMSO 1:1	24	45	80:20 (*12*)	**4e** (20), **2a** (54)
16	CuOTf□•PhH	none	MeCN-DMSO 1:1	1.5	63	98:2 (51)	**2a** (35)
17	CuOTf□•PhH	morpholine (3.2)	MeCN-DMSO 1:1	1.5	75	98:2 (66)	**2a** (35)
18	CuOTf□•PhH	K_3PO_4 (2.5)	MeCN-DMSO 1:1	1.5	70	95:5 (54)	**2a**, (30)
19	CuOTf□•PhH	K_2CO_3 (2.5)	MeCN-DMSO 1:1	1.5	80	93:7 (60)	**2a**, (20)
20[e]	$Cu(MeCN)_4BF_4$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	93	89:11 (76)	**2a** (5)
21	$Pd(OCOCF_3)_2$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	5	1:99 (3)	**2a** (95)
22	$Ni(OTf)_2$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	5	1:99 (5)	**2a** (95)
23	$Sc(OTf)_3$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	7	1:99 (5)	**2a** (93)
24	$Os(NH_3)_5(OTf)_3$	DIPEA (2.0)	CH_2Cl_2-DMSO 4:1	1.5	10	1:99 (9)	**2a** (90)

[a] Conditions: λ^3-iodane **2a** (1.0 equiv.), morpholine (1.2 equiv.), solvent (10 mL/1 mmol of **2a**), room temperature. [b] Determined by LC-MS assay. [c] Yields correspond to the major product. [d] Isolated yields of >95% pure indole **3a**. [e] λ^3-Iodane **2a'** possessing Ph moiety instead of a mesityl ligand was used.

Kinetic Experiments

Order of the Reaction in Cu(I) Catalyst

The order in Cu(I) catalyst was determined by studying the initial rates of the **3a** formation at 23 °C in DMSO-d_6 at various concentrations of $(CuOTf)_2$●PhH.

Experimental. To the iodonium salt **2a** (17.5 mg, 0.025 mmol) was added a certain amount of $(CuOTf)_2$●PhH stock solution [prepared by dissolving $(CuOTf)_2$●PhH (15.75 mg, 0.031 mmol) in degassed DMSO-d_6 (5 mL)], followed with degassed DMSO-d_6 (for volumes of the stock solution and amounts of DMSO-d_6, morpholine see Table S2).

Table S2. Volumes of the $(CuOTf)_2$●PhH stock solution, DMSO-d_6 and morpholine used in experiments to measure the reaction order in $(CuOTf)_2$●PhH

entry	$(CuOTf)_2$●PhH, mol%	Volume of stock solution, µL	Volume of DMSO-d_6, µL	Volume of morpholine, µL
1	5.00	100	900	3
2	7.50	150	850	3
3	10.00	200	800	3
4	12.50	250	750	3
5	15.00	300	700	3
6	17.50	350	650	3
7	20.00	400	600	3

The amount of 3-morpholin-4-yl-1*H*-indole **3a** was determined by integrating a peak at 3.83 ppm corresponding to the *N*-methyl group of **3a** (see Figure S1). Yields of **3a** in percents from NMR experiments were converted to concentrations and used to construct kinetic curves (see Table S3).

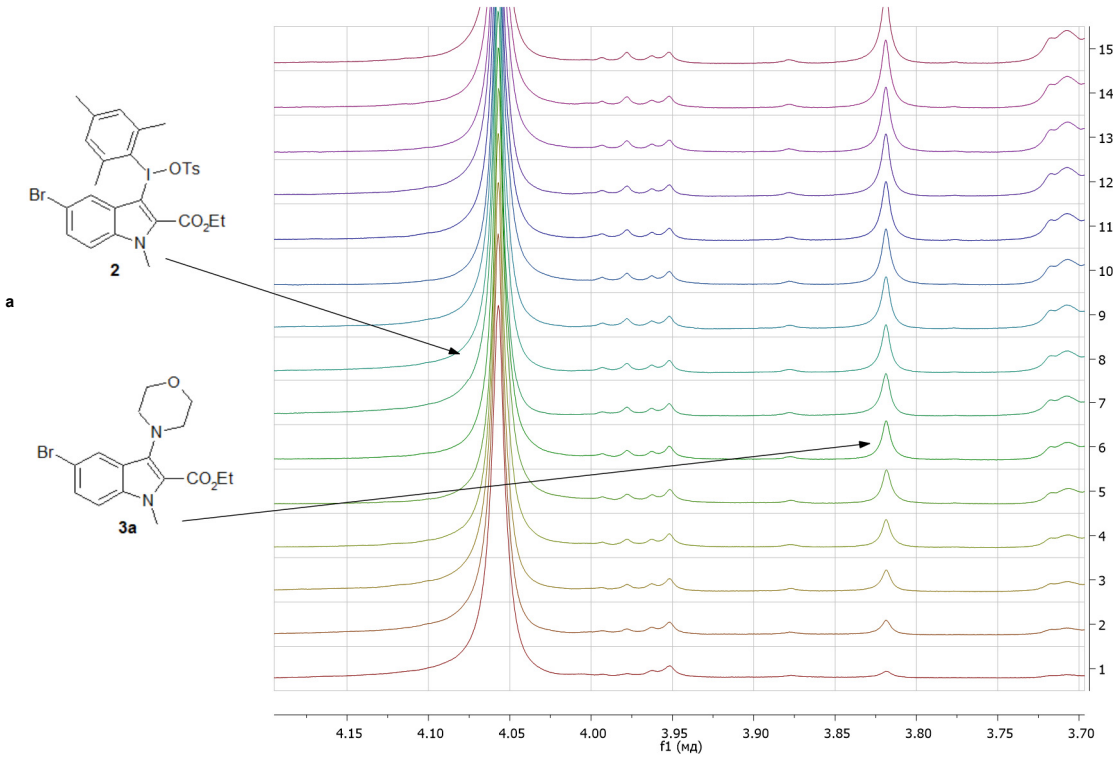


Figure S1. Kinetic profile of **3a** formation at various concentrations of $(CuOTf)_2$●PhH in DMSO-d_6 at 23 °C.

Table S3. Concentration of **3a**·(10^{-3} M) vs time in the reaction of **2a** with morpholine at various amounts of $(CuOTf)_2$●PhH

time (s)	$(CuOTf)_2$●PhH, mol%						
	5.00	**7.50**	**10.00**	**12.50**	**15.00**	**17.50**	**20.00**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
160	0.231	0.331	0.469	0.515	0.759	0.883	1.044
320	0.307	0.471	0.650	0.851	1.034	1.686	2.002
480	0.382	0.629	0.877	1.230	1.789	2.535	2.892
640	0.461	0.743	1.084	1.583	2.348	3.296	3.782
800	0.536	0.863	1.332	1.973	2.860	3.969	4.540
960	0.620	0.978	1.538	2.319	3.344	4.678	5.340
1120	0.702	1.079	1.763	2.653	3.842	5.315	6.131
1280	0.785	1.177	1.996	2.992	4.371	5.897	6.838
1440	0.841	1.319	2.234	3.314	4.846	6.511	7.462
1600	0.899	1.372	2.404	3.649	5.277	6.994	8.064
1760	0.958	1.477	2.604	3.940	5.698	7.427	8.570
1920	1.062	1.599	2.811	4.272	6.114	7.826	9.090
2080	1.130	1.703	2.992	4.566	6.489	8.241	9.628
2240	1.199	1.827	3.169	4.888	6.839	8.664	10.086
2400	1.309	1.901	3.324	5.168	7.230	8.991	10.464

Kinetic curves for reactions at various amounts of $(CuOTf)_2$●PhH were constructed by *TableCurve* software and described by equation ($y = a + b \cdot x^c$). To calculate rate coefficients $k_{obs.}$, each of the equations ($y = a + b \cdot x^c$) was differentiated by time and evaluated at x=320 sec. A plot of the initial rates ln(Δ[**3a**]/Δt) versus ln[$(CuOTf)_2$●PhH] gave a straight line (R^2=0.989), indicative of a 1st order dependence on [$(CuOTf)_2$●PhH] (see Figure S2).

The calculated k_{obs}=1.646 M●s^{-1}.

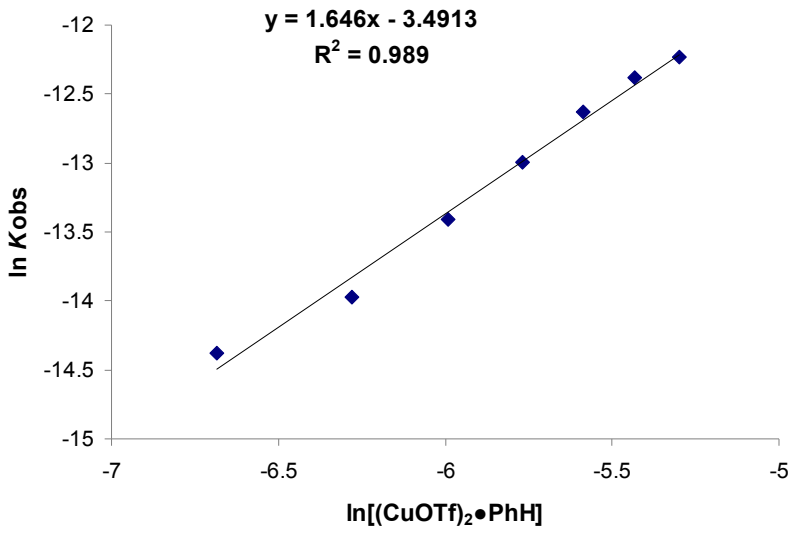


Figure S2. Plot of initial rates vs concentration of $(CuOTf)_2$●PhH in DMSO-d_6 at 23 °C.

Order of the Reaction in Morpholine

The order in morpholine was determined by measuring the initial rates of the **3a** formation at 23 °C in DMSO-d_6 at various concentrations of the morpholine.

Experimental. The iodonium salt **2a** (17.5 mg, 0.025 mmol) and morpholine (0.5–2 equiv) were placed in an NMR tube and 100 μL of the $(CuOTf)_2$●PhH stock solution [prepared by dissolving $(CuOTf)_2$●PhH (15.75 mg, 0.031 mmol) in degassed DMSO-d_6 (5 mL)] was added, followed with 900 μL of degassed DMSO-d_6.

The amount of 3-morpholin-4-yl-1*H*-indole **3a** was determined by integrating a peak at 3.83 ppm corresponding to the *N*-methyl group of **3a**. Yields of **3a** in percents were converted to concentrations and used to construct kinetic curves (see Table S4).

Table S4. Concentration of **3a**·(10^{-3} M) vs time in the reaction of **2a** with morpholine at various amounts of morpholine

time (s)	Morpholine, equiv			
	0.5	**1**	**1.5**	**2**
0	0.000	0.000	0.000	0.000
160	0.264	0.259	0.381	0.405
320	0.351	0.360	0.585	0.674
480	0.414	0.406	0.826	0.994
640	0.488	0.541	0.942	1.209
800	0.533	0.578	1.112	1.421
960	0.594	0.703	1.325	1.610
1120	0.636	0.743	1.443	1.739
1280	0.668	0.862	1.470	1.796
1440	0.683	0.946	1.572	1.919
1600	0.739	1.027	1.665	1.982
1760	0.778	1.103	1.716	2.153
1920	0.807	1.129	1.854	2.212
2080	0.838	1.219	1.948	2.327
2240	0.882	1.248	2.048	2.392
2400	0.930	1.326	2.193	2.511

Kinetic curves for reactions at various amounts of morpholine were constructed by *TableCurve* software and described by equation ($y = a + b \cdot x^c$). To calculate rate coefficients $k_{obs.}$, each of the equations ($y = a + b \cdot x^c$) was differentiated by time and evaluated at x=320 sec. A log plot of initial rate ln(Δ[**3a**]/Δt) versus ln[morpholine] gave a straight line (R^2=0.9909), indicative of a 1st order dependence on [morpholine] (see Figure S3).

The calculated k_{obs}=1.0796 M●s^{-1}.

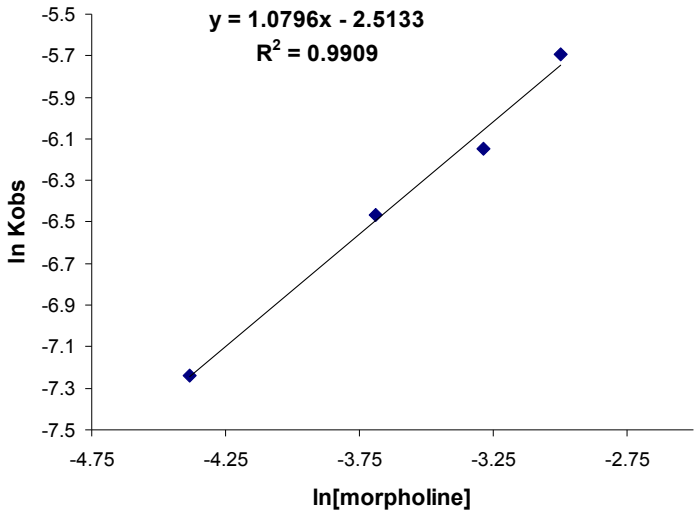


Figure S3. Plot of initial rates vs concentration of morpholine in DMSO-d_6 at 23 °C (5 mol% $(CuOTf)_2$●PhH)).

Order of the Reaction in λ^3-Iodane 2a

The order in **2a** was determined by studying the initial rates of the **3a** formation at 23 °C in DMSO-d_6 at various concentrations of iodonium salt **2a**.

Experimental. The λ^3-iodane **2a** (0.5-2 equiv) and morpholine (3 μL) were placed in an NMR tube and 150 μL of the $(CuOTf)_2$●PhH stock solution [prepared by dissolving $(CuOTf)_2$●PhH (15.75 mg, 0.031 mmol) in degassed DMSO-d_6 (5 mL)] was added, followed with 850 μL of degassed DMSO-d_6.

The amount of 3-morpholin-4-yl-1*H*-indole **3a** was determined by integrating a peak at 3.83 ppm corresponding to the *N*-methyl group of **3a**. Yields of **3a** in percents were converted to concentrations and used to construct kinetic curves (see Table S5).

Table S5. Concentration of **3a**·(10^{-3} M) vs time in the reaction of **2a** with morpholine at various amounts of λ^3-iodane **2a**

time (s)	Iodonium salt 2a, equiv			
	0.5	**1**	**1.5**	**2**
0	0.000	0.000	0.000	0.000
160	0.227	0.331	0.269	0.293
320	0.359	0.471	0.440	0.481
480	0.523	0.629	0.557	0.544
640	0.623	0.743	0.711	0.715
800	0.720	0.863	0.826	0.816
960	0.854	0.978	0.956	0.949
1120	0.966	1.079	1.071	1.003
1280	1.077	1.177	1.157	1.103
1440	1.169	1.319	1.235	1.277
1600	1.273	1.372	1.328	1.245
1760	1.353	1.477	1.427	1.321
1920	1.449	1.599	1.500	1.512
2080	1.550	1.703	1.606	1.596
2240	1.608	1.827	1.672	1.762
2400	1.706	1.901	1.764	1.851

Kinetic curves for reactions at various amounts of λ^3-iodane **2a** were constructed by *TableCurve* software and described by equation ($y = a + b \cdot x^c$). To calculate rate coefficients $k_{obs.}$, each of the equations ($y = a + b \cdot x^c$) was differentiated by time and evaluated at x=320 sec. A log plot of initial rate ln(Δ[**3a**]/Δt) versus ln[morpholine] gave a straight line (R^2=0.8889), indicative of a zeroth order dependence on [**2a**] (see Figure S4).

The calculated k_{obs}= –0.0766 M●s^{-1}.

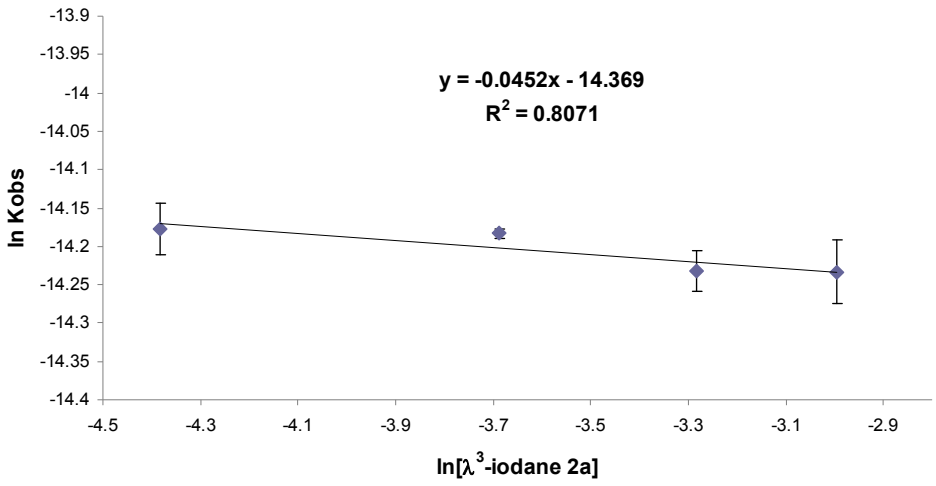


Figure S4. Plot of initial rates vs concentration of iodoium salt **2a** in DMSO-d_6 at 23 ^{o}C (7.5 mol% $(CuOTf)_2$●PhH)).

The non-catalyzed fragmentation of 2a in the presence of DIPEA and morpholine in DMSO-d_6 at 23 ^{o}C.

In an oven-dried NMR-tube iodonium salt **2a** (50 mg, 0.072 mmol) was weighted, followed by morpholine (7.5 mg, 7.5 mL, 0.086 mmol, 1.2 equiv), DIPEA (18.6 mg, 25 mL, 0.144mmol, 2 equiv) and DMSO-d_6 (1 mL) was added shortly before the beginning of ^{1}H-NMR experiment. The amount of product **4a** was determined by integrating a peak at 3.76 ppm corresponding to the *N*-methyl group of **4a** (see Figure S5).

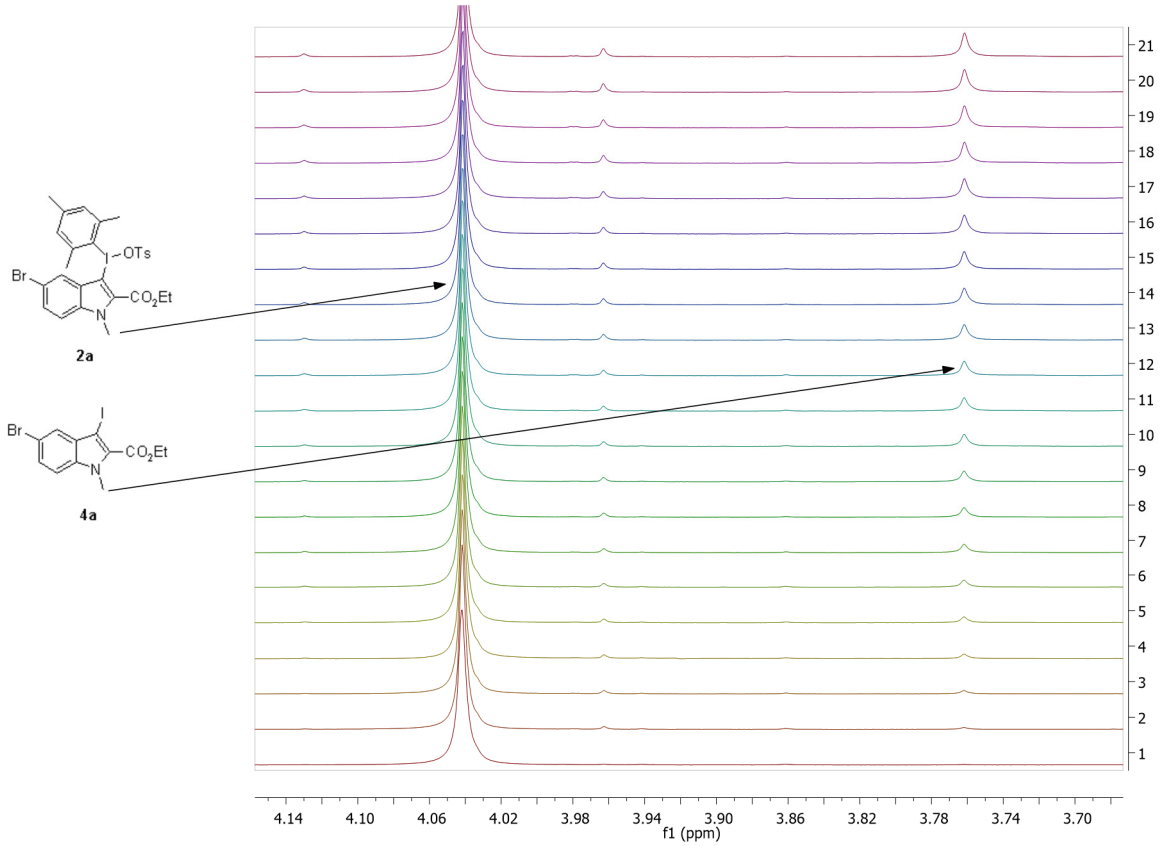


Figure S5. The non-catalyzed fragmentation **2a** in DMSO-d_6 at 23 °C.

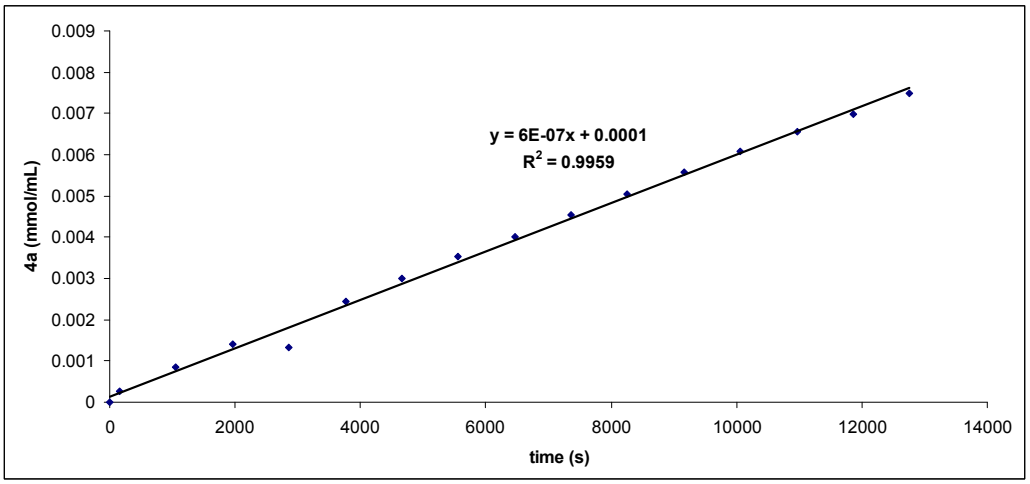


Figure S6. Kinetic data for the non-catalyzed fragmentation of **2a** in DMSO-d_6 at 23 °C.

Cyclic Voltammetry Experiments

Cyclic voltammetry measurements were made using a *PARstat 2273* instrument at a scan rate of 100 mV/s, at 23 ºC with a glassy carbon disk electrode (d = 6 mm) as the working electrode, and a saturated calomel electrode (SCE) as the reference electrode. *n*-Bu_4NBF_4 (0.1 M) was used as the supporting electrolyte. All experiments were performed in an extra-dry MeCN (freshly distilled from calcium hydride prior the use) and under atmosphere of argon. All of the potentials are reported versus SCE at a scan rate of 100 mV/s.

The cyclic voltammetry of $Cu(MeCN)_4BF_4$ (0.01 mM in 10 mL of MeCN containing 0.1 M $n$$Bu_4NBF_4$) showed reversible reduction peaks (Ep= –0.87 V and Ep= –0.51 V vs SCE) and reversible oxidation peaks (Ep= 0.85 V and 0.65 V) (see Figure S6). The reduction peak at Ep= –0.87 V was assigned to the reduction of Cu(I) to Cu(0), and the reversible peak (Ep= –0.51 V) was assigned to the oxidation of Cu(0) to Cu(I). The oxidation peak at Ep= 0.85 V was assigned to the oxidation of Cu(I) to Cu(II), whereas the reversible peak (Ep= 0.65 V) corresponds to the reduction of Cu(II) to Cu(I).

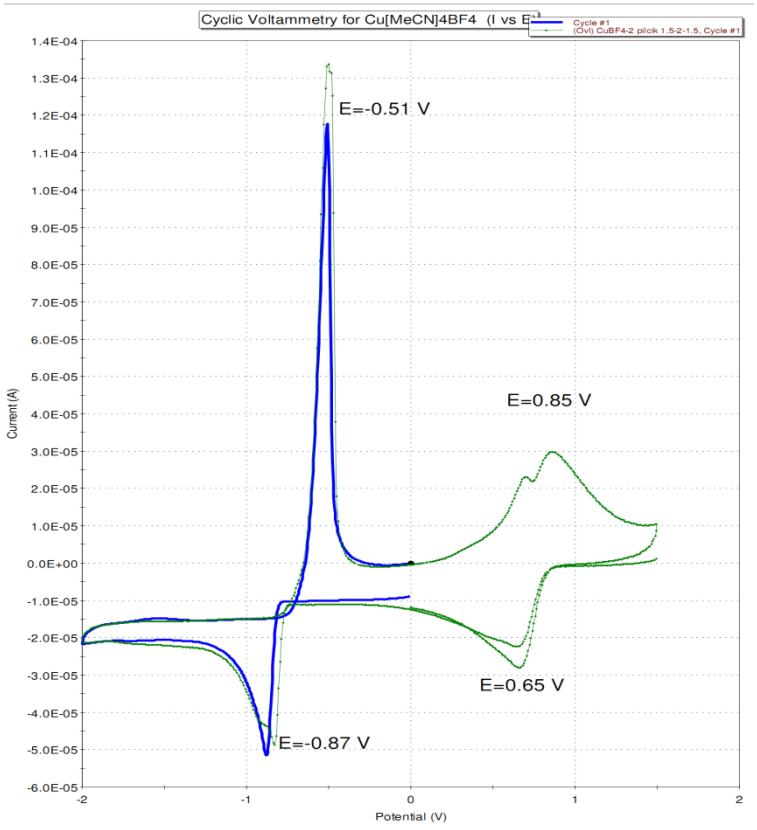


Figure S6. Cyclic voltammogram of $Cu(MeCN)_4BF_4$.

The cyclic voltammogram of iodonium salt **2a** reduction (0.01 mM in 10 mL of MeCN containing 0.1 M $n$$Bu_4NBF_4$) contained a number of irreversible peaks (Ep= –0.76 V, Ep= –1.82 V, Ep= –2.11 V and Ep= –2.34 V vs SCE) (see Figure S7). The reduction peak at Ep= –0.76 V was assigned to the reduction of iodonium salt **2a**. The other reduction peaks correspond to products of

reductive fragmentation of iodonium salt **2a**. Thus, the peak Ep= –1.82 V was assigned to 3-iodoindole **4a** (Figure S7b), the signal at Ep= –2.11 V corresponds to the reduction potential of Mes-OTs (Ep= –2.20 V; see Figure S7c) and the peak at Ep= –2.34 V was assigned to reduction of Mes–I (Ep= –2.44 V; Figure S7d).

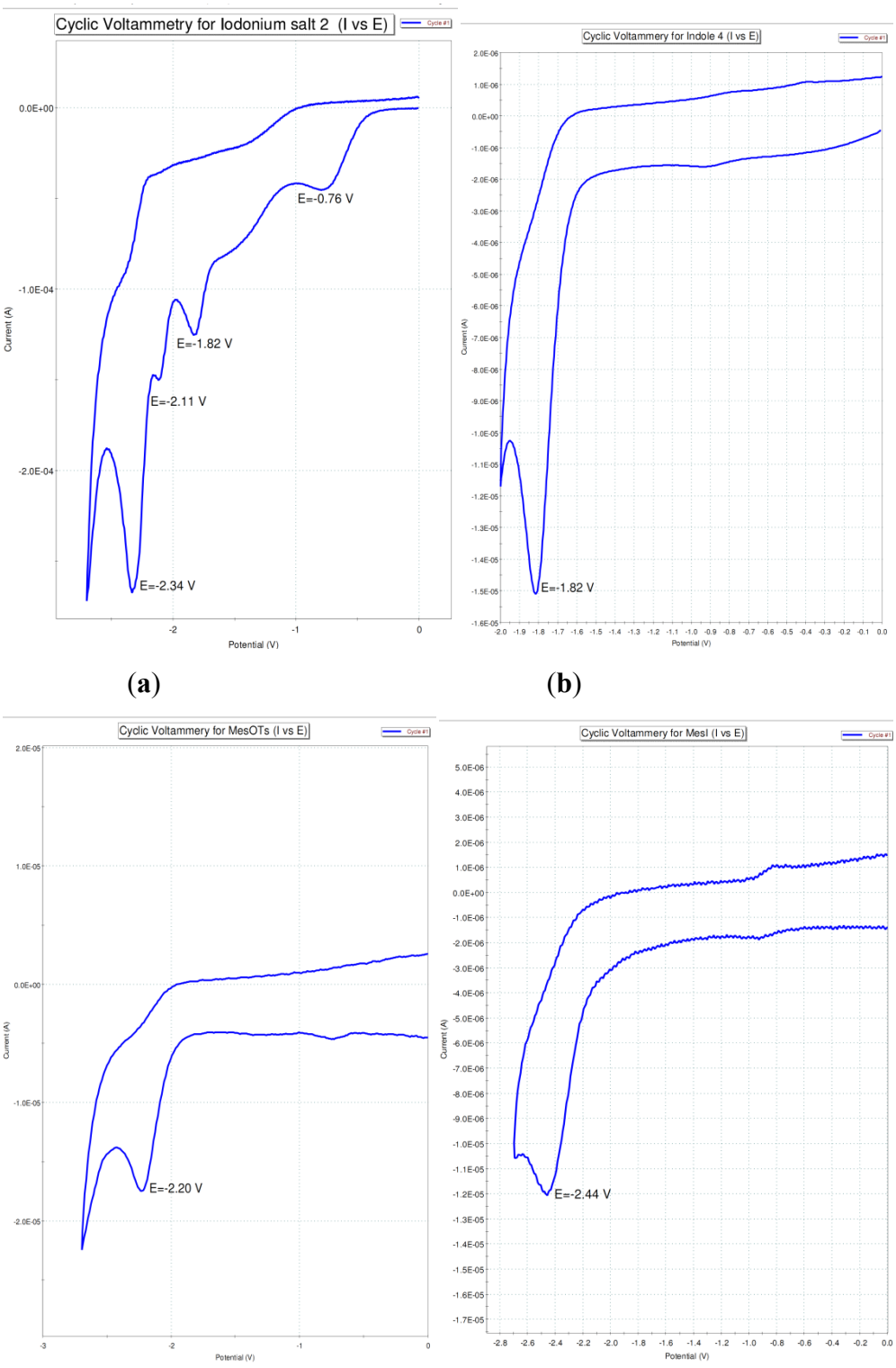
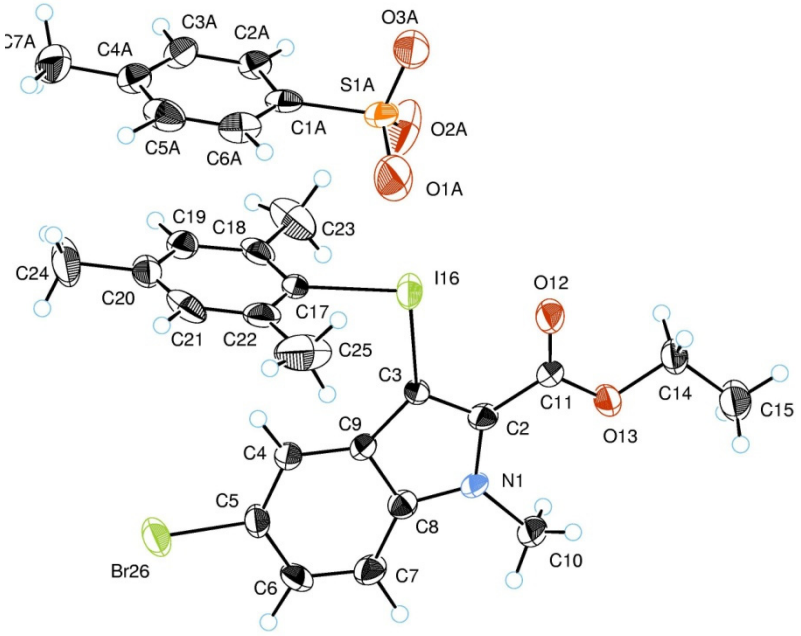


Figure S7. Voltammograms for reduction of: (**a**) iodonium salt **2a**; (b) indole **4a**; (c) Mes-I; (d) Mes-OTs.

X-Ray Structure, Crystal Data and Structure Refinements for 2a



Empirical formula	$C_{21}H_{22}BrINO_2 \cdot C_7H_7O_3S$
Formula weight	698.41
Temperature (K)	173
Radiation type	Mo *Kα*
Wavelength	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a=13.9499(5), b=13.1575(4), c=15.5683(7) Å, β=104.197(2)°
Volume (Å^3)	2770.2 (2)
Z	4
Density (calculated, g/cm^3)	1.675
μ (mm^{-1})	2.71
Crystal size (mm)	0.36 × 0.12 × 0.11
Diffractometer	Bruker-Nonius KappaCCD
Absorption correction	By Gaussian integration based on twelve indexed crystal faces
T_{min}, T_{max}	0.683, 0.742
No. of measured, independent and	11273, 6335, 3752
R_{int}	0.037
$2\theta_{max}$ (°), $(\sin\theta/\lambda)_{max}$ (Å^{-1})	55, 0.650
Index ranges	$-18 \le h \le 18$, $-15 \le k \le 17$, $-20 \le l \le 20$
$R[F^2 > 3\sigma(F^2)]$, $wR(F^2)$, S	0.064, 0.114, 1.09
R- and $wR(F^2)$-index	0.124, 0.128
No. of reflections	3735
No. of parameters	334
No. of restraints	0
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	3.73, −4.89