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Synthesis of Novel 4-Amino-tetrahydro-pyrrolo[1,2-*a*]quinazoline Derivatives

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Keywords **– Pyrrolo[1,2-*a*]quinazolines, hydrazides of cyclohexene carboxylic acids, 2-oxo-glutaric acid, stereospecific decarboxylation, amide linker**

Fused quinazolines such as pyrrolo[1,2-*a*]quinazolines are an important class of polyheterocyclic compounds found in natural alkaloids and are known to possess a variety of biological activities.

Our group is interested in the synthesis of new classes of pyrrolo[1,2-*a*] quinazoline derivatives from anthranylhydrazides of *N'*-cyclohexene dicarboxylic acids [1]. We present here the synthesis of amide-linked-conjugates between 1,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*]quinazoline-3a-carboxylic acid and 4-methyl-6-aryl-cyclohex-3-ene (**3**).

Decarboxylation of substituted monohydrazides of 6-aryl-cyclohex-3-ene 1,1-dicarboxylic acids proceeds stereospecifically and leads to 1,6-*cis*-disubstituted-cyclohex-3-enes **1**. It was found that pyridine was a far better solvent for this process than acetic acid or DMF that were described earlier.

Due to the presence of anthranilic acid moiety these decarboxylated hydrazides **1** undergo formation of pyrrolo[1,2-*a*]quinazolines **3**, when treated with 2-oxo-glutaric acid (**2**).

Differently substituted cyclohexene carboxylic acids, are interesting molecular platforms in terms of medicinal chemistry.

The target compounds **3** were obtained in good to excellent yields. Thus, for the first time *N*-substituted-4-amino-1,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*]quinazoline ring system was generated in a chemoselective process without a concurrent formation of phthalazino[1,2-*b*]quinazoline derivatives. Products **3** are obtained and characterized as a mixture of C(3a)-diastereoisomers, except for **3a** which gave separable 2.5:1 mixture of isomers. In the latter case it was possible to prove that the 1,6-*cis*-arrangement of cyclohexene unit is retained as coupling constant analysis and 2D NOESY cross peaks in product **3a** showed a pattern similar to that of **1a**.

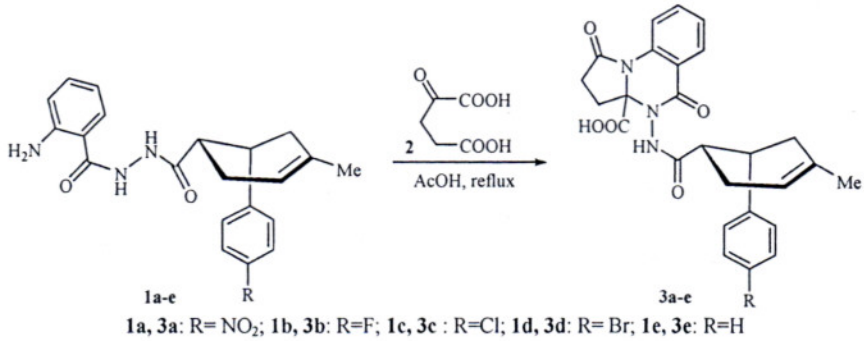
TABLE I
SYNTHESIS OF HYDRAZIDES **1a-e** AND AMIDE-LINKED PYRROLO[1,2-*a*]QUINAZOLINE – CYCLOHEXENE CONJUGATES **3a-e**

Entry	R	Yield of **1**, %[a]	m.p., °C of **1**	Yield of **3**, %[b] (mix. of diastereoisomers)	d.r.
1	NO_2	**1a**, 95	223-224	**3a**, 83	2.5:1
2	F	**1b**, 80	102-104	**3b**, 88	1:1
3	Cl	**1c**, 89	232	**3c**, 89	1:1
4	Br	**1d**, 84	205-207	**3d**, 87	1:1
5	H	**1e**, 68	108-110	**3e**, 78	1.5:1

[a] – pyridine, 2h
[b] – AcOH, 2h

References

[1] D. Zicāne, I. Rāviņa, Z. Tetere, M. Petrova. Chemistry of Heterocyclic Compounds, Vol. 43, 2007, pp. 755-759



1a, 3a: R= NO_2; **1b, 3b**: R=F; **1c, 3c** : R=Cl; **1d, 3d**: R= Br; **1e, 3e**: R=H