J. Pharm. Pharmacol. 1998, 50 (Supplement): 245

Relationship of structural and electronic properties to antimycobacterial activity of a series of 2-heteroarylcarboxamidrazones

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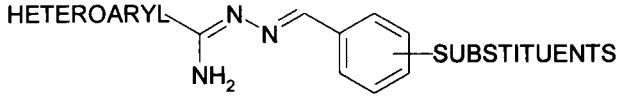
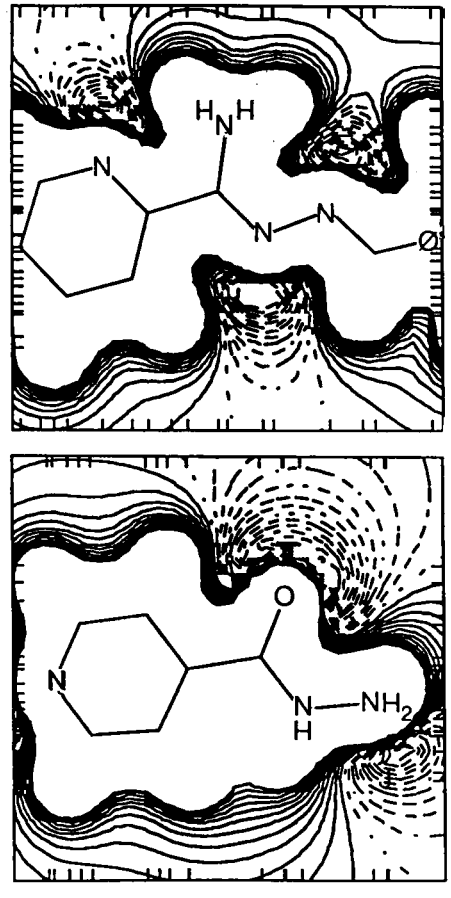
N^1-benzylideneheteroarylcarboxamidrazones can have antimycobacterial activity (Mamolo et al. 1992): against *M. fortuitum* the minimum inhibitory concentration for **1** is 6.3-12.5 μg ml^{-1}, compared with 3 μg ml^{-1} for isoniazid (Billington et al. 1998). We have determined crystal structures for amidrazones **1** - **4**



(1-4)

with heteroaryl ring R1 and aryl R2 respectively: **(1)** 2-pyridyl and *p*-(1,1-dimethylpropyl)phenyl, **(2)** pyrazinyl and 2-naphthyl, **(3)** pyrazinyl and 1-naphthyl, **(4)** 2-quinolyl and *m*-hydroxyphenyl. Successive small twists of up to 5° about formally double bonds in the chain and 10° about single bonds incline the planes of R1 and R2 to each other by 10-14°. An important conformational restraint is the universal intramolecular hydrogen bonding from the amino group to N atoms in the heterocycle and the chain. Surprisingly, the N atom in the chain which adjoins the amino group and should draw negative charge from it only accepts a hydrogen bond in one case. Except in **1**, where the alkyl substituent that enhances lipophilicity and biological activity may prevent it, molecules stack pairwise with R1 of one molecule over R2 of the other. However, the inclination of these rings must limit pi-electron interactions.

Ab initio molecular orbital calculations in the 3-21G basis set were carried out on a model amidrazone **1a** obtained from **1** by deletion of the alkyl substituent and also on isoniazid. Electrostatic potential (ESP) maps are reproduced below for the relevant portion of **1a** and isoniazid. Solid contours represent positive potential and dashed contours negative potential, which is concentrated around heteroatom lone pairs. Despite the common antimicrobial activity, there are marked differences in ESP when the molecules are aligned with the formally similar heterocycle and N-N unit in corresponding orientations.



Billington et al (1998), Drug Design and Discovery, *in press.*
Mamolo M.G. et al, (1992), Farmaco, 1055-1066