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Automated synthesis and antimycobacterial activity of a series of 2-heteroarylcarboxamidrazones and related compounds

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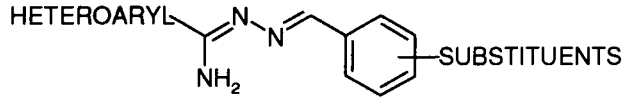
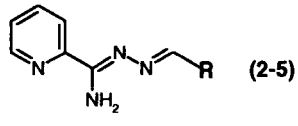
Some N^1-benzylideneheteroarylcarboxamidrazones (**1**) are known to have antimycobacterial activity [Mamolo et al (1992, 1993a, 1993b), Mamolo & Vio (1996)].

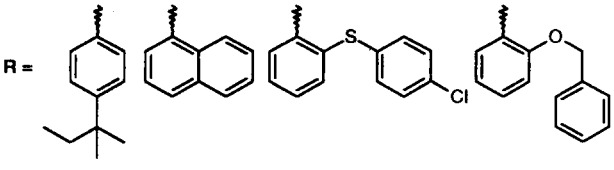


(1)

The key structural features which were identified as associated with antimycobacterial activity are as follows: the amidrazone moiety is to be connected to a pyridine-based group and hydrophobic substituents on the benzylidene group are essential, preferably at the 2-position. In an ongoing programme concerning the discovery of new antimycobacterial agents we synthesised and tested a range of heteroarylcarboxamidrazones against *M. fortuitum* reference strain NCTC 10394 in a rapid screen as a model for *M.tuberculosis*. (Billington *et al* 1998). A diverse range of substituents had been included in the aryl hydrazone portion of the amidrazones (**1**).



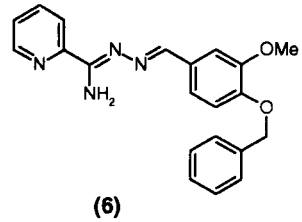
(2-5)



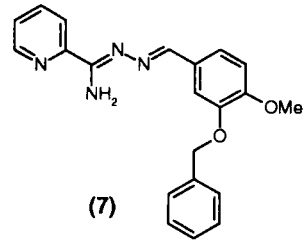
(2) **(3)** **(4)** **(5)**

From this set compounds **2-5** were the most active. It appears that the ortho-substituted benzylidene fragment must have the possibility to be essentially planar. The major departure from this trend is the most active compound (**2**) which features a substituted benzylidene which is not only a para-substituted but also non-planar. Compounds **2-5** were used as lead structures for the preparation of further focused libraries. Thus, matrices of functionalised carboxamidrazones and hydrazines were combined with a range of carbonyl components in a automated manner, to give the corresponding N^1-benzylidenecarboxamidrazones and hydrazones. The products, which were usually crystalline, were isolated by robotic trituration with a suitable solvent and characterised by automated APCI-MS. The crude materials were screened against *M. fortuitum*. Compounds exhibiting a zone of inhibition of the organism on an agar plate were purified, where necessary, and MICs were obtained in Middlebrook 7H9 broth.

In summary, changing from the 2-pyridylcabox amidrazone series to the 4-pyridylcaboxamidrazone series gave virtually identical activity profiles over a wide range isomeric structures. The most active compounds discovered were an isomeric pair **6** and **7**. In contrast, changing from 2-pyridylcaboxamid-razones to 2-pyridylhydrazones resulted in a complete loss of activity.



(6)



(7)

Billington et al (1998), Drug Design and Discovery, *in press.*
Mamolo M.G. et al, (1992), Farmaco, 1055-1066
Mamolo M.G. et al, (1993a), Farmaco, 529-538
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