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1-*N*-(Arylmaleamoyl)-3,5-bis(phenylmethylene)-4-piperidones: a novel class of antimycobacterial agents

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Various acyl groups possessing markedly divergent topography were placed on the nitrogen atom of the antimycobacterial agent 3,5-bis(phenylmethylene)-4-piperidone (**1**). Some of the *N*-maleamoyl analogues of **1** displayed antitubercular properties thereby affording an insight into the structural requirements for interactions at a putative auxiliary binding site in the bacterium.

Tuberculosis gives rise to intense suffering and death. Currently this infection causes approximately two million fatalities each year (World Health Organization 2004). One of the reasons for the proliferation of this disease is the development of drug resistance by the tubercule bacillus and therefore the need for the discovery of entirely new classes of antimycobacterials is of paramount importance (Nayyar and Jain 2005). The objective of this communication is to disclose the discovery of certain 1-*N*-(arylmaleamoyl)-3,5-bis(phenylmethylene)-4-piperidones as novel antimycobacterial agents which serve as a stimulus for further development.

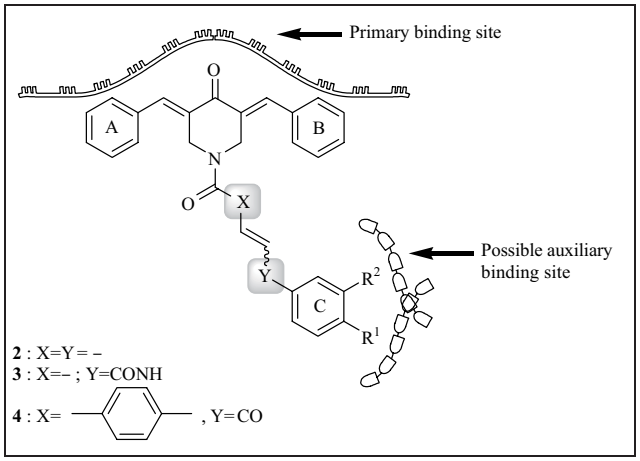

Fig.: Structures of compounds in series **2**–**4**. The aryl substituents in ring C were as follows: **a**: $R^1 = R^2 = H$; **b**: $R^1 = Cl$, $R^2 = H$; **c**: $R^1 = R^2 = Cl$; **d**: $R^1 = NO_2$, $R^2 = H$; **e**: $R^1 = CH_3$, $R^2 = H$; **f**: $R^1 = OCH_3$, $R^2 = H$

Table: Evaluation of the compounds in series 2–4 for growth inhibiting properties of *Mycobacterium tuberculosis* $H_{37}Rv$

	R^1/R^{2a}	Percentage inhibition at 6.25 μg/mL		
		2	**3**	**4**
a	H	24	0	8
b	4-Cl	0	0	0
c	3,4-Cl_2	2	74	0
d	4-NO_2	0	98	6
e	4-CH_3	8	4	0

Major interests of this laboratory have been the syntheses and bioevaluation of novel acyclic Mannich bases of conjugated styryl ketones (Dimmock and Kumar 1997). Representative compounds alkylate thiols but not hydroxy or amino groups which are found in nucleic acids (Mutus et al. 1989; Dimmock et al. 1983) and hence may be devoid of genotoxic properties. A number of these compounds have antibacterial properties (Dimmock and Wong 1976) but significant murine toxicity is generally present (Dimmock et al. 1991). However by preparing conjugated enones from 4-piperidones (a cyclic Mannich base), the problem of murine toxicity was greatly reduced. For example, a dose of 300 mg/kg of 3,5-bis(phenylmethylene)-4-piperidone (**1**) was not fatal to mice (Dimmock et al. 2002). In addition, the hydrochloride salt of **1** completely inhibited the growth of *Mycobacterium tuberculosis* $H_{37}Rv$ at a concentration of 6.25 μg/mL.

The objective of the present study was to evaluate various *N*-acyl analogues of **1** as potential antimycobacterials. The 3,5-bis(phenylmethylene)-4-oxo-piperidinyl group was considered to act at the primary binding site and by choosing different *N*-acyl groups, some of the structural requirements for alignment at a possible auxiliary binding site may emerge. Recently series **2**–**4** were prepared for bioevaluation and the compounds were well tolerated in mice (Dimmock et al. 2002, 2003). In these compounds the location of the terminal aryl ring relative to the heterocycle will be influenced by the presence or absence of the linker groups X and Y as well as the stereochemistry of the olefinic double bond. The evaluation of six compounds in each of series **2**–**4** having similar aryl substituents is presented in the Table.

The data reveal that series **3** is a novel group of antimycobacterial agents while the bioevaluation indicates that the *N*-acyl group in series **2** and **4** likely impedes alignment of the 3,5-bis(phenylmethylene)-4-oxo-piperidinyl pharmacophore at the primary binding site. In the case of the *N*-maleamoyl derivatives, **3c**, **d**, **f** displayed marked antimycobacterial properties while **3a**, **b**, **e** were virtually bereft of activity at the concentrations employed. The molar refractivity (MR) figures of the aryl substituents of **3c**, **d**, **f** are 12.06, 8.39 and 8.90, respectively, while in the case of **3a**, **b**, **e** the MR values are 2.06, 7.06 and 6.68, respectively (Hansch and Leo 1979). Thus the size of the substituents in ring C likely significantly influences antimycobacterial potencies. On the other hand, no correlations were discerned between the Hammett σ or Hansch π values of the R^1 and R^2 atoms or groups with the relative ability to inhibit the growth of *M. tuberculosis* revealing the absence of correlations between bioactivity and the electronic and hydrophobic properties of the aryl substituents.

The three series of compounds were chosen to explore the hypothesis that the location of ring C in relation to the 3,5-bis(phenylmethylene)-4-oxo-piperidyl group influences antimycobacterial properties. Molecular models of **2a**, **3a** and **4a** were constructed and the C-4 atoms of rings A, B and C were designated A′, B′ and C′, respectively. The distances d_1, d_2 and d_3 are the spans between A′−B′, B′−C′ and C′−A′, respectively, while ψ_1 is the angle between the A′−B′ and B′−C′ axes. The figures for d_1−d_3 and ψ_1 (values of **2a**, **3a** and **4a** in parentheses) are as follows, namely d_1 (12.44, 12.22, 12.24), d_2 (6.37, 10.05, 5.81), d_3 (12.96, 10.81, 17.41) and ψ_1 (80.06, 51.29, 147.08). These data reveal substantial divergences in the relative locations of ring C which may well contribute significantly to the variation in the antimycobacterial potencies observed.

In conclusion, this study has revealed the need for two further lines of experimentation in the development of candidate antimycobacterial agents. First, series **3** should be expanded with special attention being directed to determining whether antimicrobial potencies are positively correlated with the size of the aryl substituents in ring C. Second, new *N*-acyl analogues of **1** should be prepared in which the linker groups X and/or Y are varied and the relative locations of ring C to the putative pharmacophore determined by molecular modeling. The resultant biodata may reveal that optimal van der Waals bonding between ring C and a complementary portion of the auxiliary binding site has occurred. In such cases it is likely that the *N*-acyl group will assist the interaction of the ligand with important biomacromolecules thereby leading to potent antimycobacterial agents.

Experimental

1. Syntheses of compounds

The preparation of the hydrochloride salt of **1** used a literature method (Dimmock et al. 1990). Series **2** and **4** were synthesized as described in the literature (Dimmock et al. 2002) and series **3** has been reported previously (Dimmock et al. 2003).

2. Molecular modeling

Energy minimization as well as distance and angle calculations were accomplished using a commercial software programme (CAChe 2001).

3. Antitubercular evaluation

Assessment of the antitubercular properties of **1a** hydrochloride and series **2**–**4** was made using *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar blue assay (Collins and Franzblau 1997).

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