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Antimycobacterial activity of new N^1-[1-[1-aryl-3-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo]propyl]-pyridine-2-carboxamidrazone derivatives

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ABSTRACT

N^1-[1-[1-aryl-3-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo]propyl]-pyridine-2-carboxamidrazone derivatives were design, synthesized and tested for their in vitro antimycobacterial activity. The new compounds showed a moderate antimycobacterial activity against the tested strain of *Mycobacterium tuberculosis* H37Ra and a significant antimycobacterial activity against several mycobacteria other than tuberculosis strains.

Tuberculosis (TB) is a chronic infection and one of the most widespread disease in the world and it's the second cause of death from a single infectious agent. The *M. tuberculosis* is the causative pathogen and the re-emergence of the extensively multidrug-resistant strains of *M. tuberculosis* (MDR) together with the high incidence of severe disseminated infections produced by mycobacteria other than tuberculosis (MOTT) necessitates the development of new antimycobacterial therapeutic agents. In this context, imidazole derivatives have shown antimycobacterial activity associated with good antifungal activity.[1,2] In general, the common goal of the azole antifungal agents is the inhibition of cytochrome P450-dependent lanosterol 14-α-demethylase (P450, CYP51). Interestingly, it has been shown that a CYP51-like gene of *M. tuberculosis* (MT) H_{37}Rv strain may also be exploited as a target for novel drugs.[3] This gene encodes a mycobacterial sterol 14-α-demethylase (MT $P450_{14DM}$), whose substrates are 14-α-methyl sterols, and that forms complexes with antifungal azole inhibitors of $P450_{DM}$.

To obtain compounds with both antifungal and antimycobacterial properties, we design and synthesized the series of derivatives **1a**–**n** in which, the imidazol-1-yl and the pyridine-2-carboxamidrazone nuclei are present simultaneously. We tested the combination of the two moieties because the first is essential for the antifungal activity of a number of azole drugs, and the latter is important for the antimycobacterial activity of a number of derivatives (Fig. 1).[4–10]

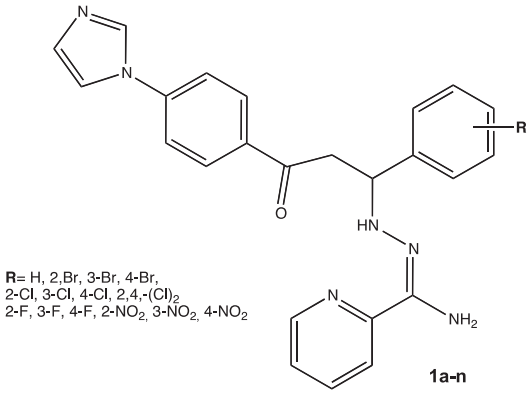

Figure 1. Structure of new derivatives **1a**–**n**.

The N^1-[1-[1-aryl-3-[4-(1*H*-imidazol-1-yl)phenyl]-3-oxo]propyl]-pyridine-2-carboxamidrazone derivatives **1a**–**n** (Table 1, supplementary data) were prepared by reacting pyridine-2-carboxamidrazone **3**, prepared from 2-cyanopyridine and hydrazine

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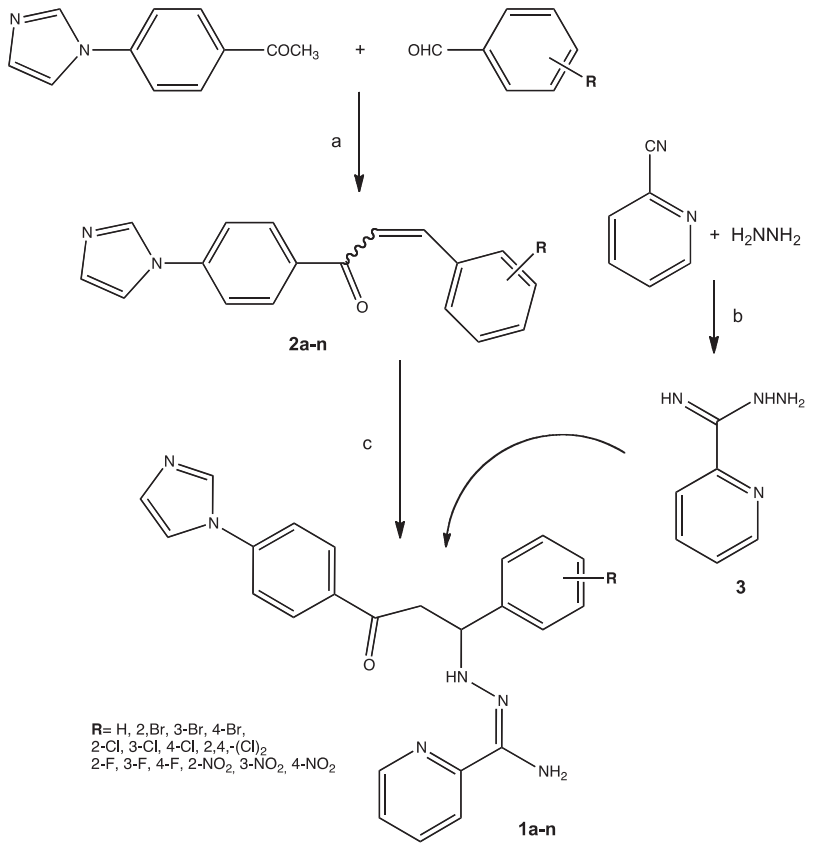

Scheme 1. Synthetic route for the synthesis of compounds **1a**–**n**. Reagents and conditions: (a) BF_3-AcOH 72 h rt; (b) EtOH 36 h 0 °C; (c) EtOH 48 h rt.

hydrate in accordance with a slightly modified method previously described,[11] with the corresponding 3-aryl-1-[4-(1*H*-imidazol-1-yl)phenyl]-propenones **2a**–**n**, which in turn were obtained, accordingly by a conventional procedure,[12] by treating 1-(4-imidazol-1-yl-phenyl)-ethanone **4** with aromatic aldehydes in the presence of the boron trifluoride-acetic acid complex (Scheme 1).

Compounds **1a**–**n** were preliminary tested against a Gram positive bacterial strain (*S. aureus* ATCC 25923), a Gram negative strain (*E. coli* ATCC 25922) and a fungal strain of *Candida albicans* 685. We performed the zone of inhibition assays for all the synthesized compounds in comparison with Cefalotin and Amphotericin B, as standard references.

As shown in Table 2, all the tested compounds (at dose of 20 μg) revealed an antibacterial activity, in particular towards the Gram positive strain of *S. aureus*, where all the chlorinated derivatives showed a inhibition zone ranging from 17 to 22 mm in comparison to Cefalotin (dose 30 μg; zone 31 mm), used as a standard reference. Regarding the antifungal activity (Table 2), all the compounds showed a weak inhibition towards *C. albicans* 865, clinical isolate strain, with diameter values ranging from 4 to 13 mm at 20 μg dose (Amphotericin B; 5 μg and 16 mm).

The derivatives **1a**–**n** were tested against a strain of *M. tuberculosis* H37Ra and in all cases were observed to result in *MIC values* ranging from 4.4 to 36 μM. Furthermore all the synthesized compounds were tested against seven strains of MOTT and several derivatives showed interesting antimycobacterial activity (Table 3). In particular, the 2,4-dichloro derivative **1h** showed the best MIC values towards *M. intracellulare* and *M. avium* (33.3 μM) and against *M. kansasii* (MIC = 4.2 μg/ml; INH=>467, 116 and 29.2 μM respectively). The entire series **1a**–**n** revealed a potent antimycobacterial activity towards *M. gordonae*, with the best values for the bromo derivatives **1c, d** (MIC = 2.0 μM), and *M. scrofulaceum* (MIC = 8.8 μM for all the nitro derivatives **1l-n**) compared to reference standard drug isoniazid (MIC = 116 μM).

Towards *M. marinum* and *M. Bovis*, once again, the bromo derivative **1d**, it proved to be the more active compound of the series (MIC = 8.2 μM).

Table 2
Antibacterial and antifungal activities of the tested compounds **1a**–**n**; zone inhibition test

Cpd.	R	*S. aureus ATCC 25923*	*E. coli ATCC 25922*	*C. albicans* 685
		Inhibition diameter (millimeter) after 24 h[a]		
1a	H	14	7	5
1b	2-Br	19	5	8
1c	3-Br	19	8	13
1d	4-Br	20	6	8
1e	2-Cl	20	6	7
1f	3-Cl	22	7	11
1g	4-Cl	20	8	9
1h	2,4-Cl_2	17	6	8
1i	2-F	14	7	5
1j	3-F	16	7	11
1k	4-F	20	6	6
1l	2-NO_2	13	6	4
1m	3-NO_2	13	5	10
1n	4-NO_2	13	5	5
INH		—	—	—
Cefalotin[b]		31	11	—
Amph. B[c]		—	—	16

[a] 20 μg dose cpd **1a**–**n**.
[b] 30 μg disk.
[c] 5 μg disk.