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Hetaryl- and heteroarylvinyl-substituted nitrofurans identified as non-cytotoxic selective antitubercular agents

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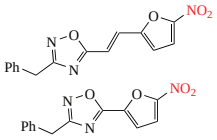
New (*E*)-5-[2-(5-nitrofuran-2-yl)vinyl]-1,2,4-oxadiazoles and 5-(5-nitrofuran-2-yl)-1,2,4-oxadiazoles were synthesized *via* the base-promoted condensation of nitrofuran-containing acyl chlorides with amidoximes. Testing these compounds against Gram-negative *E. coli*, Gram-positive *B. subtilis* and *S. aureus* as well as *M. tuberculosis* HRv37 strain revealed three compounds being selectively antimycobacterial. None of these compounds displayed any cytotoxicity towards human pancreatic epithelioid carcinoma cell line, PANC-1.



M. tuberculosis HRv37	*E. coli*	*B. subtilis*	*S. aureus*	PANC-1 cells (mM)
μg ml^{-1}				
6.2	>200	>200	>200	>250
3.1	>200	>200	>200	>250

Keywords: nitrofurans, 1,2,4-oxadiazoles, amidoximes, olefin linker, direct bond, antibacterial assay, antimycobacterial assay, MTT assay, cell viability.

Although numerous various nitro heterocyclic moieties have manifested themselves as a source of antibacterial (and, specifically, antimycobacterial) leads,[1] the conjugation of classical nitrofurans to various heterocyclic motifs not only can render these compounds generally non-cytotoxic[2] but also can direct their activity towards a specific type of antibacterial property, that does not affect the microbiome at large.[3] Moreover, nitrofurans proved to be versatile synthetic intermediates *en route* to other furan derivatives accessed *via* nucleophilic substitution of the nitro group.[4]

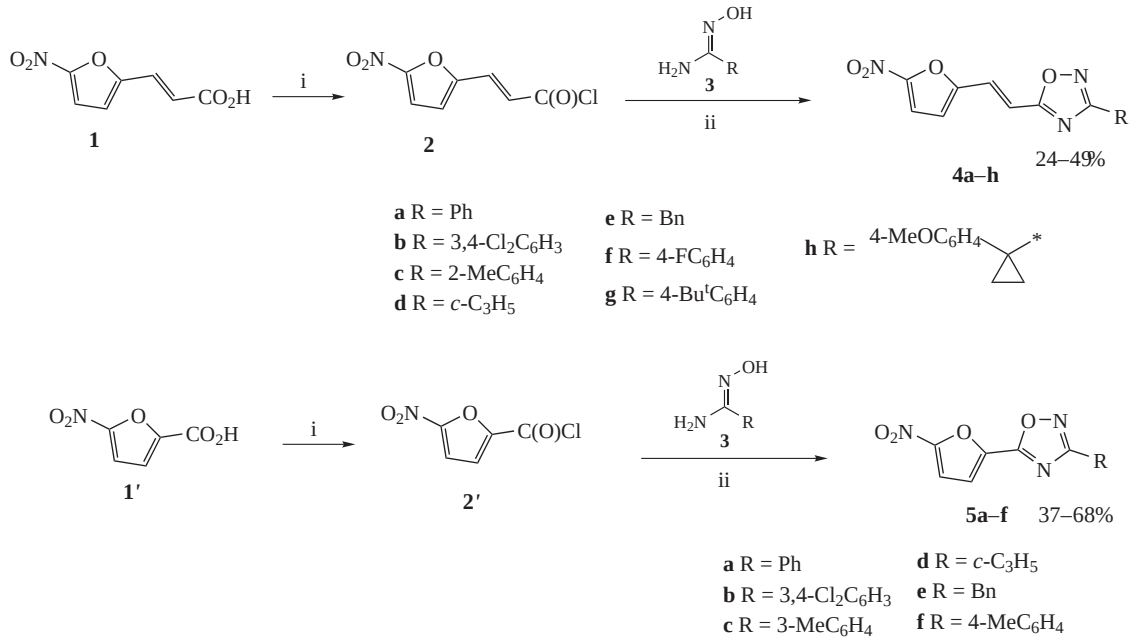
A few years ago, we[5] and others[6] have already explored this strategy successfully by conjugating privileged[7] aminoalkylimidazoles and pyrimidines to nitrofuranoyl moiety, which resulted in compounds that were found to be selectively antimycobacterial. Inspired by this strategy, and also by the apparently privileged character of 1,2,4-oxadiazole heterocyclic motif (particularly its peptidomimetic characters[8]), we set off to investigate an opportunity to design a series of compounds wherein a pharmacophoric nitrofuran moiety would be linked (directly or through a short linker at position 5) to a set of 1,2,4-oxadiazoles bearing diverse groups at position 3 (Scheme 1). Profiling of such a small compound library would either prove or disprove our idea of seeing selective antimicrobial (or perhaps cytotoxic) effects from these compounds. Herein, we report the results obtained in the course of realizing this strategy.

Synthesis of the target compounds **4a**–**h** and **5a**–**f** was achieved from carboxylic acids **1** and **1′**, respectively, which were converted to acyl chlorides **2** and **2′** according to the literature procedure (see Scheme 1).[9,10] The latter were condensed with a series of amidoximes **3** in refluxing 1,4-dioxane in the presence of triethylamine to furnish compounds **4a**–**h** and **5a**–**f** in moderate to good yields.[†]

Compounds **4a**–**h** and **5a**–**f** thus obtained were profiled, spectrophotometrically, against a small panel of bacterial pathogens Gram-negative *Escherichia coli* (ATCC 25922) as well as Gram-positive *Bacillus subtilis* (BKM-B-2605D) and *Staphylococcus aureus* (ATCC-25923). Additionally, their activity was assessed against drug-sensitive strain HRv37 of *Mycobacterium tuberculosis*. The data in Table 1 revealed that none of the compounds tested displayed any appreciable activity against Gram-negative *E. coli* as well as Gram-positive *B. subtilis* and *S. aureus*. At the same time, selected compounds (in particular, **4e**, **5d** and **5e**) displayed selective potency against *M. tuberculosis* HRv37 strain. Examination of the structures of these compounds reveals common features. Moreover, none of these compounds displayed any cytotoxicity towards human pancreatic epithelioid carcinoma cell line, PANC-1.

In summary, we have performed the synthesis of several conjugates of 1,2,4-oxadiazoles with nitrofurans. Contrary to common expectations, that all such compounds should have some degree of broad antibacterial activity, none of the compounds synthesized were active against common pathogens (Gram-negative *E. coli* as well as Gram-positive *B. subtilis* and *S. aureus*). On the contrary, selected compounds sharing common structural features were discovered as potent antimycobacterial agents, devoid of general cytotoxicity. These findings set the

[†] To a solution of amidoxime **3** (1 mmol) in dry 1,4-dioxane (5 ml), acyl chloride **2** (1.05 mmol) and triethylamine (1.2 mmol) were added under ice-cooling, and the mixture was stirred at room temperature for 60 min and then refluxed for 6–12 h (TLC monitoring). 1,4-Dioxane was removed *in vacuo*, and the residue was treated with water (10 ml), filtered and dried. The residue was purified by chromatography on silica gel using 0→1% MeOH in CH_2Cl_2 as eluent.



Scheme 1 *Reagents and conditions*: i, $SOCl_2$, reflux, 2 h; ii, NEt_3, 1,4-dioxane, reflux, 6–12 h.

Table 1 Activity of nitrofurans **4a**–**h** and **5a**–**f** measured against several bacterial strains as well as *Mycobacterium tuberculosis*.

Compound	*M. tuberculosis* (HRv37)	*B. subtilis* (BKM-B-2605D)	*S. aureus* (ATCC-25923)	*E. coli* (ATCC 25922)
	μg ml^{-1}			
4a	>100	>200	>200	>200
4b	>100	>200	>200	>200
4c	50	200	>200	>200
4d	12.5	>200	>200	>200
4e	6.2	>200	>200	>200
4f	>100	200	>200	200
4g	>100	>200	>200	>200
4h	>100	100	>200	100
5a	>100	>200	>200	>200
5b	100	200	>200	200
5c	>100	>200	>200	200
5d	6.2	>200	>200	200
5e	3.1	>200	>200	>200
5f	12.5	>200	>200	>200

ground for further design of selective, non-cytotoxic anti-mycobacterials.

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Online Supplementary Materials

Supplementary data associated with this article (experimental procedures, analytical data and copies of ^{1}H and ^{13}C NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2022.07.008.

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