Synthesis and anti-tubercular activity of 2-[Ar-CH=N-NR-CO(CH2)n]thiophene and 2-(Ar-CH=N-NH-CO)furan derivatives

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Abstract

The synthesis and anti-tubercular activity of the new thienyl and furanyl derivatives are reported.

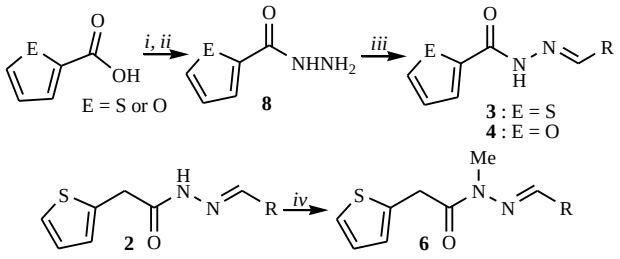
Introdução

Thiophene and its derivatives have been well studied as materials, *e.g.*, in applications in organic electronics and photonics[1,2] and in the medical area. In the medical area, the thiophene nucleus is present in many natural and synthetic products having a wide range of pharmacological activities, such as antiviral, anticancer, antibacterial, antifungal, and anti-inflammatory agents[3].

Due to the promising anti-TB activities of acetamido derivatives, **1**[4–6] and more recently acetohydrazide derivatives of thiophene, **2**[7], we have followed up this study with work on further acylhydrazonyl derivatives of thiophene **3** and **6**, and in addition, on a series of furanyl compounds **4**, see Scheme 1.

Resultados e Discussão

The synthesis of the compounds, **3** or **4**, were achieved by reactions of arylaldeydes with **8**, generated from methyl thiene-2-carboxylate or methyl furan-2-carboxylate, respectively. Methylation of **2**[7] and **3** by methyl iodide produced **6**, respectively, see Scheme 1. All compounds were characterized by HRMS, IR and NMR spectroscopy and tested against *M. tuberculosis, see* Table 1.



Scheme 1. *Reagents and conditions:* (*i*) $SOCl_2$, MeOH, 0°C-r.t., 24h, 98-100%; (*ii*) $N_2H_4.H_2O$ (55%), EtOH, 80°C, 2-18h, 75-80%; (*iii*) EtOH, RCHO, r.t, 1-72h, 40-97%; (*iv*) *a*: acetone, K_2CO_3, r.t., 30 min, *b*: CH_3I, 40°C, 2-24h, 65-89%.

Table 1. Compounds studied and the results of biological activity against *M. tuberculosis* H37Rv (ATTC27294) obtained [a,b].

Compound	MIC (μM)	Compound	MIC (μM)
3a (R=5-O_2N-thien-2-yl)	Insol.	**4b** (R= 5-O_2N-furan-2-yl)	100.3
3b (R=5-O_2N-furan-2-yl)	Insol.	**4c** (R=pyridin-2-yl)	Inact.
3c (R=pyridin-2-yl)	108.2	**4d** (R=2-HOC_6H_4)	Insol.
3d (R=2-HOC_6H_4)	Insol.	**4e** (R=4-HOC_6H_4)	Inact.
3e (R=4-HOC_6H_4)	404.8	**4f** (R=2,3(HO)$_2C_6H_3$)	Inact.
3f (R=2,4-(HO)$_2C_6H_3$)	380.2	**4g** (R=2-HO-4-MeC_6H_3)	Insol.
3g (R=3,4-(HO)$_2C_6H_3$)	Inact.	**4h** (R=2-HO-5-MeC_6H_3)	Insol.
3h (R=2-HO-4-MeC_6H_3)	Insol.	**4i** (R=2-HO-3-MeOC_6H_3)	401.3
3i (R=2-HO-5-MeC_6H_3)	Inact.	**4j** (R=2-HO-4-MeOC_6H_3)	Insol.
3j (R=2-HO-3-MeOC_6H_3)	180.5	**4k** (R= 4-HO-3-ClC_6H_3)	Inact.
3k (R= 2-HO-4MeOC_6H_3)	Insol.	**6a** (R=5-O_2N-thien-2-yl)	10.5
3l (R= 2-HO-3-O_2NC_6H_3)	171.2	**6b** (R= 5-O_2N-furan-2-yl)	179.2
3m (R=2-HO-5-O_2NC_6H_3)	Insol.	**6c** (R=pyridin-2-yl)	Inact.
3n (R=4-HO-3-ClC_6H_3)	88.8	**2a** (R= 5-O_2N-thien-2-yl)[7]	9.0
4a (R= 5-O_2N-thien-2-yl)	Insol.	**2b**(R= 5-O_2N-furan-2-yl)[7]	8.5
Ethambutol	15.3	Isoniazide	0.46

[a]Ins = insoluble; [b]Inact = inactive:>100μg/mL

Conclusões

The most active compounds against *M. tuberculosis* are **2a**, **2b** and **6**. Moderate activity was displayed by **4b** and certain derivatives of series **3** where aryl is an *o*-hydroxyphenyl derivative or pyridin-2-yl.

Agradecimentos

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