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Thiophene containing triarylmethanes as antitubercular agents☆

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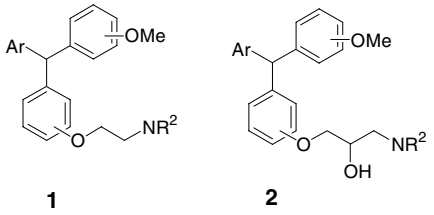
Abstract—A new series of thiophene containing triarylmethane derivatives were synthesized from the Friedel–Crafts alkylation of diarylcarbinols followed by incorporation of amino alkyl chains. These were evaluated against *Mycobacterium tuberculosis* $H_{37}R_v$ and showed the activity in the range of 3.12–12.5 μg/mL in vitro.

Tuberculosis is the leading infectious disease caused by *Mycobacterium tuberculosis*.[1,2] The situation is becoming alarming with the recent emergence of multi-drug-resistant (MDR) strains and its synergy with global human immunodeficiency virus (HIV).[3] The search for more effective agents against *M. tuberculosis* (MT) is ongoing in an attempt to enhance survival and reduce morbidity, as proven by the high number of patents of new antitubercular agents in the past decade.[4]

Because of this, there is an urgent need for anti-TB drugs with improved properties such as enhanced activity against MDR strains, reduced toxicity, shortened duration of therapy, rapid mycobactericidal mechanism of action and the ability to penetrate host cells and exert anti-mycobacterial effects in the intracellular environment.

We have been involved in the design, synthesis and bio-evaluation of new antitubercular agents and several triarylmethane (TRAM) derivatives **1** and **2** (Fig. 1) with antitubercular activity were reported.[4] The structural pharmacophore is based on a triarylmethane nucleus containing phenanthrene, indole and anthracene rings and exhibited 1.56–25 μg/mL antitubercular activity in vitro. In order to optimize the anti-TB activity of



1 **2**

Ar = 9-phenanthrenyl, (1-Benzenesulfonyl-1*H*-indol-3-yl), pyridine-3-yl, 9-anthracenyl

Figure 1. Structures of antitubercular triarylmethanes with basic amino alkyl or amino hydroxy alkyl side chains.

TRAMs, we planned to systematically substitute the aryl group with rings having aromatic properties.

Thiophene containing compounds are well known to exhibit various biological activities such as BACE1 inhibitors,[5] anti-inflammatory agents,[6] anti-HIV PR inhibitors[7] and anti-breast cancer.[8] Thus, we decided to replace one of the aryl rings with thiophene in the triarylmethane nucleus. We also intended to incorporate chlorine and thiomethoxy substituted phenyl ring since it is generally observed that the presence of chlorine or thiomethoxy in a molecule profoundly affected its biological properties.[9–11] Moreover, several amino alcohol derivatives such as ethambutol are well known to have antitubercular activity (Fig. 2).[12] Thus in our programme also, we intended to incorporate 2-hydroxy-amino functionality on thiophene containing pharmacophore for further diversification and designed to synthesize **3**, **4** and **5** as our target molecules (Fig. 2).

Keywords: Thiophene; Antitubercular; Friedel–Crafts alkylation.
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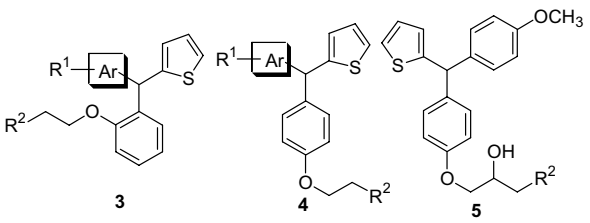


Figure 2. General structures of designed molecules.

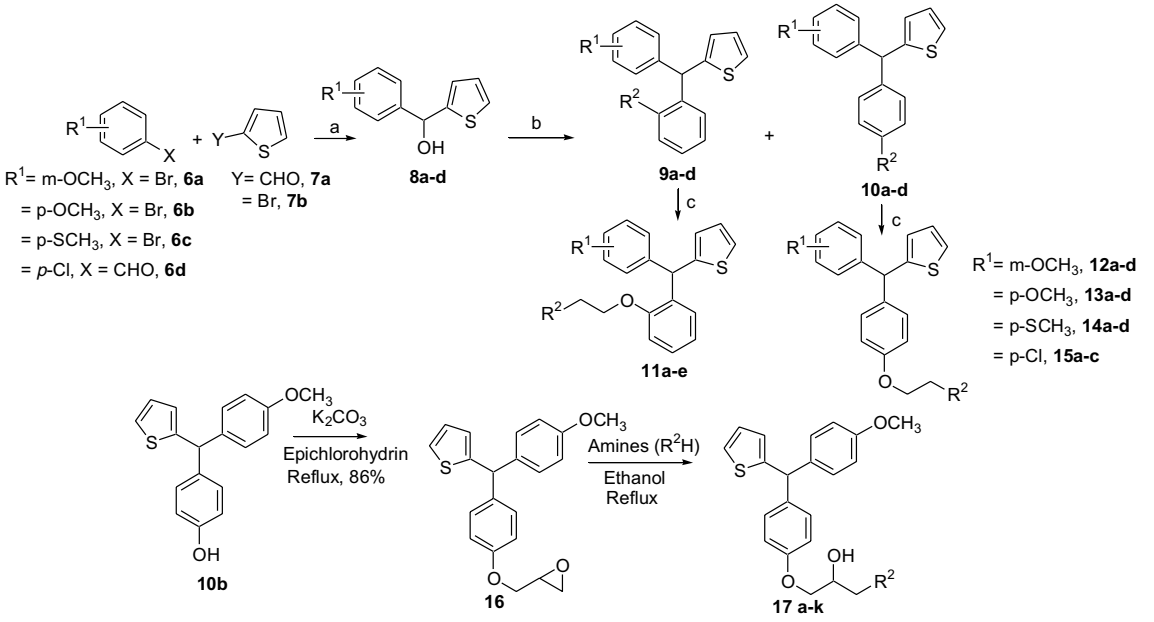
The title compounds were synthesized essentially following the steps as depicted below. Nucleophilic addition of Grignard reagents **6a**–**c** and **7b** onto thiophene-2-carbaldehyde **7a** and *p*-chloro benzaldehyde **6d**, respectively, in THF furnished the carbinol derivatives **8a**–**d** in excellent yields. Out of various protic acids used in Friedel–Crafts alkylation, concd H_2SO_4 (cat.) in dry benzene gave better results. Thus, FC alkylation of **8a**–**d**with phenol led to the mixtures of **9a**–**d** as minor and **10a**–**d** as major products. The compounds **9a**–**d** were characterized from its deshielded doublet aromatic protons and singlet methine proton resonances, respectively, than corresponding para isomers **10a**–**d** due to the presence of $-I$ inductive effect of *ortho*-hydroxy group. The structural identity of **9a**–**d** and **10a**–**d** was further confirmed by their ^{13}C NMR and mass spectrum fragmentation analysis. In this competitive reaction, the generation of compounds **9a**–**d** and **10a**–**d** could be attributed to the fact that Friedel–Crafts alkylation occurs via attack of phenol at both *ortho* and *para* positions of the benzene nucleus with the carbinol **8a**–**d**.

Friedel–Crafts alkylated products **9a**–**d** and **10a**–**d** were then aminoethylated with different dialkylaminoethyl chloride hydrochloride chains in the presence of K_2CO_3 and acetone and furnished **11a**–**e**, **12a**–**d**, **13a**–**d**, **14a**–**d** and **15a**–**c** in good yields (Scheme 1). The corresponding salts were obtained after treating the amines with ethanolic HCl. Initial bioevaluation of the compounds **11a**–**e** and **12a**–**d**, **13a**–**d**, **14a**–**d** and **15a**–**c** gave interesting antitubercular activity results in vitro. The compound **10b** was reacted with epichlorohydrin in presence of K_2CO_3 to furnish the oxirane **16** in good yield (86%). The oxirane was then reacted with selected primary and secondary amines to furnish a variety of 2-hydroxy amino alkyl derivatives (**17a**–**k**) (Scheme 1).

Biology determination of activity in vitro: The activity of the compounds against *M. tuberculosis* $H_{37}R_v$ was determined by agar microdilution technique.[13] (details are described in experimental section). The activity of the compounds **11a**–**e**, **12a**–**d**, **13a**–**d**, **14a**–**d**, **15a**–**c** and **17a**–**k** in vitro is shown below (Table 1).

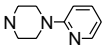
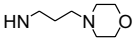
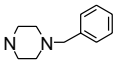
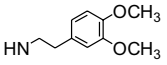
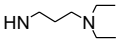
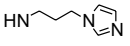
A closer look into the biological results of the above compounds reveals that in a given diarylmethylphenol series (**10a**–**d**), **10b** containing *p*-OCH_3 gave better activity. On the other hand, **11a**–**e** with *ortho* substituent did not exhibit good activity (>12.5 μg/mL). Among the pair of compounds **12a**, **12b**; **13a**, **13b**; **14a**, **14b** and **15a**, **15b**, increasing the alkyl chain on nitrogen gave better activity. Increase in polarity of the side chain reduces the activity (**12c**, **13c**, **14c** and **15c**). Incorporation of 2-hydroxy-amino functionality on the pharmacophore for better activity was not encouraging.

In conclusion we have synthesized thiophene containing several triarylmethane (TRAM) derivatives as new series of antitubercular compounds with antimycobacterial activity. The compounds containing increased amount of alkyl group on nitrogen of the side chain were active



Scheme 1. Reagents and conditions: (a) Mg, THF, 0 °C, rt, 2 h, **8a** (69%), **8b** (71%), **8c** (74%) and **8d** (79%); (b) phenol, concd H_2SO_4 (cat.), dry benzene, reflux, 2 h, **9a** (12%), **9b** (9%), **9c** (11%) and **9d** (12%); (c) alkylaminoethyl hydrochloride ($ClCH_2CH_2R^2{\cdot}HCl$), anhyd K_2CO_3, dry acetone, reflux, 6–7 h, (yields given in Table 1).

Table 1.

Entry	Compound	R^1	R^2	Yield[a] (%)	MIC (μg/mL) agar microdilution method[13]
1	**10a**	*m*-OCH_3	OH	61	>12.5
2	**10b**	*p*-OCH_3	OH	59	3.12
3	**10c**	*p*-SCH_3	OH	63	>12.5
4	**10d**	*p*-Cl	OH	58	>12.5
5	**11a**	*p*-OCH_3	$N(CH_3)_2$	71	>12.5
6	**11b**	*p*-OCH_3	$N(CH_2CH_3)_2$	76	>12.5
7	**11c**	*p*-OCH_3		78	>12.5
8	**11d**	*p*-OCH_3		73	>12.5
9	**11e**	*p*-OCH_3		68	>12.5
10	**12a**	*m*-OCH_3	$N(CH_3)_2$	71	12.5
11	**12b**	*m*-OCH_3	$N(CH_2CH_3)_2$	78	3.12
12	**12c**	*m*-OCH_3		82	12.5
13	**12d**	*m*-OCH_3		79	3.12
14	**13a**	*p*-OCH_3	$N(CH_3)_2$	79	12.5
15	**13b**	*p*-OCH_3	$N(CH_2CH_3)_2$	72	6.25
16	**13c**	*p*-OCH_3		76	>12.5
17	**13d**	*p*-OCH_3		72	12.5
18	**14a**	*p*-SCH_3	$N(CH_3)_2$	70	>12.5
19	**14b**	*p*-SCH_3	$N(CH_2CH_3)_2$	71	3.12
20	**14c**	*p*-SCH_3		76	>12.5
21	**14d**	*p*-SCH_3		78	3.12
22	**15a**	*p*-Cl	$N(CH_3)_2$	71	6.25
23	**15b**	*p*-Cl	$N(CH_2CH_3)_2$	76	3.12
24	**15c**	*p*-Cl		69	12.5
25	**17a**	*p*-OCH_3		80	>12.5
26	**17b**	*p*-OCH_3		77	>12.5
27	**17c**	*p*-OCH_3		83	>12.5
28	**17d**	*p*-OCH_3		70	>12.5
29	**17e**	*p*-OCH_3		86	>12.5
30	**17f**	*p*-OCH_3		81	>12.5
31	**17g**	*p*-OCH_3		77	>12.5
32	**17h**	*p*-OCH_3		76	12.5
33	**17i**	*p*-OCH_3		79	12.5
34	**17j**	*p*-OCH_3		85	>12.5
35	**17k**	*p*-OCH_3		81	>12.5
36	Rifampin	—	—	—	0.1
37	Isoniazid (INH)	—	—	—	0.05

[a] Isolated yield after silica gel column chromatography.

with MIC 3.12 μg/mL and might be a lead for further optimization and development.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.10.083.

References and notes

1. (a) Tuberculosis, HIV/Aids and Malaria, The status and impact of the three diseases. WHO, Geneva, 2005; (b) Raviglione, M. C. *Tuberculosis* **2003**, *83*, 4; (c) Espinal, M. A. *Tuberculosis* **2003**, *83*, 44.
2. (a) Young, D. B.; Duncan, K. *Ann. Rev. Microbiol.* **1995**, *49*, 641; (b) Schaeffer, M. L.; Khoo, K. H.; Besra, G. S.; Chatterjee, D.; Brennan, P. J.; Belisle, J. T.; Inamine, J. M. *J. Biol. Chem.* **1999**, *274*, 31625; (c) Collins, L.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004; (d) Saito, H.; Tomioka, H.; Sato, K.; Emori, M.; Yamane, T.; Yamashita, K.; Hosoe, K.; Hidaka, T. *Antimicrob. Agents Chemother.* **1991**, *35*, 542.
3. De Jong, B. C.; Israelski, D. M.; Corbett, E. L.; Small, P. M. Clinical management of tuberculosis in the context of HIV infection. *Annu. Rev. Med.* **2004**, *55*, 283.
4. (a) Panda, G.; Shagufta; Mishra, J. K.; Chaturvedi, V.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2004**, *12*, 5269; (b) Panda, G.; Shagufta; Srivastava, A. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5222; (c) Panda, G.; Mishra, J. K.; Sinha, S.; Gaikwad, A. K.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. *Arkivoc* **2005**, *2*, 29; (d) Shagufta; Kumar, A.; Panda, G.; Siddiqi, I. *J. Mol. Model.* **2007**, 99; (e) Panda, G.; Parai, M. K.; Das, S. K.; Shagufta; Sinha, M.; Chaturvedi, V.; Srivastava, A. K.; Manju, Y. S.; Gaikwad, A.; Sinha, S. *Eur. J. Med. Chem.* **2007**, *42*, 410.
5. Giordanetto, F.; Karlsson, O.; Lindberg, J.; Larsson, L.-O.; Linusson, A.; Evertsson, E.; Morgan, D. G. A.; Inghardt, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5222.
6. Kumar, P. R.; Raju, S.; Goud, P. S.; Sailaja, M.; Sarma, M. R.; Reddy, G. O.; Kumar, M. P.; Reddy, V. V. R. M. K.; Suresha, T.; Hegdeb, P. *Bioorg. Med. Chem.* **2004**, *12*, 1221.
7. Bonini, C.; Chiummiento, L.; Bonis, M. D.; Funicello, M.; Lupattelli, P.; Suanno, G.; Berti, F.; Campaner, P. *Tetrahedron* **2005**, *61*, 6580.
8. Brault, L.; Migianu, E.; Néguesque, A.; Battaglia, E.; Bagrel, D.; Kirsch, G. *Eur. J. Med. Chem.* **2005**, *40*, 757.
9. Savini, L.; Chiasserini, L.; Gaeta, A.; Pellerano, C. *Bioorg. Med. Chem.* **2002**, *10*, 2193.
10. Madrid, P. B.; Polgar, W. E.; Tolla, L.; Tangaa, M. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3014.
11. Das, S. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Gaikwad, A. N.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5586.
12. (a) Wilkinson, R. G.; Cantrall, M. B.; Shepherd, R. G. *J. Med. Chem.* **1962**, *5*, 835; (b) Shepherd, R. G.; Wilkinson, R. G. *J. Med. Chem.* **1962**, *5*, 823.
13. Siddiqi, S.. In *Clinical Microbiology Handbook*; ASM Press: Washington, DC, 1992; Vol. 1.
Agar microdilution method: Drug susceptibility and determination of MIC of the test compounds/drugs against *M. tuberculosis* $H_{37}R_v$ were performed by agar microdilution method where serial twofold dilutions of each test compound were added into 7H10 agar and *M. tuberculosis* $H_{37}R_v$ was used as test organism. MIC is the concentration of the compound that completely inhibits the growth and colony forming ability of *M. tuberculosis*. In a 24-well plate, 3 mL Middle brook 7H11 agar medium with OADC supplement is dispensed in each well. The test compound is added to the middle brook medium agar before in duplicate so that final concentration of test compound in each well is 12.5, 6.25, 3.125 and 1.56 μg/mL, respectively. The known CFU of $H_{37}R_v$ culture was dispensed on top of agar in each well in negative pressure biosafety hood. The plates are then incubated at 37 °C/5% CO_2 incubator. The concentration at which complete inhibition of colonies was observed was taken as MIC of test drug..