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Bioorganic & Medicinal Chemistry Letters 17 (2007) 5586–5589
Bioorganic & Medicinal Chemistry Letters

Design, synthesis and antitubercular activity of diarylmethylnaphthol derivatives☆

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Received 24 February 2007; revised 2 July 2007; accepted 30 July 2007
Available online 22 August 2007

Abstract—A new series of diarylmethylnapthyloxy ethylamines were synthesized by aminoalkylation of diarylmethylnaphthols which were obtained by Friedel–Crafts alkylation on 1- and 2-naphthols using diarylcarbinols as the alkylating agents. The title compounds were evaluated for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}R_v$ in vitro and showed MIC in the range of 3.12–25 μg/ml.

The prevalence of TB infection has steadily risen in the past decade and the appearance of multi-drug-resistant (MDR) strains, with the threat of global human immunodeficiency virus (HIV), has led to declare tuberculosis as 'a global epidemic' which is evident from the fact that 100 million people are infected annually, 10 million develop the disease, with five million of these progressing to the infectious stage and finally three million dying.[1] Resistance has surfaced for all clinically prescribed antitubercular drugs.[2,3] The search for more effective agents against *Mycobacterium tuberculosis* (MT) and *M. avium* complex (MAC) is ongoing in an attempt to enhance better antitubercular activity and to shorten the treatment regimen.[4]

Towards an ongoing programme for developing new antitubercular agents, we have recently reported antitubercular activity of several diaryloxy methanophenanthrene derivatives **1** and **2** and 4-[10-(methoxybenzyl)-9-anthryl]phenol derivatives **3** (Fig. 1) with basic amino alkyl or amino hydroxyl alkyl side chains.[5] These compounds are phenanthrene and anthracene containing triarylmethane derivatives and exhibited 1.56–25 μg/mL

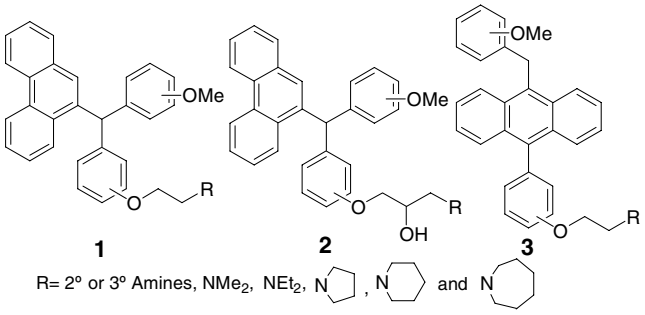

Figure 1. Structures of diaryloxy methanophenanthrenes and 4-[10-(methoxybenzyl)-9-anthryl]-phenols with basic amino alkyl or amino hydroxy alkyl side chains.

antitubercular activity in vitro. Most importantly, in case of phenanthrene containing triarylmethane derivatives, one compound has demonstrated significant antitubercular activity in a mouse model of tuberculosis infection.[5a] In order to understand the structural features of triarylmethane derivatives necessary for enhanced anti-tubercular activity, we embarked on the design, synthesis and antitubercular activity of certain focused libraries of triarylmethane derivatives through the incorporation of naphthol moiety as one of the aryl substituents in triarylmethane nucleus. We also intend to incorporate fluorine- and chlorine-substituted phenyl ring since it is observed that the presence of chlorine or

Keywords: Diarylmethylnaphthol derivatives; Fridel-Crafts; Antitubercular.
☆ CDRI communication No. 7164.
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doi:10.1016/j.bmcl.2007.07.089

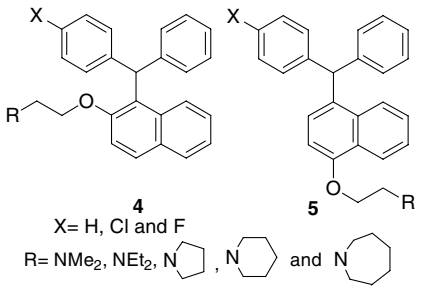
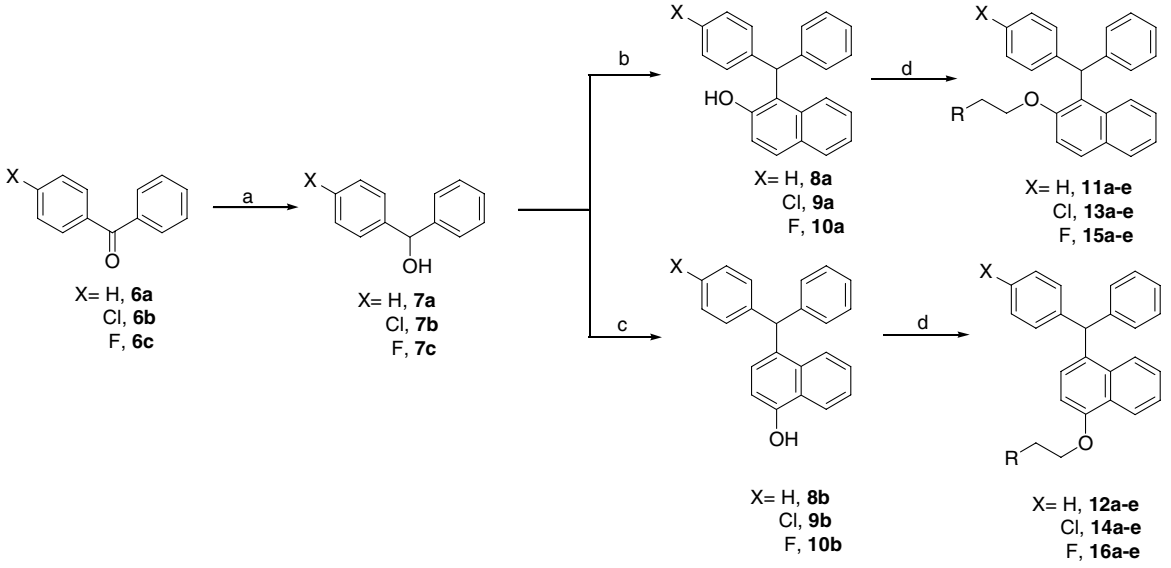


Figure 2. General structures of designed molecules.

fluorine in a molecule can profoundly affect its biological properties. Thus, we designed to synthesize **4** and **5** as our target molecules (Figure 2).

The title compounds were synthesized essentially following the steps as depicted in Scheme 1. Reduction of commercially available benzophenones **6a–c** with sodium borohydride in methanol furnished the corresponding benzhydrol derivatives **7a–c** in excellent yields. Next, carbinols **7a–c** were used as alkylating agents in the Friedel–Crafts alkylation of 1- and 2-naphthols. In every case, the reaction was performed by refluxing a mixture of 1- or 2-naphthol and carbinols **7a** or **7b** or **7c** in dry benzene in the presence of a catalytic amount of conc. H_2SO_4. It is well known that Friedel–Crafts alkylation reaction of 2-naphthol occurs at its 1-position whereas the same reaction occurs at 2- and 4 positions in case of 1-naphthol.[6] Thus, when 2-naphthol was used in the above reaction, only *ortho*-hydroxy substituted diarylmethylnaphthols **8a**, **9a** and **10a** were obtained in every case, which is consistent with the reactivity of 2-naphthol in Friedel–Crafts reactions. Similarly, the use of 1-naphthol furnished *para*-hydroxy substituted diarylmethylnaphthols **8b**, **9b** and **10b** along with *ortho*-hydroxy substituted products in very minor amount and the minor ortho isomers were not separable from the unreacted 1-naphthol by chromatography method. Thus, major isomers **8b**, **9b** and **10b** were separated and characterized. Depending on the nature of benzhydrols, the above Fridel-Crafts reaction sequence thus provides an easy access to the synthesis of symmetric as well as unsymmetric diarylmethylnaphthols. The reaction of **8a**, **9a** and **10a** with different dialkylaminoethyl chloride hydrochloride chains in the presence of anhydrous K_2CO_3 in dry acetone under reflux condition led to the formation of diarylmethylnapthyloxy ethylamines **11a–e**, **13a–e** and **15a–e** in good yields. Similarly, compounds **8b**, **9b** and **10b** on reaction with different dialkylaminoethyl chloride hydrochlorides gave diarylmethylnapthyloxy ethylamines **12a–e**, **14a–e** and **16a–e** in good yields.

All the synthesized final molecules were evaluated against *M. tuberculosis* $H_{37}R_v$ strains following micro almar blue assay and agar microdilution technique[7,8] and their results are shown in Table 1. Out of thirty molecules tested, **11a–e**, **15b** and **15d** showed MIC of 3.12 μg/mL and **13a–e**, **15a** and **15c**, showed MIC of 6.25 μg/mL in agar microdilution technique. Other compounds of the series showed MIC of 12.5 μg/mL or above. A closer look into the structure–activity of relationship of the above compounds reveals that in every structurally isomeric pair of diarylmethylnapthyloxy ethylamines (such as **11a** and **12a**; **13a** and **14a**; **15a** and **16a**, etc.), *ortho*-substituted diarylmethylnapthyloxy ethylamines **11a–e**, **13a–e** and **15a–e** are more active than their *para*-substituted counterparts **12a–e**, **14a–e** and **16a–e**. Among all the *ortho*-substituted diarylmethylnapthyloxy ethylamines **11a–e**, **13a–e** and **15a–e**, diphenylmethylnapthyloxy ethylamines **11a–e** showed better activity (except for **15b** and **15d)** than the rest of



Scheme 1. Reagents and conditions: (a) $NaBH_4$, methanol, 0 °C rt, 2 h, **7a** (95%), **7b** (96%) and **7c** (95%); (b) 2-naphthol, dry benzene, reflux, 2 h, **8a** (89%), **9a** (84%) and **10a** (85%); (c) 1-naphthol, dry benzene, reflux, 2 h, **8b** (73%), **9b** (70%) and **10b** (68%); (d) dialkylaminoethyl chloride hydrochloride ($ClCH_2CH_2R.HCl$), anhyd K_2CO_3, dry acetone, reflux, 8–10 h, (yields given in Table 1).

Table 1. Synthesized diarylmethyl naphthol derivatives with in vitro antitubercular activity against *M. tuberculosis* $H_{37}R_v$

Serial No.	Compound	X	R	Yield[a] (%)	MIC[b] (μg/mL) MABA	MIC (μg/mL) Agar microdilution method
1	**11a**	H	$N(CH_3)_2$	70	6.25	3.12
2	**11b**	H	$N(C_2H_5)_2$	67	6.25	3.12
3	**11c**	H		80	6.25	3.12
4	**11d**	H		81	6.25	3.12
5	**11e**	H		69	6.25	3.12
6	**12a**	H	$N(CH_3)_2$	78	12.5	6.25
7	**12b**	H	$N(C_2H_5)_2$	73	6.25	12.5
8	**12c**	H		68	6.25	12.5
9	**12d**	H		63	12.5	>12.5
10	**12e**	H		63	12.5	12.5
11	**13a**	Cl	$N(CH_3)_2$	66	3.12	6.25
12	**13b**	Cl	$N(C_2H_5)_2$	68	3.12	6.25
13	**13c**	Cl		74	3.12	6.25
14	**13d**	Cl		70	3.12	6.25
15	**13e**	Cl		69	3.12	6.25
16	**14a**	Cl	$N(CH_3)_2$	79	NA	>12.5
17	**14b**	Cl	$N(C_2H_5)_2$	67	12.5	12.5
18	**14c**	Cl		61	NA	12.5
19	**14d**	Cl		62	NA	12.5
20	**14e**	Cl		69	NA	>12.5
21	**15a**	F	$N(CH_3)_2$	69	3.12	6.25
22	**15b**	F	$N(C_2H_5)_2$	75	6.25	3.12
23	**15c**	F		79	3.12	6.25
24	**15d**	F		83	6.25	3.12
25	**15e**	F		76	6.25	12.5
26	**16a**	F	$N(CH_3)_2$	74	NA	>12.5
27	**16b**	F	$N(C_2H_5)_2$	73	NA	>12.5
28	**16c**	F		69	6.25	12.5
29	**16d**	F		79	12.5	12.5

Table 1 (*continued*)

Serial No.	Compound	X	R	Yield[a] (%)	MIC[b] (μg/mL) MABA	MIC (μg/mL) Agar microdilution method
30	**16e**	F		65	12.5	>12.5
31	Rifampin	—	—	69	0.2	0.2
32	Isoniazid (INH)	—	—	—	0.025	0.025

[a] Isolated yield after silica gel column chromatography.
[b] NA means not active at MIC of 12.5.

compounds in this series with a chloro or fluoro substituent on the *para*-position of a phenyl ring. This result indicated that presence of chloro or fluoro substituent on one phenyl ring has no beneficial effect on the antitubercular activity of diarylmethylnapthyloxy ethylamines. Further, within a particular series antitubercular activity almost remains unchanged on changing the basic alkylaminoethyl side chains.

The in vitro cytotoxicity of compounds **11a–e**, **15b** and **15d** (having a MIC of 3.12 μg/mL in agar microdilution technique) in VERO cell lines was determined using a dye reduction assay following three days exposure to test compounds as previously described.[5e] All these compounds were found to be toxic and hence not suitable for in vivo evaluation.

In conclusion, a series of diarylmethylnapthyloxy ethylamines were synthesized by aminoalkylation of diarylnaphthols obtained by Friedel–Crafts alkylation of 1- and 2-naphthols using diarylcarbinols as the alkylating agents. *Ortho*-substituted diarylmethylnapthyloxy ethylamines **11a–e**, **13a–e** and **15a–e** are more active than their *para*-substituted counterparts **12a–e**, **14a–e** and **16a–e**. Among the *ortho*-substituted diarylmethylnapthyloxy ethylamines, **11a–e**, **15b** and **15d** showed promising activity in vitro. It is conceivable that these triarylmethane derivatives containing naphthalene ring might act as a lead for optimizing antitubercular activity. It will be interesting to prepare new analogues of the most active compounds, which may be nontoxic with significant anti-tubercular activity.

Acknowledgements

S.K.D. thanks CSIR for providing fellowship (NET SRF). The Department of Science and Technology (DST) and Indian Council of Medical Research (ICMR), New Delhi, India, supported this project.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.089.

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