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Synthesis and antitubercular activity of 2-hydroxy-aminoalkyl derivatives of diaryloxy methano phenanthrenes☆

Gautam Panda,[a,*] Shagufta,[a] Anil K. Srivastava[b] and Sudhir Sinha[c]

[a]*Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, UP, India*
[b]*Microbiology Division, Central Drug Research Institute, Lucknow 226001, UP, India*
[c]*Drug Target Discovery and Development Division, Central Drug Research Institute, Lucknow 226001, UP, India*

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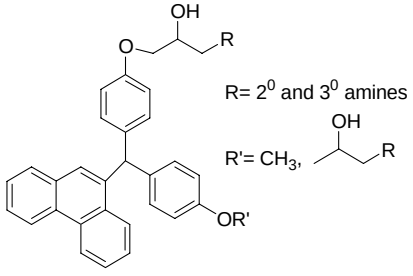
Abstract—A series of 2-hydroxy-aminoalkyl derivatives of diaryloxy methano phenanthrenes were synthesized from nucleophilic opening of oxirane with different amines. These compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}R_v$ in vitro and showed MIC in the range of 3.12–25 μg/ml.

1. Introduction

Despite having modern and sophisticated methods of prevention, early detection, diagnosis, and thereafter treatment for TB patients, the appearance of multi-drug-resistant (MDR) strains, with the threat of global human immunodeficiency virus (HIV), has led to declare tuberculosis as 'global emergency' by WHO (World Health Organization).[1–4] Resistance has been surfaced for all old drugs and for newly appearing drugs.[5,6] The funds for developing antituberculosis agents are increasing enormously from academic and pharmaceutical institutions. Thus, there is an urgent need for anti-TB agents having new mechanism of action, which will be able to minimize the chances of MDR strains.

Phenanthrene and their substituted analogs are well known to exhibit various biological activities such as antimicrobial,[7] cytotoxic,[8] antifungal,[9] and antimalarial.[10] Recently, we have reported that diaryloxy methanophenanthrenes and anthracene derivatives having enough hydrophobicity through a number of aryl rings served as a lead for developing antitubercular agents.[11] This result prompted us to take diaryloxy methanophenanthrenes as an active pharmacophore for further diversification. However, several amino alcohol derivatives **2**, **3**, **4**, **5**, and **6** along with ethambutol **1** are well known to have antitubercular activity (Fig. 1).[12] Considering antitubercular activity of amino alcohol derivatives, we incorporated this moiety on diaryloxy methanophenanthrene pharmacophore and thus designed to synthesize **7** as our target molecule.



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2. Chemistry

In our program toward synthesizing 2-hydroxy-amino alkyl derivatives, the compound **8**[11a] was reacted with epichlorohydrin in the presence of K_2CO_3 to furnish the oxirane **9** 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 (**10a**–**m**), Scheme 1 (see Table 1).

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* Corresponding author. Tel.: +915222364635; fax: +915222223938; e-mail addresses: gautam_panda@lycos.com; bapi.rm@yahoo.com

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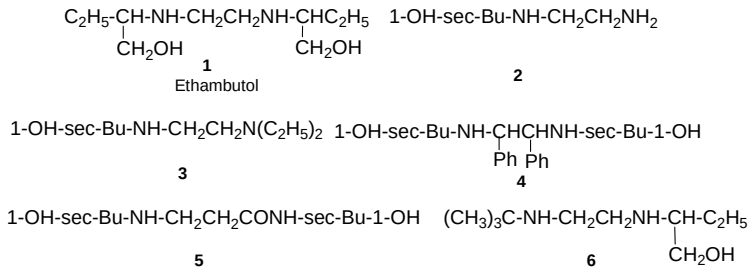
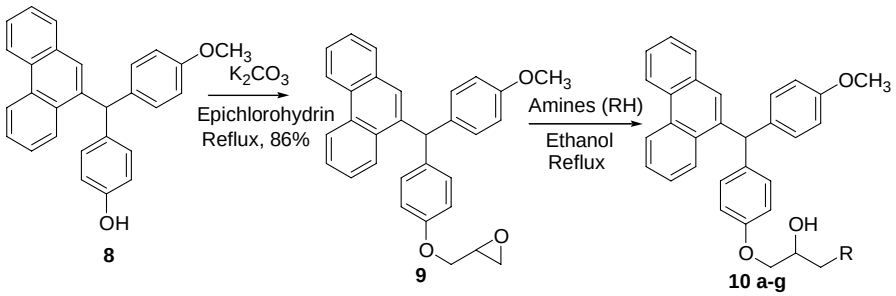


Figure 1.



Scheme 1.

Table 1. Synthesis of 2-hydroxy-amino alkyl derivatives (**10a**–**m**)

Compound	Amines (RH)	Yield **10a**–**m** (%)
10a	Cycloheptylamine	73
10b	Cyclohexylamine	84
10c	Cyclopropylamine	74
10d	*n*-Butylamine	69
10e	Morpholine	73
10f	*N*-Methyl-piperazine	70
10g	*N*-Benzyl-piperazine	60
10h	Piperidine	96
10i	Diethylamine	72
10j	Pyrrolidine	75
10k	1-(3-Aminopropyl)imidazole	76
10l	1-(2-Aminoethyl)-pyrrolidine	67
10m	4-(2-Aminoethyl)-morpholine	74

All the 2-hydroxy-amino alkyl derivatives **10a**–**m** were active against *Mycobacterium tuberculosis* (Table 3). We became interested in synthesizing their *bis*-2-hydroxy-amino alkyl derivatives to evaluate their antitubercular activity. Toward this objective, the *bis*-phenolic derivative **11**[11a] was reacted with epichlorohydrin in the presence of K_2CO_3 to furnish the *bis*-oxirane **12** (90%). Nucleophilic addition of different amines gave *bis*-2-hydroxy-amino alkyl derivatives (**13a**–**d**), Scheme 2 (see Table 2).

3. Biology

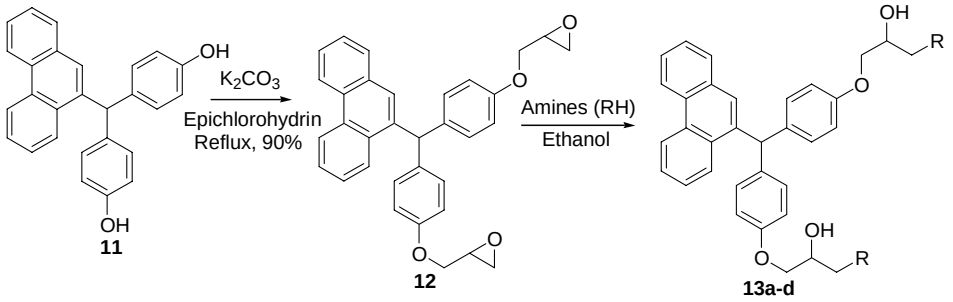
3.1. Determination of antitubercular activity in vitro

The activity of the compounds (**10a**–**m** and **13a**–**d**) against *M. tuberculosis* $H_{37}R_v$ was determined through agar microdilution technique,[13] and standard BACTEC radiometric growth assay[13] and their results are shown in Table 3.

3.2. Structure/activity relationship

In our earlier paper,[11a] it was noted that diaryloxy methano phenanthrene derivatives showed antitubercular activity with MIC ranging from 6.25 to 12.5 μg/mL. Interestingly, introducing 2-hydroxy-amino-alkyl moiety on the diaryloxymethanophenanthrene pharmacophore gave better antitubercular activity in compounds **10a**–**m** and **13a**–**d**. Among all the compounds tested, two compounds **10a** and **10k** showed MIC of 3.12 μg/ml and six compounds **10b**, **10d**, **10i**, **10m**, **13a**, and **13c** showed MIC of 6.25 μg/ml. Compound **10c** having cyclopropyl amine gave MIC 25 μg/ml, whereas cyclohexyl and cycloheptyl amine containing compounds **10b** and **10a** showed MIC of 6.25 and 3.12 μg/ml, respectively, implying that increasing the ring size of the amines gave a lower order of MIC for antitubercular activity. Compounds containing *n*-butylamine **10d** and diethyl amine **10i** showed MIC of 6.25 μg/ml, whereas compounds containing piperidine **10h** and pyrrolidine **10j** gave MIC 12.5 μg/ml. Thus, change of cyclic amines to acyclic amines gave better antitubercular activity. Compound **10e** containing morpholine ring showed MIC of 25 μg/ml. Introduction of 4-(2-amino ethyl) chain onto morpholine in **10m** gave better activity (MIC 6.25 μg/ml). Further, replacement of morpholine with imidazole in **10k** gave MIC of 3.12 μg/ml. Thus, incorporation of imidazole ring with a longer aliphatic chain gave better activity. Introduction of another 2-hydroxy-aminoalkyl group on diaryloxy methano phenanthrene in **13a**–**d** does not have much effect on activity.

In conclusion, a series of 2-hydroxy-amino alkyl derivatives of diaryloxy methano phenanthrenes that have been synthesized demonstrated significant antitubercular activity. Compounds containing cycloheptyl amine **10a** and imidazole ring with long aliphatic chain



Scheme 2.

Table 2. Synthesis of *bis*-2-hydroxy-amino alkyl derivatives (**13a**–**d**)

Compound	Amines (RH)	Yield (%)
13a	Piperidine	94
13b	Pyrrolidine	64
13c	Cyclohexylamine	66
13d	*N*-Methyl-piperazine	72

Table 3. In vitro antituberculosis activity of **10a**–**m** and **13a**–**d** against *M. tuberculosis* $H_{37}R_v$

Compound	MIC (μg/mL)	
	Agar micro dilution method	BACTEC method
9	25	ND
10a	3.12	3.12
10b	12.5	6.25
10c	25	25
10d	6.25	6.25
10e	25	ND
10f	12.5	12.5
10g	25	ND
10h	12.5	12.5
10i	6.25	6.25
10j	12.5	12.5
10k	3.12	3.12
10l	25	25
10m	6.25	6.25
13a	6.25	12.5
13b	12.5	12.5
13c	6.25	12.5
13d	12.5	12.5
Rifampin	0.1	0.2
Isoniazid (INH)	0.05	0.025

ND means not done in that particular test system.

10k seem to have an encouraging effect on activity. This suggests that incorporation of amino alcohol moiety through opening of oxirane with various nitrogen containing nucleophiles might be a suitable pharmacophore for optimizing antitubercular activity of diaryloxy methano phenanthrenes.

4. Experimental

4.1. Typical procedure for 10a–10m

The compound **9** (300 mg, 0.67 mmol) and amine (1.05 mmol) were taken in ethanol (20 mL) and refluxed for 7 h. The ethanol was removed and the residue was column chromatographed over silica gel and elution with 5% methanol in chloroform furnished the compounds **10a**–**10m**.

4.1.1. 1-Cycloheptylamino-3-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-propan-2-ol 10a. Pale yellow solid, 275 mg (74%), mp 72 °C. IR (KBr): 3370, 2923, 1603, 1507, 1246, 1177, 1033, 801, 746 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.70–8.60 (m, 2H), 8.01 (d, 1H, J = 7.8 Hz), 7.63–7.45 (m, 5H), 7.13–7.01 (m, 5H), 6.82–6.77 (m, 4H), 6.11 (s, 1H), 4.15–4.01 (m, 1H), 3.92–3.90 (m, 2H), 3.74 (s, 3H), 3.00 (br s, 1H), 2.90–2.64 (m, 3H), 1.84–1.80 (m, 2H), 1.64–1.38 (m, 10H). MS: 560 (M^{+1}). Anal. $C_{38}H_{41}NO_3$; Calcd: C, 81.54; H, 7.38; N, 2.50%. Found: C, 81.59; H, 7.42; N, 2.55%.

4.1.2. 1-Cyclopropylamino-3-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-propan-2-ol 10c. Pale yellow solid, (275 mg, 94%), mp 60 °C. IR (KBr): 3344, 3015, 2936, 1607, 1508, 1243, 1178, 1037, 832, 743 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.73–8.62 (m, 2H), 8.03 (d, 1H, J = 8.1 Hz), 7.69–7.44 (m, 5H), 7.14 (s, 1H), 7.03 (d, 4H, J = 8.4 Hz), 6.82 (m, 4H, J = 8.4 Hz), 6.14 (s, 1H), 4.07–4.03 (m, 1H), 3.95–3.88 (m, 2H), 3.78 (s, 1H), 2.94–2.82 (m, 2H), 2.38 (br s, 2H), 2.20–2.14 (m, 1H), 0.47–0.36 (m, 4H). MS: 504 (M^{+1}). Anal. $C_{34}H_{33}NO_3$; Calcd: C, 81.08; H, 6.60; N, 2.78%. Found: C, 81.12; H, 6.65; N, 2.83%.

4.1.3. 1-{4-[(4-Methoxy-phenyl)-phenanthren-9-yl-methyl]-phenoxy}-3- morpholin-4-yl-propan-2-ol 10e. Pale yellow solid, 260 mg (73%), mp 72 °C. IR (KBr): 3417, 2928, 1609, 1504, 1243, 1174, 1113, 1032, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.73–8.63 (m, 2H), 8.03 (d, 1H, J = 8.1 Hz), 7.69–7.44 (m, 5H), 7.14 (s, 1H), 7.05 (d, 4H, J = 8.3 Hz), 6.86–6.80 (m, 4H), 6.14 (s, 1H), 4.13–4.06 (m, 1H), 3.97–3.95 (m, 2H), 3.78 (s, 3H), 3.74–3.70 (m, 4H), 2.68–2.63 (m, 2H), 2.56–2.42 (m, 4H). MS: 534 (M^{+1}). Anal. $C_{35}H_{35}NO_4$; Calcd: C, 78.77; H, 6.11; N, 2.62%. Found: C, 78.81; H, 6.17; N, 2.67%.

Acknowledgments

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