4-[10-(Methoxybenzyl)-9-anthryl]phenol derivatives as new antitubercular agents[#]

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Dedicated to Dr. Nitya Anand on the occasion of his 80th birthday

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Abstract

A series of 4-[10-(methoxybenzyl)-9-anthryl]phenyloxyalkylamine derivatives was prepared by aminoalkylation of 4-[10-(methoxybenzyl)-9-anthryl]phenols obtained by Friedel-Crafts reaction of 9-anthryl(methoxyphenyl)methanols. The title compounds were teated against *Mycobacterium tuberculosis* $H_{37}R_v$ and showed antitubercular activity in the range of 12.5–25 μg/mL.

Keywords: 9-Anthryl(methoxyphenyl)methanols, aminopropan-2-ols, Friedel-Crafts reaction, antitubercular agents

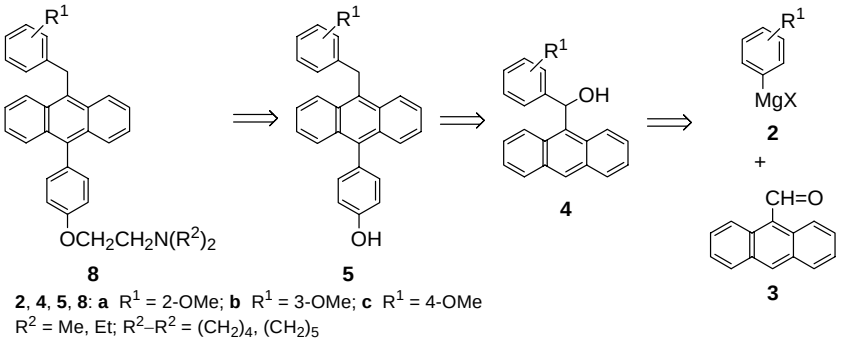
Introduction

Tuberculosis (TB) is a growing global health problem because of lack of proper therapeutic agents for its remedy.[1] There is another serious and alarming problem due to the resurgence of TB especially for the synergy with global human immunodeficiency virus (HIV) and the emergence of multi-drug-resistant (MDR) strains.[2] Thus, there is an urgent need for developing new anti-tubercular drugs which will effectively kill MDR strains, less toxic, shortened duration of therapy, rapid mycobactericidal mechanism of action in the intracellular environment.

Halogen derivatives of benzo[*h*]chromene and benzo[*a*]anthracenes are known for antitumor, antimicrobial and other biological activities.[3] Benzophenone derivatives also possess antimycobacterial activity.[3] In our recent paper,[4] we have described that diaryloxymethano-phenanthrenes with basic amino substituents could serve as a lead for antitubercular agents. With this knowledge at hand, we became interested in methoxybenzyl- and hydroxyphenyl-substituted

anthracene derivatives carrying a basic amino side chain and in studying the effect on the growth of *M. tuberculosis*. These compounds are sufficiently hydrophobic, a requirement for good antitubercular activity. Thus, we chose *N*-[2-[4-[10-(methoxybenzyl)-9-anthryl]phenoxy]alkyl)-amines **8** as targets for developing antitubercular agents. The synthesis and biological evaluation of a series of compounds of the structural prototype **8** is the subject of this paper.

Retrosynthetic analysis of *N*-[2-[4-[10-(methoxybenzyl)-9-anthryl]phenoxy]alkyl)amines **8** requires 4-[10-(methoxybenzyl)-9-anthryl]phenols **5** as precursors obtainable by Friedel-Crafts alkylation of 9-anthryl(methoxyphenyl)methanols **4**,[5] which in turn, can be synthesized by the addition of bromoanisole-derived Grignard reagents **2** to anthracene-9-carbaldehyde **3** (Scheme 1).



Scheme 1. Retrosynthesis of target compounds 8.

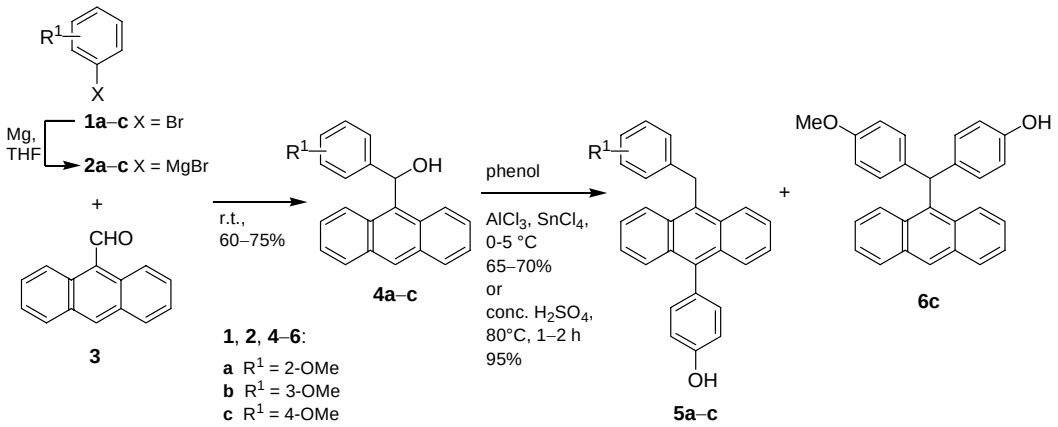
Results and Discussion

Chemistry

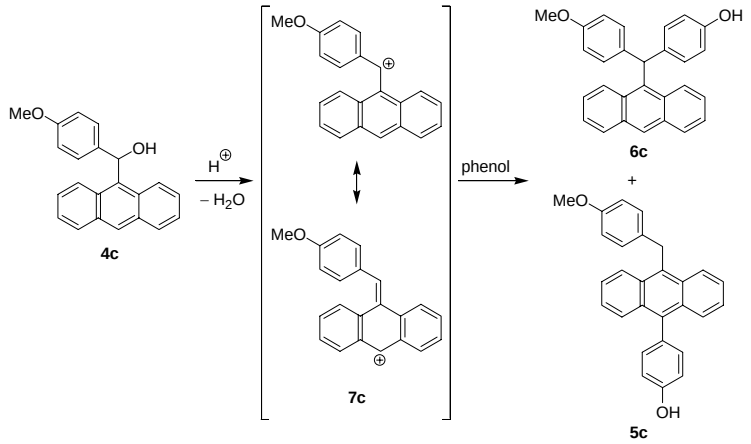
The reaction of Grignard reagents **2a–c** derived from bromoanisoles **1a–c** with anthracene-9-carbaldehyde **3** furnished 9-anthryl(methoxyphenyl)methanols **4a–c** in 60–75% yield (Scheme 2). Subsequent Friedel-Crafts alkylation of 9-anthryl(methoxyphenyl)methanols **4a–c** with phenol in the presence of $AlCl_3/SnCl_4$ or conc. H_2SO_4 provided 4-[10-(methoxybenzyl)-9-anthryl]phenols **5a–c**. In the case of the 4-methoxy-substituted compound **5c** a sideproduct 4-[9-anthryl(4-methoxyphenyl)methyl]phenol **6c** was isolated as well (Scheme 2).

Upon Lewis acid complexation or protonation of 4-[10-(methoxybenzyl)-9-anthryl]phenols **5a–c** the formation of a cationic intermediate is presumed, which undergoes electrophilic substitution at phenol. The reaction of 9-anthryl(4-methoxyphenyl)methanol **4c** with phenol in the presence of conc. H_2SO_4 is assumed to proceed via the cationic intermediate **7c** as resembled by resonance structures such as 9-anthryl(4-methoxyphenyl)methyl cation and 1-(4-methoxy-benzylidene)-9,10-dihydroanthracen-9-yl cation (Scheme 3) giving rise to the formation of 4-[10-(4-methoxybenzyl)-9-anthryl]phenol **5c** and 4-[9-anthryl(4-methoxyphenyl)methyl]phenol **6c** as major and minor products, respectively.

Both isomers **5c** and **6c** were characterized by ^{1}H NMR spectra: The methylene group of **5c** gives rise to a singlet at δ 4.85 (2H), the ^{1}H NMR spectrum of **6c** exhibits two singlets (1H each) at δ 6.97 (methine proton) and δ 8.44 (10-H of the anthracene moiety). The mass spectra of both isomers are characteristic as well: **5c** gives rise to a peak *m/z* 283, assigned to the [10-(4-hydroxyphenyl)-9-anthryl]methyl cation, whereas the fragment ion *m/z* 213 of **6c** is attributed to the (4-hydroxyphenyl)(4-methoxyphenyl)methyl cation.



Scheme 2. Synthesis of 4-[10-(methoxybenzyl)-9-anthryl]phenols **5a**–**c** via 9-anthryl(methoxyphenyl)methanols **4a**–**c**, and formation of 4-[9-anthryl(4-methoxyphenyl)methyl]phenol **6c**.



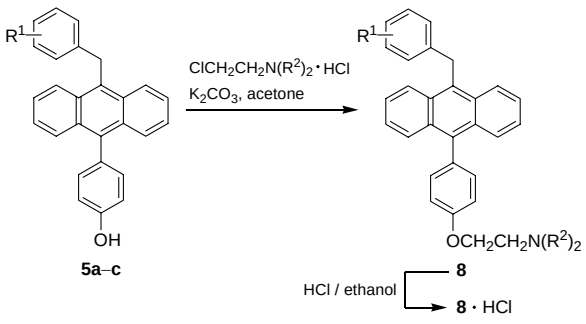
Scheme 3. Resonance structures of carbocation intermediate **7c**; formation of phenols **5c** and **6c**.

The target as possible antitubercular agents were the aminoalkoxy derivatives **8**. The reaction of **5a**–**c** with different alkylamine hydrochlorides in the presence of K_2CO_3 and acetone led to the formation of compounds **8** in good yields (Scheme 4). By treatment of amines **8** with ethanolic hydrogen chloride the corresponding salts **8**·HCl were prepared. The salts **8**·HCl were tested and found active against *M. tuberculosis* with MIC in the range of 12.5–25 μg/mL (Table 1). Therefore, *N*-[4-[10-(methoxybenzyl)-9-anthryl]phenoxy]alkylamine derivatives were selected as active the pharmacophore, and further synthetic transformations were performed.

Table 1. *In vitro* antitubercular activity of **8**·HCl and **10** against *M. tuberculosis* $H_{37}R_v$

	MIC [μg/mL]		
Compound	Agar dilution Method	BACTEC Method	MABA Method
8aa·HCl	n.a.	n.a.	n.a.
8ab·HCl	n.a.	n.a.	n.a.
8ac·HCl	25	12.5	12.5
8ad·HCl	25	n.d.	12.5
8bc·HCl	25	n.d.	12.5
8bd·HCl	n.a.	n.a.	n.a.
8ca·HCl	25	n.a.	12.5
8cb·HCl	25	n.d.	12.5
8cc·HCl	25	n.d.	12.5
8cd·HCl	25	12.5	25
10aa	n.a.	n.a.	n.a.
10ab	n.a.	n.a.	n.a.
10ac	n.a.	n.a.	n.a.
10ad	n.a.	n.a.	n.a.
10ba	25	n.d.	25
10bb	n.a.	n.d.	n.a.
10bc	n.a.	n.d.	25
10bd	25	n.d.	n.a.
10be	n.a.	n.d.	n.a.
10cb	25	n.d.	n.a.
10cc	25	n.d.	25
10cd	n.a.	n.d.	n.a.
10cf	n.a.	n.d.	n.a.

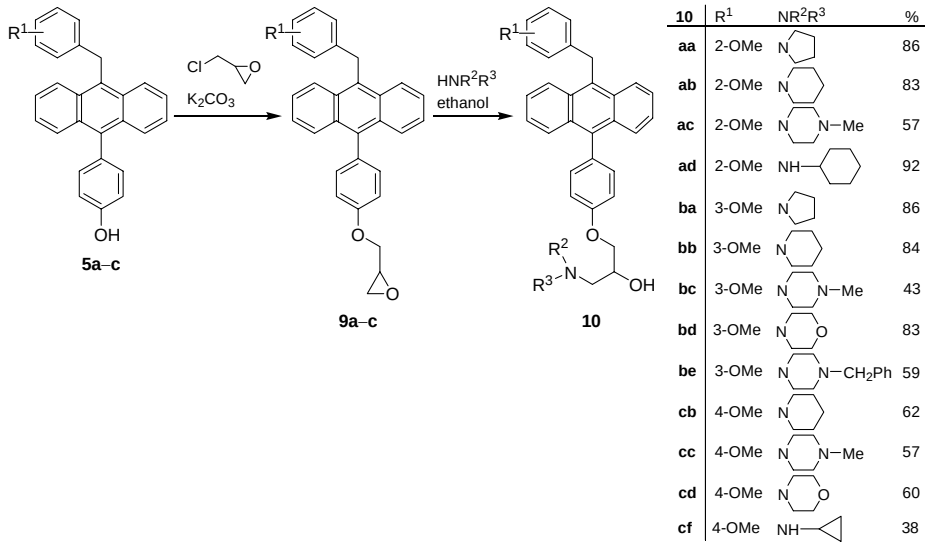
n.a.: not active at 25 μg/mL; n.d.: not determined.



8· HCl	R^1	$N(R^2)_2$	%
aa	2-OMe	$N(CH_3)_2$	93
ab	2-OMe	$N(CH_2CH_3)_2$	83
ba	3-OMe	$N(CH_3)_2$	54
bb	3-OMe	$N(CH_2CH_3)_2$	80
bc	3-OMe	N	80
bd	3-OMe	N	90
ca	4-OMe	$N(CH_3)_2$	67
cb	4-OMe	$N(CH_2CH_3)_2$	99
cc	4-OMe	N	80
cd	4-OMe	N	80

Scheme 4. Synthesis of *N*-[2-[4-[10-(methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-dialkyl-amines **8** and hydrochlorides **8**·HCl.

We were interested to study the effect of 3-amino-2-hydroxy-1-propoxy substituents attached to the [(methoxybenzyl)anthryl]phenyl pharmacophore. Towards this objective, phenols **5a**–**c** were treated with epichlorohydrin in the presence of K_2CO_3 to furnish the epoxides **9a**–**c** in good yields (58–87%). The epoxides **9a**–**c**, in turn, reacting with commercially available amines afforded a variety of 1-aminopropan-2-ol derivatives **10** (Scheme 5).



10	R^1	NR^2R^3	%
aa	2-OMe	N	86
ab	2-OMe	N	83
ac	2-OMe	N N–Me	57
ad	2-OMe	NH	92
ba	3-OMe	N	86
bb	3-OMe	N	84
bc	3-OMe	N N–Me	43
bd	3-OMe	N O	83
be	3-OMe	N N–CH_2Ph	59
cb	4-OMe	N	62
cc	4-OMe	N N–Me	57
cd	4-OMe	N O	60
cf	4-OMe	NH	38

Scheme 5. Synthesis of 3-(dialkylamino)-1-[4-[10-(methoxybenzyl)-9-anthryl]phenoxy]propan-2-ols **10**.

Biology

The in vitro activity of the products against *M. tuberculosis* $H_{37}R_v$ was determined by agar micro dilution technique, standard BACTEC radiometric growth assay and micro almar blue assay (MABA).[6–8] These compounds were tested at different concentrations to evaluate the anti-tubercular activity of products **8**·HCl and **10** (Table 1).

The 10-(methoxybenzyl)-substituted anthracenes were synthesized and tested to study the effect of 2-, 3-, and 4-methoxy substituents on the antitubercular activity. It is noteworthy that all anthracene derivatives **8aa**·HCl, **8ab**·HCl and **10aa**–**ad** with *o*-methoxybenzyl groups showed no antitubercular activity at 25μg/mL, whereas the *m*- and *p*-methoxybenzyl-substituted derivatives except **8bd**·HCl, **10bb**, **10be**, **10cd**, and **10cf** showed activity in the range of 12.5–25 μg/mL. This is possibly due to better exposed *m*- and *p*-methoxy substituents on the anthracene skeleton. Thus, anthracenes with *p*- and *m*-methoxybenzyl groups at position 10 and alkylaminoalkoxy-phenyl substituents attached to position 9 exhibit a better antitubercular activity in vitro.

Summary

The analysis of *in vitro* data for the compounds **8**·HCl and **10** clearly suggests that these classes of compounds are indeed antitubercular. We are reporting for the first time that substituted

anthracenes with methoxybenzyl at 9-position and hydroxyphenyl with alkylaminohydrochloride chains at 10-position might be a suitable pharmacophore for developing antitubercular agents. A rational and logical design of a compound retaining the antitubercular activity with lower value of MIC may be a favorable molecule. Syntheses of the compounds and their biological evaluation towards this direction are currently underway.

Experimental Section

General Procedures. All the reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by spraying the plates with 2% $CeSO_4$ in 2 N H_2SO_4 and warming on a hot plate or in an oven at about 100 °C. For column chromatography silica gel 60–120 mesh was used. IR spectra were recorded on Perkin Elmer 881 or FT IR 820/PC instrument. Electron impact mass spectra (EI-MS) were recorded on JEOL (Japan) /D-300 instrument, and FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon /Xenon (6 KV, 10 MA) as the FAB gas. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Advance DPX 200 MHz spectrometer using TMS as internal reference. Elemental analyses were carried out on a Carlo ERBA-1108 analyzer. Commercially available grades of organic solvents of adequate purity were used. Acetone after heating at reflux with $KMnO_4$ for 4 h was distilled and stored in a bottle over dry K_2CO_3. Benzene was refluxed over freshly cut sodium metal pieces and kept over molecular 3 Å sieves. Tetrahydrofuran is dried over calcium sulphate and refluxed over lithium aluminum hydride; peroxides were removed by passage through a column of alumina, followed by distillation and storage over molecular sieves 3Å.

9-Anthryl(2-methoxyphenyl)methanol (4a). To a solution of 2-bromoanisol **1a** (8.98 mL, 72.63 mmol) in dry THF (20 mL) was added magnesium (1.97 g, 82.28 mmol), and the mixture was stirred at room temperature for 2h. To the Grignard reagent **2a** thus formed was added anthracene-9-carbaldehyde **3** (5 g, 24.2 mmol) in THF (25 mL), and the reaction mixture was stirred for 3–4 h. After quenching with saturated aq. NH_4Cl (ca. 20 mL) THF was removed in vacuo. The mixture was extracted three times with ethyl acetate, the extract was washed with brine and dried over sodium sulfate. After concentration of the product solution the residue was chromatographed on silica gel with 10% ethyl acetate in hexane (R_f = 0.7) furnishing **4a** (4.5 g, 60%) as a yellow semi solid. IR (neat): 3262, 1593, 1456, 1237, 1035 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.43 (1H, s), 8.42 (2H, d, *J* = 8.6 Hz), 7.94 (2H, d, *J* = 8.4 Hz), 7.39–7.30 (7H, m), 6.86 (1H, t, *J* = 7 Hz), 6.63 (1H, d, *J* = 7 Hz), 6.57 (1H, d, *J* = 7 Hz), 4.08 (1H, s), 3.81 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.0, 132.3, 131.4, 130.9, 129.6, 128.9, 126.5, 125.9, 125.3, 121.1, 111.0, 69.4, 55.9. MS (FAB): *m/z* (%) 314 (100) [M$^+$], 297 (90) [M –OH]. Anal. Calcd for $C_{22}H_{18}O_2$ (314.38): C, 84.05; H, 5.77. Found: C, 84.99; H, 5.80.

9-Anthryl(3-methoxyphenyl)methanol (4b). As described for **4a**, 3-bromoanisol **1b** (9.19 mL,

72.5 mmol) in dry THF (25 mL), magnesium (1.97 g, 82.0 mmol) and anthracene-9-carbaldehyde **3** (5 g, 24.2 mmol) in THF (25 mL) furnished **4b** (5.75 g, 75%) as a yellow semi solid, R_f = 0.7 (10% ethyl acetate/hexane). IR (neat): $\tilde{\nu}$ 3409, 1599, 1488, 1256, 1045, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.46 (1H, s), 8.34 (2H, d, *J* = 8.3 Hz), 8.01 (2H, d, *J* = 8.2 Hz), 7.46–7.35 (4H, m), 7.17 (1H, t, *J* = 7.8 Hz), 7.06 (1H, s), 6.86 (1H, d, *J* = 7.6 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 3.72 (3H, s), 2.62 (1H, d, *J* = 3.8 Hz). MS (FAB): *m/z* (%) 314 (100) [M^+], 297 (90) [M -OH]. Anal. Calcd for $C_{22}H_{18}O_2$ (314.38): C, 84.05; H, 5.77. Found: C,84.19; H, 5.81.

9-Anthryl(4-methoxyphenyl)methanol (4c). As described for **4a**, 4-bromoanisol **1c** (16.15 g, 0.086 mol) in dry THF (20 mL), magnesium (2.06 g, 0.086 mol) and anthracene-9-carbaldehyde **3** (5.94 gm, 0.028 mol) in THF (25 mL) furnished **4c** (6.0 g, 66%) as a yellow semisolid. R_f = 0.7 (10% ethyl acetate/hexane). IR (neat): $\tilde{\nu}$ 3510, 2362, 1604, 1507, 1242, 1169, 732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.46 (1H, s), 8.36 (2H, d, *J* = 9 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 8.01 (1H, d, *J* = 9 Hz), 7.47–7.34 (5H, m), 7.27 (1H, d, *J* = 9 Hz), 6.79 (2H, d, *J* = 10 Hz), 3.74 (3H, s), 2.64 (1H, d, *J* = 5.4 Hz). MS (EI): *m/z* (%) 314 (100) [M^+], 297 (90) [M –OH], 107 (20) [$OCH_3C_6H_5$]. Anal. Calcd for $C_{22}H_{18}O_2$ (314.38): C, 84.05; H, 5.77. Found: C, 84.22; H, 5.78.

4-[10-(2-Methoxybenzyl)-9-anthryl]phenol (5a). To a solution of carbinol **4a** (3.0 g, 9.55 mmol) and phenol (3.15 mL, 38.22 mmol) in dry benzene (40 mL) was added a catalytic amount of conc. H_2SO_4, and the mixture was heated at 80 °C for 1h. After cooling, the reaction mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with ethyl acetate. The concentrated extract was subjected to column chromatography on silica gel and elution with 15% ethyl acetate in hexane (R_f = 0.6) furnishing **5a** (2.6 g, 69%) as a white solid; mp 115 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ 3441, 1599, 1490, 1232 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (2H, d, *J* = 8.2 Hz), 7.74 (2H, d, *J* = 7.6 Hz), 7.41–7.24 (6H, m), 7.23 (1H, d, *J* = 8Hz), 7.05 (2H, d, *J* = 8Hz), 6.90 (1H, d, *J* = 8 Hz), 6.61 (1H, t, *J* = 7 Hz), 6.46 (1H, d, *J* = 7 Hz), 5.20 (1H, bs), 4.98 (2H, s), 4.06 (3H, s). MS (FAB): *m/z* (%) 390 (100) [M^+], 297 (60) [M –C_6H_4OH], 121 (30) [$OCH_3C_6H_4CH_2$]. Anal. Calcd for $C_{28}H_{22}O_2$ (390.47): C, 86.13; H, 5.68. Found: C, 86.51; H 5.91.

4-[10-(3-Methoxybenzyl)-9-anthryl]phenol (5b). As described for **5a**, **4b** (3.83 g, 12.19 mmol) and phenol (4.02 g, 48.79 mmol) furnished **5b** (2.69 g, 56%) as white solid; mp 108 °C (dichloromethane), R_f = 0.6 (15% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 3414, 1601, 1440, 1379, 1253, 1141, 1037, 757 cm^{-1}. ^1H NMR(200 MHz, $CDCl_3$): δ 8.23 (2H, d, *J* = 8.6 Hz), 7.77 (2H, d, *J* = 8.4 Hz), 7.49–7.27 (6H, m), 7.19 (1H, s), 7.14 (2H, d, *J* = 8 Hz), 6.75 (2H, d, *J* = 8 Hz), 6.71 (1H, d, *J* = 8.1 Hz), 4.99 (2H, s), 3.66 (3H, s), 3.03 (1H, bs); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.9, 162.0, 147.7, 142.4, 137.4, 136.3, 135.6, 135.3, 134.6, 133.1, 130.7, 129.8, 125.8, 120.6, 119.7, 115.8, 60.1, 38.7. MS(FAB): *m/z* (%) 390 (100) [M^+], 283 (40) [M –$OCH_3C_6H_5$]. Anal. Calcd for $C_{28}H_{22}O_2$ (390.47): C, 86.13; H, 5.68. Found: C, 87.22; H, 5.89.

4-[10-(4-Methoxybenzyl)-9-anthryl]phenol (5c). As described for **5a**, **4c** (2.85 g, 9.07 mmol) and phenol (1.28 g, 13.61 mmol) furnished **5c** (1.6 g, 55%) as a white solid; mp 194 °C (dichloromethane); R_f = 0.6 (15% ethyl acetate/hexane). ^1H NMR (200 MHz, $CDCl_3$): δ 9.04 (1H, s), 8.15 (2H, d, *J* = 8.7 Hz), 7.72 (2H, d, *J* = 8.7 Hz), 7.3 (2H, t, *J* = 6.9 Hz), 7.22 (2H, d, *J*

= 8.1 Hz), 7.16 (2H, d, *J* = 8.4 Hz), 7.02 (2H, d, *J* = 8.4 Hz), 6.98 (2H, d, *J* = 8.4 Hz), 6.64 (2H, d, *J* = 8.4 Hz), 4.85 (2H, s), 3.58 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.2, 156.2, 136.6, 132.4, 131.8, 131.3, 130.0, 129.5, 129.1, 128.5, 127.4, 125.0, 124.2, 124.1, 115.0, 113.3, 54.6, 32.2. MS (FAB): *m/z* (%) 390 (100) [M^+], 297 (10) [M –C_6H_4OH), 283 (30) [M –$OCH_3C_6H_4$]. Anal. Calcd for $C_{28}H_{22}O_2$ (390.47): C, 86.13; H, 5.68. Found: C, 87.41; H, 5.71.

4-[9-Anthryl(4-methoxyphenyl)methyl]phenol (6c). To a solution of carbinol **4a** (2.85 g, 9.07 mmol) and phenol (1.28 g, 13.61 mmol) in dry benzene (40 mL) was added a catalytic amount of conc. H_2SO_4, and the mixture was heated at 80 °C for 1h. After cooling, the reaction mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with ethyl acetate. The concentrated extract was subjected to column chromatography on silica gel and elution with 15% ethyl acetate in hexane furnishing **5c** (R_f = 0.6) and **6c** (R_f = 0.5) as a brown solid (100 mg, 5%); mp 78 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ 3431, 1605, 1507, 1443, 1245, 1172, 1028 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.44 (1H, s), 8.14 (2H, d, *J* = 9 Hz), 8.00 (2H, d, *J* = 8.5 Hz), 7.45–7.20 (4H, m), 7.14–6.90 (4H, m), 6.97 (1H, s), 6.77 (2H, d, *J* = 8 Hz), 6.69 (2H, d, *J* = 8 Hz), 3.75 (3H, s). MS (FAB): *m/z* (%) 390 (100) [M^+], 297 (40) [M –C_6H_4OH). Anal. Calcd for $C_{28}H_{22}O_2$ (390.47): C, 86.13; H, 5.68. Found: C, 86.31; H, 5.78.

***N*-[2-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-dimethylamine (8aa).** A mixture of **5a** (0.99 g, 2.56 mmol), anhydrous K_2CO_3 (1.769 g, 12.8 mmol), 1-(2-chloroethyl)-dimethylamine hydrochloride (0.554 g, 3.846 mmol) and dry acetone (50 mL) was heated at reflux for 7 h. K_2CO_3 was filtered off and acetone was distilled off. The residue was extracted with ethyl acetate, the extract was washed with water, brine and dried over anhydrous Na_2SO_4. Column chromatography on silica gel and elution with 35% ethylacetate in hexane (R_f = 0.4) furnished **8aa** (1.1 g, 93%) as a brown solid; mp 112 °C. IR (KBr): $\tilde{\nu}$ 3440, 1633, 769 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.19 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8 Hz), 7.40–7.20 (7H, m), 7.12 (2H, d, *J* = 8 Hz), 6.90 (1H, d, *J* = 7 Hz), 6.53 (1H, t, *J* = 7 Hz), 6.36 (1H, d, *J* = 7 Hz), 4.98 (2H, s), 4.22 (2H, t, *J* = 6.2 Hz), 4.07 (3H, s), 2.84 (2H, t, *J* = 6.2 Hz), 2.41 (6H, s). MS (FAB): *m/z* (%) 462 (100) [M^+], 390 (10) [M –$CH_2CH_2N(CH_3)_2$], 354 (10) [M –$OCH_3C_6H_4$].

2-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]-*N*,*N*-dimethylethanamine hydrochloride (8aa·HCl). Product **8aa** was dissolved in absolute ethanol (20 mL) and ethanolic HCl was added dropwise until the pH of the mixture was acidic. After removing ethanol the residue was recrystallized from a mixture of absolute ethanol and dry ether to give **8aa**·HCl (1.2 g, 95%) as a brown solid; mp 134 °C. Anal. Calcd for $C_{32}H_{32}ClNO_2$ (498.05): C, 77.17; H, 6.48; N, 2.81. Found: C, 76.20; H, 6.66; N 2.45.

***N*-[2-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-diethylamine (8ab).** As described for **8aa**, **5a** (0.99 g, 2.56 mmol), anhydrous K_2CO_3 (1.769 g, 12.8 mmol), 1-(2-chloro-ethyl)diethylamine hydrochloride (0.661 g, 3.846 mmol) and dry acetone (20 mL) furnished **8ab** (1.05 g, 83%) as a yellow solid, mp 144 °C (dichloromethane). R_f = 0.5 (50% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 2927, 1507, 1244, 759 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.09 (2H, d, *J* = 8.6 Hz), 7.66 (2H, d, *J* = 8 Hz), 7.36–7.26 (7H, m), 7.14 (2H, d, *J* = 8.6 Hz), 6.90 (1H, d, *J* = 7.5 Hz), 6.53 (1H, t, *J* = 7 Hz), 6.38 (1H, d, *J* = 7 Hz), 4.91 (2H, s), 4.12 (2H, t, *J* =

6.2 Hz), 3.98 (3H, s), 2.91 (2H, t, *J* = 6.2 Hz), 2.64 (4H, q, *J* = 7.2 Hz), 1.06 (6H, t, *J* = 7 Hz). MS (FAB): *m/z* (%) 490 (100) [M^+], 390 (20) [M –$CH_2CH_2N(CH_2CH_3)_2$].

2-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]-*N*,*N*-diethylethanamine hydrochloride (8ab·HCl). As described for **8aa**.HCl, product **8ab** was converted into **8ab**·HCl (1.272 g, 94%), as a brown solid; mp 154 °C. Anal. Calcd for $C_{34}H_{36}ClNO_2$ (526.11): C, 77.62; H, 6.90; N, 2.66. Found: C, 77.99; H, 7.10; N, 2.90.

***N*-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-dimethylamine (8ba).** As described for **8aa**, **5b** (250 mg, 0.64 mmol), anhydrous K_2CO_3 (0.44 g, 3.2 mmol), 1-(2-chloro-ethyl)dimethylamine hydrochloride (0.144 g, 0.96 mmol) and dry acetone (50 mL) furnished **8ba.** 160 mg, 54%) as a white solid; mp 122 °C. R_f = 0.6 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 2934, 1601, 1451, 1243, 1175, 1035 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.73 (2H, d, *J* = 8.4 Hz), 7.45–7.27 (6H, m), 7.16 (1H, s), 7.14 (2H, d, *J* = 8 Hz), 6.74 (2H, d, *J* = 8 Hz), 6.72 (1H, d, *J* = 8.2 Hz), 5.03 (2H, s), 4.22 (2H, t, *J* = 7 Hz), 3.69 (3H, s), 2.84 (2H, t, *J* = 7 Hz), 2.41 (6H, s). MS (FAB): *m/z* (%) 462 (100) [M^+], 390 (50) [M –$CH_2CH_2N(CH_3)_2$].

2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]-*N*,*N*-dimethylethanamine hydrochloride (8ba·HCl). As described for **8aa**·HCl, product **8ba** yielded **8ba**·HCl. (190 mg, 94%) as a white solid; mp 131 °C. Anal. Calcd for $C_{32}H_{32}ClNO_2$ (498.05): C, 77.17; H, 6.48; N, 2.81. Found: C, 77.11; H, 6.95; N, 2.85.

***N*-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-diethylamine (8bb).** As described for **8aa**, **5b** (400 mg, 1.02 mmol), anhydrous K_2CO_3 (709 mg, 5.12 mmol), 1-(2-chloro-ethyl)diethylamine hydrochloride (265 mg, 1.53 mmol) and dry acetone (20 mL) furnished **8bb**, 400 mg, 80%) as a white solid; mp 115 °C. R_f = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 2932. 1597, 1507, 1454, 1240, 1038 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.73 (2H, d, *J* = 8.4 Hz), 7.45–7.27 (6H, m), 7.16 (1H, s), 7.14 (2H, d, *J* = 8 Hz), 6.74 (2H, d, *J* = 8 Hz), 6.72 (1H, d, *J* = 8.1 Hz), 5.03 (2H, s), 4.19 (2H, t, *J* = 7 Hz), 3.70 (3H, s), 2.98 (2H, t, *J* = 7 Hz), 2.72 (4H, q, *J* = 7 Hz), 1.15 (6H, t, *J* = 7 Hz). MS (FAB): *m/z* (%) 490 (70) [M^+], 390 (20) [M –$CH_2CH_2N(CH_2CH_3)_2$].

2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]-*N*,*N*-diethylethanamine hydrochloride (8bb·HCl). As described for **8aa**·HCl, product **8bb** yielded **8bb**·HCl. (450mg, 98%) as a yellow solid; mp 126 °C. Anal. Calcd for $C_{34}H_{36}ClNO_2$ (526.11): C, 77.62; H, 6.90; N, 2.66. Found: C, 77.99; H, 7.04; N, 2.80.

1-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]pyrrolidine (8bc). As described for **8aa**, **5b** (400 mg, 1.02 mmol), anhydrous K_2CO_3 (709 mg, 5.13 mmol), 1-(2-chloroethyl)-pyrrolidine hydrochloride (265 mg, 3.846 mmol) and dry acetone (50 mL) yielded **8bc** (400 mg, 80%) as a yellow solid; mp 131 °C (dichloromethane). R_f =0.6 (50% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2926, 1507, 1246, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.72 (2H, d, *J* = 8.4 Hz), 7.46–7.27 (6H, m), 7.16 (1H, s), 7.14 (2H, d, *J* = 8 Hz), 6.73 (2H, d, *J* = 8 Hz), 6.72 (1H, d, *J* = 8.2 Hz), 5.03 (2H, s), 4.26 (2H, t, *J* = 7 Hz), 3.70 (3H, s), 3.01 (2H, t, *J* = 7 Hz), 2.71–2.68 (4H, m), 1.90–1.82 (4H, m). MS (FAB): *m/z* (%) 488 (40) [M^+], 390 (20) [M –$CH_2CH_2N(CH_2)_4$], 98 (100) [$CH_2CH_2N(CH_2)_4$].

1-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]pyrrolidine hydrochloride (8bc·HCl). As described for **8aa**·HCl, product **8bc** afforded **8bc**·HCl. (444 mg, 90%) as a brown solid; mp 141 °C. Anal. Calcd for $C_{34}H_{34}ClNO_2$ (524.09): C, 77.92; H, 6.54; N, 2.67. Found: C, 78.02; H, 6.87; N, 2.83.

1-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]piperidine (8bd). As described for **8aa**, **5b** (400 mg, 1.02 mmol), anhydrous K_2CO_3 (709 mg, 1.54 mmol), 1-(2-chloroethyl)-piperidine hydrochloride (250 mg, 1.54 mmol) and dry acetone (50 mL) gave **8bd** (460 mg, 90%) as a yellow solid; mp 138 °C (dichloromethane). R_f = 0.6 (50% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2929, 1507, 1246, 755 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.73 (2H, d, *J* = 8.4 Hz), 7.47–7.27 (6H, m), 7.16 (1H, s), 7.14 (2H, d, *J* = 8 Hz), 6.74 (2H, d, *J* = 8 Hz), 6.72 (1H, d, *J* = 8.2 Hz), 5.03 (2H, s), 4.25 (2H, t, *J* = 7 Hz), 3.70 (3H, s), 2.87 (2H, t, *J* = 7Hz), 2.61–2.56 (4H, m), 1.70–1.48 (6H, m). MS (FAB): *m/z* (%) 502 (100) [M^+], 390 (10) [M – $CH_2CH_2N(CH_2)_5$].

1-[2-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]piperidine hydrochloride (8bd·HCl). As described for **8aa**·HCl, product **8bd** afforded **8bd**·HCl (480 mg, 89%) as a yellow solid; mp 145 °C. Anal. Calcd for $C_{35}H_{36}ClNO_2$ (538.12): C, 78.12; H, 6.74; N, 2.60. Found: C, 78.19; H, 7.01; N, 2.87.

***N*-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-dimethylamine (8ca).** As described for **8aa**, **5c** (250 mg, 0.641 mmol), anhydrous K_2CO_3 (443 mg, 3.205 mmol), 1-(2-chloroethyl)dimethylamine hydrochloride (138 mg, 0.961 mmol) and dry acetone (30 mL) furnished **8ca** (200 mg, 67%) as a white solid; mp 110 °C (dichloromethane). R_f = 0.6 (40% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 3468, 2930, 2361, 1241, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (2H, d, *J* = 8.8 Hz), 7.73 (2H, d, *J* = 8 Hz), 7.47–7.25 (6H, m), 7.14 (2H, d, *J* = 8 Hz), 7.09 (2H, d, *J* = 8 Hz), 6.77 (2H, d, *J* = 8.7 Hz), 5.00 (2H, s), 4.23 (2H, t, *J* = 6 Hz), 3.73 (3H, s), 2.85 (2H, t, *J* = 6 Hz), 2.42 (6H, s).; MS (FAB): *m/z* (%) 461 (100) [M^+], 390 (20) [M – $CH_2CH_2N(CH_3)_2$].

***N*-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-dimethylamine hydrochloride (8ca·HCl).** As described for **8aa**·HCl, product **8ca** afforded **8ca**·HCl (295 mg, 92%), as a white solid; mp 119 °C. Anal. Calcd for $C_{32}H_{32}ClNO_2$ (498.05): C, 77.17; H, 6.48; N, 2.81. Found: C, 77.13; H, 6.85; N, 2.84.

***N*-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-diethylamine (8cb).** As described for **8aa**, compound **5c** (300 mg, 0.796 mmol), anhydrous K_2CO_3 (532 mg, 3.845 mmol), 1-(2-chloroethyl)diethylamine hydrochloride (198 mg, 1.154 mmol) and dry acetone (20 mL) gave **8cb** (370 mg, 99%) as a yellow solid; mp 129 °C (dichloromethane). R_f = 0.6 (65% ethylacetate/hexane) IR (KBr): $\tilde{\nu}$ 3459, 2962, 2361, 1507, 1239, 778 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (2H, d, *J* = 8.6 Hz), 7.74 (2H, d, *J* = 8.8 Hz), 7.47–7.28 (6H, m), 7.14 (2H, d, *J* = 8 Hz), 7.09 (2H, d, *J* = 8 Hz), 6.77 (2H, d, *J* = 8.7 Hz), 5.00 (2H, s), 4.20 (2H, t, *J* = 6 Hz), 3.73 (3H, s), 2.99 (2H, t, *J* = 6 Hz), 2.71 (4H, q, *J* = 6 Hz), 1.13 (6H, t, *J* = 7 Hz). MS (FAB): *m/z* (%) 489 (50) [M^+], 390 (100) [M –$CH_2CH_2N(CH_2CH_3)_2$].

***N*-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]-*N*,*N*-diethylamine hydrochloride (8cb·HCl).** As described for **8aa**·HCl, product **8cb** afforded **8cb**·HCl., (380 mg, 90%) as a white solid; mp 135 °C. Anal. Calcd for $C_{34}H_{36}ClNO_2$ (526.11): C, 77.62; H, 6.90; N, 2.66. Found: C, 77.20; H, 7.05; N, 2.58.

1-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]pyrrolidine (8cc). As described for **8aa**, compound **5c** (300 mg, 0.769 mmol), anhydrous K_2CO_3 (532 mg, 3.84 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (195 mg, 1.154 mmol) and dry acetone (30 mL) yielded **8cc** (300 mg, 80%) as a yellow solid; mp 138 °C (dichloromethane). R_f = 0.5 (50% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2938, 2360, 1510, 1244, 1035 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.73 (2H, d, *J* = 8.8 Hz), 7.47–7.28 (6H, m), 7.15 (2H, d, *J* = 8 Hz), 7.09 (2H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 8.8 Hz), 4.99 (2H, s), 4.26 (2H, t, *J* = 6 Hz), 3.72 (3H, s), 3.00 (2H, t, *J* = 6 Hz), 2.71–2.70 (4H, m), 1.89–1.82 (4H, m); MS (FAB): *m/z* (%) 487 (40) [M^+], 390 (100) [M – $CH_2CH_2N(CH_2)_4$].

1-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]pyrrolidine hydrochloride (8cc·HCl). As described for **8aa**·HCl, product **8cc** afforded **8cc**·HCl., (360mg, 89%) as a white solid; mp 143 °C. Anal. Calcd for $C_{34}H_{34}ClNO_2$ (524.09): C, 77.92; H, 6.54; N, 2.67. Found: C, 77.99; H, 6.73; N, 2.60.

1-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]piperidine (8cd). As described for **8aa**, **5c** (300 mg, 0.769 mmol), anhydrous K_2CO_3 (532 mg, 3.845 mmol), 1-(2-chloroethyl)piperidine hydrochloride (212 mg, 1.154 mmol) and dry acetone (30 mL) furnished **8cd** (310 mg, 80%) as a yellow solid; mp 152 °C (dichloromethane). R_f = 0.6 (55% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2935, 1607, 1510, 1245, 1036, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (2H, d, *J* = 8.6 Hz), 7.73 (2H, d, *J* = 8.8 Hz), 7.47–7.27 (6H, m), 7.14 (2H, d, *J* = 8 Hz), 7.09 (2H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 8.7 Hz), 4.99 (2H, s), 4.25 (2H, t, *J* = 6 Hz), 3.72 (3H, s), 2.87 (2H, t, *J* = 6 Hz), 2.61–2.55 (4H, m), 1.69–1.42 (6H, m). MS (FAB): *m/z* (%) 501 (100) [M^+], 416 (10) [M –$N(CH_2)_5$], 390 (30) [M –$CH_2CH_2N(CH_2)_5$].

1-[2-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]ethyl]piperidine hydrochloride (8cd·HCl). As described for **8aa**·HCl, product **8cd** afforded **8cd**·HCl., (380mg, 91%) as a yellow solid; mp 159 °C. Anal. Calcd for $C_{35}H_{36}ClNO_2$ (538.12): C, 78.12; H, 6.74; N, 2.60. Found: C, 78.99; H, 6.99; N, 2.57.

2-[[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]methyl]oxirane (9a). A mixture of compound **5a** (2 g, 5.12 mmol), anhydrous K_2CO_3 (2.52 g, 18.23 mmol) and epichlorohydrin (75 mL) was heated at reflux for 12 h. K_2CO_3 was filtered off and epichlorohydrin was removed in vacuo. The residue was extracted with ethyl acetate, the extract was washed with water, brine and dried (Na_2SO_4). Column chromatography on silica gel and elution with 20% ethylacetate in hexane (R_f = 0.6) furnished **9a** (1.97 g, 86%) as a white solid; mp 190 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ 2952, 2312, 1620, 1520, 1252, 786 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.17 (2H, d, *J* = 8 Hz), 7.71 (2H, d, *J* = 7.6 Hz), 7.41–7.27 (7H, m), 7.14 (2H, d, *J* = 8.6 Hz), 7.00 (1H, d, *J* = 7.5 Hz), 6.61 (1H, t, *J* = 7 Hz), 6.46 (1H, d, *J* = 7 Hz), 4.98 (2H, s), 4.36 (2H, dd, *J* = 7, 3.2 Hz), 4.15 (1H, d, *J* = 6 Hz), 4.06 (3H, s), 3.4 (1H, m), 2.98 (1H, m), 2.84 (1H, m). MS (FAB):

m/z (%) 446 (100) [M^+], 391 (30) [M –CH_2CHCH_2O], 339 (10) [M –$OCH_3C_6H_4$]. Anal. Calcd for $C_{31}H_{26}O_3$ (446.54): C, 83.38; H, 5.87. Found: C, 82.99; H, 6.05.

2-[[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]methyl]oxirane (9b). As described for **9a**, compound **5b** (2.68 g, 6.87 mmol), anhydrous K_2CO_3 (4.6 g, 33.3 mmol) and epichlorohydrin (75 mL) furnished **9b** (1.80 g, 58%) as a white solid; mp 182 °C (dichloromethane). R_f = 0.6 (20% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2929, 2360, 1615, 1525, 1247, 782 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.69 (2H, d, *J* = 8.4 Hz), 7.44–7.31 (6H, m), 7.18 (1H, s), 7.16 (1H, d, *J* = 8 Hz), 7.12 (1H, d, *J* = 8 Hz), 6.73 (2H, d, *J* = 8 Hz), 6.72 (1H, d, *J* = 8.2 Hz), 5.03 (2H, s), 4.36 (2H, dd, *J* = 9, 3.2 Hz), 4.11 (1H, dd, *J* = 9, 3.4 Hz), 3.70 (3H, s), 3.4 (1H, m), 2.97 (1H, m), 2.83 (1H, m). MS (FAB): *m/z* (%) 446 (100) [M^+], 391 (30) [MCH_2CHCH_2O}, 326 (15) [M –$OCH_3C_6H_4CH_2$]. Anal. Calcd for $C_{31}H_{26}O_3$ (446.54): C, 83.38; H, 5.87. Found: C, 83.49; H, 6.15.

2-[[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]methyl]oxirane (9c). As described for **9a**, compound **5c** (1.30 g, 3.33 mmol), anhydrous K_2CO_3 (2.3 g, 16.65 mmol) and epichlorohydrin (75 mL) furnished **9c** (1.3 g, 87%) as a white solid; mp 171 °C (dichloromethane). R_f = 0.6 (20% ethylacetate/hexane). IR (KBr): $\tilde{\nu}$ 2927, 2362, 1608, 1510, 1244, 1033, 761 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (2H, d, *J* = 8.6 Hz), 7.71 (2H, d, *J* = 7.6 Hz), 7.42–7.26 (6H, m), 7.27 (2H, d, *J* = 8 Hz), 7.16 (2H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 8 Hz), 5.00 (2H, s), 4.35 (2H, dd, *J* = 6.2, 3.2 Hz), 4.15 (1H, m), 3.73 (3H, s), 3.45 (1H, m), 2.97 (1H, m), 2.82 (1H, m). MS (FAB): *m/z* (%) 446 (100) [M^+], 391 (25) [M –CH_2CHCH_2O], 339 (15) [M –$OCH_3C_6H_4$]. Anal. Calcd for $C_{31}H_{26}O_3$ (446.54): C, 83.38; H, 5.87. Found: C, 83.99; H, 6.15.

1-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]-3-pyrrolidin-1-ylpropan-2-ol (10aa). A mixture of **9a** (300 mg, 0.672 mmol), pyrrolidine (71 mg, 1.00 mmol) in ethanol (10 mL) was heated at reflux for 7 h. Ethanol was removed, and the residue was extracted with ethyl acetate. The extract was washed with brine and dried. Column chromatography on silica gel and elution with 90% ethyl acetate in hexane (R_f = 0.4) furnished **10aa** (300 mg, 86%) as a white solid, mp 138 °C (dichloromethane), IR (KBr): $\tilde{\nu}$ 3420, 2929, 1560, 1440, 1382, 1245, 1152, 760 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.17 (2H, d, *J* = 8.8 Hz), 7.71 (2H, d, *J* = 8.6 Hz), 7.41–7.27 (7H, m), 7.14 (2H, d, *J* = 8 Hz), 7.00 (1H, d, *J* = 8 Hz), 6.61 (1H, d, *J* =7 Hz), 6.46 (1H, d, *J* = 7 Hz), 4.98 (2H, s), 4.20–4.12 (3H, m), 4.05 (3H, s), 3.74 (1H, bs), 3.00–2.60 (6H, m), 1.86–1.84 (4H, m). MS (FAB): *m/z* (%) 518 (100) [M^+], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_4$]. Anal. Calcd for $C_{35}H_{35}NO_3$ (517.66): C, 81.21; H, 6.81; N, 2.71. Found: C, 80.99; H, 7.01; N, 3.00.

1-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]-3-piperidin-1-ylpropan-2-ol (10ab). As described for **10aa**, **9a** (300 mg, 0.768 mmol) and piperidine (0.104 mL, 1.05 mmol) in ethanol (20 mL) furnished **10ab** (340 mg, 83%) as a white solid; mp 174 °C (dichloromethane). R_f = 0.4 (90% ethyl acetate in hexane). IR (KBr): $\tilde{\nu}$ 2929, 2862, 1245, 1045, 775 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.17 (2H, d, *J* = 8 Hz), 7.71 (2H, d, *J* = 7.6 Hz), 7.41–7.27 (7H, m), 7.14 (2H, d, *J* = 8.6 Hz), 7.00 (1H, d, *J* = 7.5 Hz), 6.61 (1H, t, *J* = 7 Hz), 6.46 (1H, d, *J* = 7 Hz), 4.99 (2H, s), 4.22–4.07 (3H, m), 4.02 (3H, s), 2.60 (2H, m), 2.50 (2H, m), 2.40 (2H, m), 2.00 (1H, bs), 1.65–1.63 (4H, m), 1.57–1.49 (2H, m). MS (FAB): *m/z* (%) 532 (100) [M^+], 391 (20) [M –

$CH_2CHOHCH_2N(CH_2)_5$]. Anal. Calcd for $C_{36}H_{37}NO_3$ (531.68): C, 81.32; H, 7.01; N, 2.63. Found: C, 82.19; H, 7.15; N, 2.99.

1-[4-[10-(2-Methoxybenzyl)-9-anthryl]phenoxy]-3-(4-methylpiperazin-1-yl)propan-2-ol (10ac). A mixture of **9a** (300 mg, 0.672 mmol) and *N*-methylpiperazine (0.11 mL, 1.00 mmol) in ethanol (20 mL) was heated at reflux for 7 h. Ethanol was removed, and the residue was extracted with ethyl acetate. The extract was washed with brine and dried. Column chromatography on silica gel and elution with 5% methanol in chloroform (R_f = 0.4) furnished **10ac** (210 mg, 57%) as a white solid; mp 170 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ 2932, 2362, 1509, 1244, 1172, 1034, 740 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.17 (2H, d, *J* = 8.6 Hz), 7.71 (2H, d, *J* = 8.6 Hz), 7.41–7.27 (7H, m), 7.14 (2H, d, *J* = 8.6 Hz), 7.00 (1H, d, *J* = 8.8 Hz), 6.61 (1H, t, *J* = 7 Hz), 6.46 (1H, t, *J* = 7Hz), 4.98 (2H, s), 4.20–4.07 (3H, m), 4.06 (3H, s), 2.77–2.40 (10H, m), 2.60 (1H, bs), 2.23 (3H, s). MS (FAB): *m/z* (%) 546 (100) [M^+], 390 (30) [M – $CH_2CHOHCH_2N(CH_2)_4NCH_3$]. Anal. Calcd for $C_{36}H_{38}N_2O_3$ (546.70): C, 79.09; H, 7.01; N, 5.12. Found: C, 79.33; H, 7.15; N, 5.19.

1-(Cyclohexylamino)-3-{4-[10-(2-methoxybenzyl)-9-anthryl]phenoxy}propan-2-ol (10ad). A mixture of **9a** (300 mg, 0.672 mmol), cyclohexylamine (100 mg, 1.00 mmol) in ethanol (20 mL) was heated at reflux for 7 h. Ethanol was removed, and the residue was extracted with ethyl acetate. The extract was washed with brine and dried. Column chromatography on alumina and elution with 5% methanol in chloroform (R_f = 0.4) furnished **10ad** (330 mg, 90 %) as a white solid; mp 155 °C (dichloromethane), IR (KBr): $\tilde{\nu}$ 3434, 2378, 1650, 1212, 1048, 1161 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.17 (2H, d, *J* = 8.6 Hz), 7.71 (2H, d, *J* = 8.4 Hz), 7.41–7.27 (7H, m), 7.14 (2H, d, *J* = 8 Hz), 7.00 (1H, d, *J* = 7.5 Hz), 6.61 (1H, t, *J* = 7 Hz), 6.46 (1H, d, *J* = 8 Hz), 5.00 (2H, s), 4.19–4.17 (3H, m), 4.09 (3H, s), 3.00 (1H, d, *J* = 6 Hz), 2.95 (1H, m), 2.5 (1H, m), 2.00 (1H, bs), 1.99 (1H, d, *J* = 7 Hz), 1.70 (1H, d, *J* = 7 Hz), 1.50 (1H, d, *J* = 7 Hz), 1.40–1.10 (8H, m). MS (FAB): *m/z* (%) 546 (100) [M^+], 390 (25) [M –$CH_2CHOHCH_2NHCH(CH_2)_5$]. Anal. Calcd for $C_{37}H_{39}NO_3$ (545.71): C, 81.43; H, 7.20; N, 2.57. Found: C, 81.34; H, 7.17; N, 2.69.

1-{4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy}-3-pyrrolidin-1-ylpropan-2-ol (10ba). As described for **10aa** a mixture of **9b** (300 mg, 0.672 mmol), pyrrolidine (71 mg, 1.00 mmol) in ethanol (10 mL) furnished **10ba** (300 mg, 86%) as a white solid; mp 142 °C (dichloromethane); R_f = 0.4 (90% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 3429, 2928, 1595, 1446, 1379, 1244, 1161, 1035, 765 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (2H, d, *J* = 8.8 Hz), 7.62 (2H, d, *J* = 8.6 Hz), 7.53 (2H, t, *J* = 7.6 Hz), 7.42 (2H, d, *J* = 8 Hz), 7.34 (2H, t, *J* = 7.6 Hz), 7.21 (1H, s), 7.17 (1H, d, *J* = 8 Hz), 7.11 (1H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 7 Hz), 6.66 (1H, d, *J* = 7 Hz), 5.05 (2H, s), 4.94 (1H, d, *J* = 4 Hz), 4.05–3.99 (2H, m), 3.66 (3H, s), 2.54–2.49 (6H, m), 1.70–1.60 (4H, m). MS (FAB): *m/z* (%) 518 (100) [M^+], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_4$]. Anal. Calcd for $C_{35}H_{35}NO_3$ (517.66): C, 81.21; H, 6.81; N, 2.71. Found: C, 81.69; H, 7.11; N, 3.03.

1-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]-3-piperidin-1-ylpropan-2-ol (10bb). As described for **10aa**, a mixture of **9b** (300 mg, 0.671 mmol), piperidine (74 mg, 0.874 mmol) in ethanol (20 mL) furnished **10bb** (300 mg, 84%) as a white solid; mp 149 °C. R_f = 0.4 (5%

methanol/chloroform). IR (KBr): $\tilde{\nu}$ 2929, 1596, 1449, 1247, 1161, 1037, 768 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.36 (2H, d, *J* = 8.8 Hz), 7.62 (2H, d, *J* = 8.8 Hz), 7.52 (2H, t, *J* = 8 Hz), 7.48 (2H, t, *J* = 8 Hz), 7.43 (2H, t, *J* = 8.2 Hz), 7.29 (1H, s), 7.26 (1H, d, *J* = 8 Hz), 7.14 (1H, d, *J* = 8 Hz), 6.75 (2H, d, *J* = 8.2 Hz), 6.71 (1H, d, *J* = 8 Hz), 5.04 (2H, s), 4.99 (1H, m), 4.14–4.02 (4H, m), 3.62 (3H, s), 3.30–3.25 (4H, m), 1.52–1.48 (6H, m). MS (FAB): *m/z* (%) 532 (100) [M^+], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_5$]. Anal. Calcd for $C_{36}H_{37}NO_3$ (531.68): C, 81.32; H, 7.01; N, 2.63. Found: C, 80.99; H, 7.05; N, 2.99.

1-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]-3-(4-methylpiperazin-1-yl)propan-2-ol (10bc). As described for **10ac**, a mixture of **9b** (300 mg, 0.672 mmol), *N*-methylpiperazine (101 mg, 1.00 mmol) in ethanol (20 mL) furnished **10bc** (160 mg, 43%) as a white solid; mp 140 °C. R_f = 0.4 (5% methanol/chloroform). IR (KBr): $\tilde{\nu}$ 2932, 1605, 1448, 1383, 1243, 1147, 1041 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.36 (2H, d, *J* = 8.8 Hz), 7.63–7.28 (8H, m), 7.20 (1H, s), 7.16 (1H, d, *J* = 8 Hz), 7.10 (1H, d, *J* = 8 Hz), 6.74 (2H, d, *J* = 8 Hz), 6.66 (1H, d, *J* = 8 Hz), 5.03 (2H, s), 4.92 (1H, m), 3.90–3.00 (5H, m), 3.63 (3H, s), 2.53 (3H, s), 2.48–2.44 (8H, m). MS (FAB): *m/z* (%) 547 (100) [M^+], 390 (40) [M –$CH_2CHOHCH_2N(CH_2)_4NCH_3$]. Anal. Calcd for $C_{36}H_{38}N_2O_3$ (546.70): C, 79.09; H, 7.01; N, 5.12. Found: C, 79.55; H, 6.00; N, 5.22.

1-[4-[10-(3-Methoxybenzyl)-9-anthryl]phenoxy]-3-morpholin-4-ylpropan-2-ol (10bd). As described for **10aa**, **9b** (300 mg, 0.672 mmol), morpholine (87 mg, 1.00 mmol) in ethanol (10 mL) gave **10bd** (300 mg, 83%) as a white solid; mp 177 °C. R_f = 0.4 (90% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 3446, 2936, 1606, 1512, 1452, 1243, 1116, 1042, 764 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.25 (2H, d, *J* = 8.6 Hz), 7.71 (2H, d, *J* = 8.8 Hz), 7.44–7.24 (7H, m), 7.16 (2H, d, *J* = 8 Hz), 6.71 (3H, m), 5.04 (2H, s), 4.17–4.13 (3H, m), 3.80–3.75 (4H, m), 3.69 (3H, s), 2.74–2.50 (6H, m), 1.54 (1H, bs); MS (FAB): *m/z* (%) 534 (100) [M^+], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_4O$]. Anal. Calcd for $C_{35}H_{35}NO_4$ (533.66): C, 78.77; H, 6.61; N, 2.62. Found: C, 78.00; H, 7.01; N, 2.68.

1-(4-Benzylpiperazin-1-yl)-3-[4-[10-(3-methoxybenzyl)-9-anthryl]phenoxy]propan-2-ol (10be). As described for **10aa**, a mixture of **9b** (300 mg, 0.671 mmol), *N*-Benzylpiperidine (177 mg, 1.00 mmol) in ethanol (10 mL) furnished **10be** (250 mg, 59%) as a brown solid; mp 147 °C. R_f = 0.4 (90% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 3422, 2934, 1604, 1451, 1278, 1241, 1146, 1043, 767 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (2H, d, *J* = 8.8 Hz), 7.64–7.09 (16H, m), 6.76 (2H, d, *J* = 7 Hz), 6.67 (1H, d, *J* = 7.8 Hz), 5.04 (2H, s), 4.91 (1H, m), 4.14–3.99 (4H, m), 3.66 (3H, s), 2.51–2.40 (10H, m). MS (FAB): *m/z* (%) 624 (100) [M+2], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_4NCH_2C_6H_5$}. Anal. Calcd for $C_{42}H_{42}N_2O_3$ (622.79): C, 81.00; H, 6.80; N, 4.50. Found: C, 81.29; H, 7.00; N, 3.99.

1-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]-3-piperidin-1-ylpropan-2-ol (10cb). As described for **10ac**, a mixture of **9c** (300 mg, 0.673 mmol), piperidine (85 mg, 1.008 mmol) in ethanol (20 mL) furnished **10cb** (225 mg, 62%) as a white solid; mp 194 °C (dichloromethane); R_f = 0.4 (5% methanol in chloroform). IR (KBr): $\tilde{\nu}$ 2927, 2857, 1240, 1033, 761 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (2H, d, *J* = 8.8 Hz), 7.61 (2H, d, *J* = 8.6 Hz), 7.52 (2H, t, *J* = 7 Hz), 7.41 (2H, d, *J* = 8 Hz), 7.34 (2H, d, *J* = 7 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 4.99 (2H, s), 4.98

(1H, m), 4.02–3.96 (2H, m), 3.71 (3H, s), 3.68–3.64 (4H, m), 1.52–1.22 (6H, m). MS (FAB): *m/z* (%) 532 (100) [M^+], 390 (30) [M –$CH_2CHOHCH_2N(CH_2)_5$]. Anal. Calcd for $C_{36}H_{37}NO_3$ (531.68): C, 81.32; H, 7.01; N, 2.63. Found: C, 81.93; H, 7.61; N, 2.32.

1-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]-3-(4-methylpiperazin-1-yl)propan-2-ol (10cc). As described for **10ac**, a mixture of **9c** (300 mg, 0.672 mmol), *N*-methylpiperazine (0.11 mL, 1.00 mmol) in ethanol (20 mL) furnished **10cc** (210 mg, 57%) as a white solid; mp 173 °C (dichloromethane); R_f = 0.4 (5% methanol in chloroform). IR (KBr): $\tilde{\nu}$ 2932, 2362, 1509, 1244, 1172, 1034, 740 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (2H, d, *J* = 8.6 Hz), 7.61 (2H, d, *J* = 8.6 Hz), 7.52 (2H, t, *J* = 7 Hz), 7.41 (2H, d, *J* = 8 Hz), 7.34 (2H, d, *J* = 7 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 7.07 (2H, d, *J* = 8.8 Hz), 6.80 (2H, t, *J* = 7 Hz), 4.99 (2H, s), 4.98 (1H, m), 4.03–3.97 (4H, m), 3.70 (3H, s), 3.68–3.66 (8H, m), 2.15 (3H, s). MS (FAB): *m/z* (%) 546 (100) [M^+], 433 [M –$CH_2N(CH_2)_4NCH_3$], 390 {30) [M –$CH_2CHOHCH_2N(CH_2)_4NCH_3$]. Anal. Calcd for $C_{36}H_{38}N_2O_3$ (546.70): C, 79.09; H, 7.01; N, 5.12. Found: C, 78.87; H, 6.25; N, 5.20.

1-[4-[10-(4-Methoxybenzyl)-9-anthryl]phenoxy]-3-morpholin-4-ylpropan-2-ol (10cd). As described for **10aa**, **9c** (300 mg, 0.672 mmol), morpholine (87 mg, 1.00 mmol) in ethanol (10 mL) furnished **10cd** (215 mg, 60%) as a white solid; mp 196 °C (dichloromethane); R_f = 0.4 (90% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}$ 2928, 2361, 1244, 1034, 769 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.37 (2H, d, *J* = 8.6 Hz), 7.61 (2H, d, *J* = 8.6 Hz), 7.55 (2H, t, *J* = 6.6 Hz), 7.41 (2H, d, *J* = 8.6 Hz), 7.33 (2H, t, *J* = 6.6 Hz), 7.18 (2H, d, *J* = 8.6 Hz), 7.08 (2H, d, *J* = 8.8 Hz), 6.78 (2H, d, *J* = 8.8 Hz), 4.99 (2H, s), 4.10–3.90 (3H, m), 3.66–3.54 (4H, m), 3.65 (3H, s), 3.49–3.26 (6H, m). MS (FAB): *m/z* (%) 533 (100) [M^+], 390 (30) [M – $CH_2CHOHCH_2N(CH_2)_4O$]. Anal. Calcd for $C_{35}H_{35}NO_4$ (533.66): C, 78.77; H, 6.61; N, 2.62. Found: C, 78.99; H, 7.03; N, 2.70.

1-(Cyclopropylamino)-3-{4-[10-(4-methoxybenzyl)-9-anthryl]phenoxy}propan-2-ol (10cf). As described for **10ad**, a mixture of **9c** (300 mg, 0.672 mmol), cyclopropylamine (57 mg, 1.00 mmol) in ethanol (10 mL) furnished **10cf** (129 mg, 38%) as a white solid; mp 136 °C (dichloromethane); R_f = 0.4 (5% methanol in chloroform). IR (KBr): $\tilde{\nu}$ 3437, 2364, 1611, 1244, 1034 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.26 (2H, d, *J* = 8.6 Hz), 7.71 (2H, d, *J* = 8.4 Hz), 7.44–7.25 (4H, m), 7.14 (4H, d, *J* = 8 Hz), 6.76 (2H, d, *J* = 8 Hz), 6.74 (2H, d, *J* = 8 Hz), 5.00 (2H, s), 4.21–4.14 (2H, m), 3.79–3.75 (1H, m), 3.73 (3H, s), 3.05–2.98 (2H, m), 2.2 (1H, m), 0.53–0.44 (4H, m). MS (FAB): *m/z* (%) 503 (100) [M^+], 433 (50) [M – $CH_2NHCH(CH_2)_2$], 390 (30) [M –$CH_2CHOHCH_2NHCH(CH_2)_2$]. Anal. Calcd for $C_{33}H_{31}NO_3$ (489.60): C, 80.95; H, 6.38; N, 2.86. Found: C, 81.00; H, 6.31; N, 2.98.

Agar micro dilution method. Twofold dilutions of each test compound were added to 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 was dispensed in each well. The test compound was added to the middle brook medium agar before in duplicate so that the final concentration of the test compound in each well was 25, 12.5, 6.25,

3.125 and 1.56 μg/mL, respectively. The known CFU of the $H_{37}R_v$ culture was dispensed on top of agar in each well in a negative pressure biosafety hood. The plates were then incubated at 37 °C CO_2 incubator. The concentration at which complete inhibition of colonies was observed was taken as MIC of test drug.

BACTEC Method. A stock solution of the test compounds in DMSO (1mg/mL) was prepared and sterilized by passage through 0.22 μm filters. 50 μL were added to 4 mL radiometric 7H12 broth (BACTEC 12B; Becton Dickinson Diagnostic Instrument System US) to achieve the final concentrations. Controls received 50 μL DMSO. Isoniazid and rifampin (Sigma Chemical Co. St. Louis, MO) were included as positive drug control. In the BACTEC method, 10^4 to 10^5 CFU/mL of *M. tuberculosis* H_{37} R_v was inoculated in 4 mL fresh BACTEC 12B broth. containing the test compounds. An additional control was inoculated with 1:100 dilution of the inoculum to represent 1% of the bacterial population. (102 to 10^3 CFU/mL). The vials were incubated at 37 °C, and GI readings were recorded daily until the GI in 1:100 control had reached 30. The concentration of the drug producing final GI reading lower than those in 1:100 control was considered to have inhibited more than 90% of the bacteria and was defined as the MIC.

Micro almar blue assay (MABA). *M. tuberculosis,* $H_{37}R_a$ was used as a suitable surrogate for the virulent $H_{37}R_v$ strain. The standard antitubercular agents Rifamycin, isoniazid, *p*-amino-salicylic acid, ethambutol and ethionamide were taken as positive controls. A compound is considered active only if it shows inhibition greater than or equal to 90%.

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