Chapter 4:
Design, Synthesis and Antitubercular Activity of Diarylmethylnaphthol Derivatives
4.1. Introduction

Amongst the worldwide health threats, tuberculosis remains the leading cause of mortality from a single infectious disease because of a bacterial pathogen, *Mycobacterium tuberculosis*. The prevalence of tuberculosis infection has steadily risen in the past decade, and this increase can be attributed to a similar increase in human immunodeficiency virus (HIV) infection.¹ In many cases of the association of TB and HIV infections nearly two-thirds of the patients diagnosed with TB are also HIV-1 seropositive.² Furthermore, numerous studies have shown that TB is a cofactor in the progression of HIV infection.³ The reemergence of TB infection is further complicated by an increase in cases that are resistant to for all clinically prescribed antitubercular drugs.⁴,⁵ The appearance of multi-drug-resistant (MDR) strains of *Mycobacterium tuberculosis* and the association of TB and HIV infections have led to declare tuberculosis as ‘a global epidemic’ which is evident from the fact that 100 million people are infected annually, ten million develop the disease, with five million of these progressing to the infectious stage and finally three million dying.⁶ The WHO had estimated that if efforts to control TB are not further intensified then between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will get sick, and 35 million will die from TB. In India alone, one-person dies of TB every minute. Approximately 50% of India’s population is reported to be tuberculin test positive. Every year about 0.4 million deaths and one million new cases of tuberculosis are reported.⁷

The resistant strains of *Mycobacterium tuberculosis* have slowly emerged for conventional antitubercular drug therapy in nearly every country making effective treatment extremely expensive with often treatment failures. Antitubercular drug therapy is more problematic especially in those countries which lack the necessary health care organization to provide the long and costly treatment adapted to patients. Thus, new drugs are necessary to enhance better antitubercular activity and to shorten the treatment regimen. In the last several years, the research on *M. tuberculosis* has undergone much progress. Regimens have been optimized along with the implementation of the directly observed therapy short course (DOTS) initiative. The genome of *M. tuberculosis* was unraveled at the laboratory level⁸,⁹ and much work provided insights into the mechanisms of action of the antituberculosis drugs currently used.
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4.2 Antitubercular Drugs

The chemotherapy of tuberculosis has much evolved along the years since it started with the introduction of streptomycin in 1946. Streptomycin 7 (Figure 4.1) is an aminoglycoside antibiotic derived from *Streptomyces griseus*. It is made up of three components, streptidine, streptose and N-methyl-L-glucosamine. It is poorly absorbed from gastrointestinal tract and thus administered intramuscularly. Concentration of streptomycin of the order of 1 μg/ml inhibits the growth of *M. tuberculosis* H₃₇Rv. The drug exerts its effect by interfering with bacterial protein synthesis. It penetrates the inner membrane of *M. tuberculosis* and binds to the 30S subunit of the ribosome.¹⁰

In addition to this, the drugs that have been used to fight tuberculosis include rifampin ¹, isoniazid ², ethambutol ³, pyrazinamide ⁴, kanamycin ⁵, amikacin ⁶, capreomycin ¹A ⁸, levofloxacin ⁹, *p*-aminosalicylic acid ¹⁰, ethionamide ¹¹ and cycloserine ¹². Among them, the first line tuberculosis drugs include rifampin ¹, isoniazid ², ethambutol ³ and pyrazinamide ⁴ (Figure 4.1).

**Rifampin**

Rifampin (RIF) ¹ is extremely effective against MTB with very low MICs of 0.1 to 0.2 μg/ml.¹¹ RIF had long been believed to target the mycobacterial RNA polymerase and thereby kill the organism by interfering in the transcription process. RIF specifically inhibits the transition from synthesis of short oligoribonucleotides to full-length transcripts.

**Isoniazid (INH)**

Isoniazid (INH) ² is a prodrug that requires activation by the mycobacterial catalase peroxidase enzyme (*katG*) to an active form, which then exerts a lethal effect on intracellular targets. INH is highly active against the MTB complex pathogens (*M. tuberculosis, M. bovis, M. africanum* and *M. microti*) with very low MICs (0.02 to 0.06 μg/ml).¹² INH enters the organism through diffusion and oxygen-dependent active transport.¹³ The drug has been reported to affect virtually every aspect of mycobacterial metabolism. Many components of *M. tuberculosis* have been proposed as possible targets of INH. It inhibits the synthesis of mycolic acids (long chain α-branched β-hydroxylated fatty acids) in *M. tuberculosis* by affecting an enzyme mycolase synthase, which is unique for mycobacteria.¹⁴
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Pyrazinamide (PZA)

Pyrazinamide (PZA) 3, a structural analog of nicotinamide, is a first-line drug for short-course tuberculosis therapy. It is active against semidormant bacillus which is not affected by any other drug. It has strong synergy with INH and RIF and shortens the therapy period for tuberculosis treatment up to 6 months. It shows no significant bactericidal effect and is primarily considered a ‘sterilizing drug’.15

Ethambutol (EMB)

Ethambutol (EMB) 4, a synthetic compound with profound antimycobacterial activity, is a first line anti-TB drug. The core of the mycobacterial cell wall is the complex mycolylarabinogalactanpeptidoglycan formed by three covalently attached macromolecules, viz. mycolic acid, peptidoglycan and arabinogalactan. The target of the ethambutol lies in the pathway for the biosynthesis of cell wall arabinogalactan.16

These first-line antituberculosis drugs INZ, RIF, EMB and PZA can be given as single-drug formulations or as fixed-dose combination (FDC) formulations where two or more drugs are present in fixed proportions in the same formulation. This recommended treatment regimen is highly effective and the rates of severe adverse reactions are low. However, unpleasant side effects and relatively long course of treatment are the drawbacks, which increase the rate of non-compliance to treatment regimen. Such non-adherence with the course of treatment leads to treatment failure and the development of drug resistance.
4.3 Small Molecules as Chemical Probes and Drug Leads for TB

In addition to their long standing value as drugs and therapeutics, natural and synthetic small molecules have found great utility as chemical probes for identifying protein targets, unraveling mechanisms of action, and studying biological systems on a global scale (see: Chapter 1). In tuberculosis research, besides target identification and validation, recent efforts have been focused on discovery of new classes of antibiotics and improving the pharmacologic properties of those already in use to shorten treatment duration and expand efficacy to MDR-TB and XDR-TB. A variety of approaches have been taken in attempts to identify new drug classes; the successful outcomes of some of these studies have in turn provided new chemical probes for further study of Mtb.

Two related nitroimidazole derivatives 18 (PA-824) and 19 (OPC-67863) are among the most promising current anti-TB drug candidates. Both compounds have been shown to be prodrugs requiring activation by the same F420-dependent enzyme (Rv3547) and to inhibit the growth of Mtb and MDR-TB by inhibiting mycolic acid biosynthesis and protein synthesis. However, the active species and ultimate targets of each remain unknown. Both 18 and 19 are currently being evaluated in phase II clinical trials.

Recently, diarylquinoline 20 (TMC207) was discovered as a potent inhibitor of Mtb, M. smegmatis, and MDR-TB with ATP synthase target that appears to be essential to mycobacteria. Compound 20 was identified from a library of diarylquinolines using a whole cell screen on M. smegmatis and it appeared to be more potent than both INH and RIF and showed no cross resistance with other antimycobacterials. In mouse studies, combinations of 20 with any two of the drugs INH, RIF and PZA was more effective than the standard combination of INH, RIF, and PZA suggesting that substitution of one of them by 20 has the potential to shorten current TB therapies. Compound 20 is currently in phase II development.

Compound 17 (LL-3858 or Sudoterb) represents a new class of anti-TB compound being developed by Lupin Limited (India). 17 was reported to be active against both sensitive and drug-resistant Mtb, suggesting a new mechanism of action. In mice studies, 17 showed similar activity as INH and in combination with INH, RIF, and PZA was effective in eradicating sensitive and resistant Mtb within two months. Compound 17 is now in multidose phase I clinical development.
There are several examples of derivatives of currently used antibiotics that are showing varying degrees of antitubercular activity. Gatifloxacin (GAT, 21) and moxifloxacin (MXF, 22) are new fluoroquinolone DNA gyrase inhibitors that offer advantages over currently used second line fluoroquinolines ofloxacin and ciprofloxacin. Compound 22 displayed anti-TB activity comparable to INH in a mouse model and has been shown to kill rifampin-resistant Mtb populations and when administered with INH, RIF, and PZA, to be more effective at killing Mtb than the 3-drug treatment on its own.<sup>22</sup> Fluoroquinolines 21 and 22, currently in phase III, are the most advanced anti-TB compounds in clinical development showing promise to be the first new anti-TB drugs in nearly 30 years. Rifapentin, rifabutin, rifalazil, and rifametane, all semisynthetic derivatives of the natural product rifamycin, are in various phases of clinical trials showing enhanced activity toward Mtb and improved pharmacokinetic properties.<sup>23,24</sup>

Compound 16 (SQ109) is a derivative of ethambutol,<sup>25</sup> and was reported to act synergistically with INH and RIF and to exhibit improved pharmacokinetic profiles. Although 16 is a second generation EMB derivative, it does not appear to inhibit cell wall biosynthesis as does its parent compound. Compound 16 is currently in phase I.
evaluation. Other new classes of anti-TB compounds currently in preclinical testing include derivatives of the natural product capuramycin, oxazolidinones and β-sulfonylecarboxamides. Capuramycins inhibit translocase I, an enzyme involved in the biosynthesis of peptidoglycan, a key component of the cell wall. The most active capuramycin derivative identified to date is 13 (RS-118641). Linezolid 27 (14) is a synthetic oxazolidinone that acts by inhibiting protein synthesis. The compound was approved by the FDA and has been used on occasion in patients with MDR-TB. β-Sulfonylecarboxamide 15 (FAS20013), shown to be active against MDR- and latent TB, was designed to be a transition state mimic for β-ketoacyl synthase, the condensing enzyme required for fatty acid biosynthesis. The synthesis was inspired by the activities of the natural products cerulenin and thiolactomycin which inhibit the two-carbon homologation catalyzed by β-ketoacyl synthase.

4.4 Basis of Present Work

Towards an ongoing program for developing new antitubercular agents, we have recently reported antitubercular activity of several diaryloxy methanophenanthrene derivatives 23 and 24 and 4-[10-(methoxybenzyl)-9-anthryl]phenol derivatives 25 (Figure 4.3) with basic amino alkyl or amino hydroxyl alkyl side chains. These compounds are phenanthrene and anthracene containing triarylmethane derivatives and exhibited 1.56-25 μg/mL 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. In order to understand the structural features of triarylmethane derivatives necessary for enhanced anti-TB 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 intended to incorporate fluorine and chlorine -substituted phenyl ring since it is observed that the presence of chlorine or fluorine in a molecule can profoundly affect its biological properties. Thus, we designed to synthesize 26 and 27 as our target molecules (Figure 4.4).
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Figure 4.3 Structures of diaryloxy methanophenanthrenes and 4-[10-(methoxybenzyl)-9- anthryl] phenols with basic amino alkyl or amino hydroxy alkyl side chains.

Figure 4.4. General structures of designed molecules.

4.5 Results and Discussion

The designed compounds were synthesized essentially following the steps as depicted in Scheme 4.1. Reduction of commercially available benzophenones 28a-c with sodium borohydride in methanol furnished the corresponding benzhydrol derivatives 29a-c in excellent yields. All the reactions were very high yielding (95-96%) and the resulting diarylcarbinols were well characterised by IR, NMR and MS spectra. The carbinols 29a-c showed the characteristic IR absorption at 3392-3406 cm\(^{-1}\) due to the presence of hydroxy group. Next, carbinols 29a-c was used as alkylating agents in the Friedel-Crafts alkylation of 1- and 2-napthols. In every case, the reaction was performed by refluxing a mixture of 1- or 2-napthol and carbinols 29a, 29b or 29c in dry benzene in the presence of a catalytic amount of conc. H\(_2\)SO\(_4\) as catalyst. It is well known that Friedel-Crafts alkylation reaction of 2-napthol occurs at its 1-position whereas the same reaction occurs at 2- and 4 positions in case of 1-napthol.\(^{30}\) Thus, when 2-napthol was used in the above reaction, only ortho- hydroxy
substituted diarylmethylnaphthols 30a, 31a and 32a were obtained, which is consistent with the reactivity of 2-napthol in Friedel-Crafts reactions. Similarly, the use of 1-napthol furnished para-hydroxy substituted diarylmethylnaphthols 30b, 31b and 32b along with ortho-hydroxy substituted products in very minor amounts which were not separable from the unreacted 1-napthol by chromatography method. Thus, major isomers 30b, 31b and 32b were separated and characterized. Depending on the nature of benzhydrols, the above Friedel-Crafts reaction sequence thus provides an easy access to the synthesis of symmetric as well as unsymmetrical diarylmethylnaphthols.

The reaction of 30a, 31a and 32a with different dialkylaminoethyl chloride hydrochloride chains in the presence of anhydrous K$_2$CO$_3$ in dry acetone under reflux condition led to the formation of diarylmethylnaphtholxy ethylamines 33a-e, 35a-e and 37a-e in good yields. Similarly, compounds 30b, 31b and 32b on reaction with different dialkylaminoethyl chloride hydrochlorides gave diarylmethylnaphtholxy ethylamines 34a-e, 36a-e and 38a-e in good yields. All these compounds were well characterized by using IR, MS and $^1$H NMR techniques. The compound 33a showed the M$^+$+H peak at m/z 382 in its ESI MS spectrum. The $^1$H NMR spectrum of 33a displayed two characteristic triplets at $\delta$ 3.93 (t, 2H, $J = 6.2$ Hz) and 2.34 (t, 2H, $J = 6.2$ Hz) due to $-$OCH$_2$CH$_2$N- and $-$OCH$_2$CH$_3$N- protons respectively, and one peak at $\delta$ 2.2 (s, 6H) for N(CH$_3$)$_3$ protons. The compound 33b showed the M$^+$+H peak at m/z 410 in its ESI MS spectrum. The $^1$H NMR spectrum of 35b displayed two characteristic triplets at $\delta$ 3.94 (t, 2H, $J = 6.7$ Hz) and 0.98 (t, 6H, $J = 7.1$ Hz) due to $-$OCH$_2$CH$_2$N- and $-$CH$_2$CH$_3$ protons respectively, and one peak at $\delta$ 2.57 (m, 6H) for $-$OCH$_2$CH$_3$N- and $-$CH$_2$CH$_3$ protons. On the other hand, compound 36b, which is a structural isomer of 35b, displayed three characteristic triplets at $\delta$ 3.85 (t, 2H, $J = 6.1$), 2.90 (t, 2H, $J = 6.1$) and 1.03 (t, 6H, $J = 7.1$) due to $-$OCH$_2$CH$_2$N-, $-$OCH$_2$CH$_3$N- and $-$CH$_2$CH$_3$ protons respectively, and one peak at $\delta$ 2.59 (q, 4H, $J = 7.1$) for $-$CH$_2$CH$_3$ protons. The central methine proton of 36b appeared as a singlet at $\delta$ 6.25 whereas that of 35b appeared as a singlet at $\delta$ 6.44 due to stronger $-$I effect of the ortho-substituent in 35b than that of the para-substituent in 36b.
Scheme 4.1. Reagents and conditions: (a) NaBH₄, methanol, 0°C-rt, 2 h, 29a (95%), 29b (96%) and 29c (95%). (b) 2-napthol, dry benzene, reflux, 2 h, 30a (89%), 31a (84%) and 32a (85%). (c) 1-napthol, dry benzene, reflux, 2 h, 30b (73%), 31b (70%) and 32b (68%). (d) dialkylaminoethyl chloride hydrochloride (ClCH₂CH₂R.HCl), anhy. K₂CO₃, dry acetone, reflux, 8-10 h, (yields given in Table 4.1).

Table 4.1. Synthesized diarylmethylnapthol derivatives (33-38)a-e and their in vitro antitubercular activity against *M. tuberculosis* H₃⁷Rᵥ.

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*aIsolated yield after silica gel column chromatography.

*bNA means not active at MIC of 12.5 (μg/mL).*
4.6 Antitubercular Screening of (33-38)a-e and their Structure-Activity Relationships

All the synthesized final molecules were evaluated against *M. tuberculosis* *H*$_{37}$R$_{v}$ strains following micro almar blue assay and agar micro dilution technique$^{31,32}$ and their results are shown in Table 4.1. Out of thirty molecules tested, 33a-e, 37b and 37d showed MIC of 3.12 µg/mL, and 35a-e, 37a and 37c showed MIC of 6.25 µg/mL in agar micro dilution technique. Other compounds of the series showed MIC of 12.5µg/mL or above. A closer look into the structure-activity of relationship of the above compounds revealed that in every structurally isomeric pair of diarylmethylnapthoxy ethylamines (such as 33a and 34a; 35a and 36a; 37a and 38a etc.), *ortho-* substituted diarylmethylnapthoxy ethylamines 33a-e, 35a-e and 37a-e were more active than their *para-* substituted counterparts 34a-e, 36a-e and 38a-e. Among all the *ortho-* substituted diarylmethylnapthoxy ethylamines 33a-e, 35a-e and 37a-e, diphenylmethylnapthoxy ethylamines 33a-e showed better activity (except for 37b and 37d) than the rest of 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 diarylmethylnapthoxy ethylamines. Further, within a particular series antitubercular activity almost remains unchanged on changing the basic alkylaminoethyl side chains.

The *in vitro* cytotoxicity of compounds 33a-e, 37b and 37d (having a MIC of 3.12 µg/mL in agar micro dilution technique) in VERO cell lines was determined using a dye reduction assay following three days exposure to test compounds.$^{29e}$ All these compounds were found to be toxic and hence not suitable for *in vivo* evaluation.

4.7 Conclusion

In conclusion, a series of diarylmethylnapthoxy ethylamines were synthesized by aminoalkylation of diarylnapthols obtained by Friedel-Crafts alkylation of 1- and 2-napthols using diarylcarbinols as the alkylating agents. *ortho*-Substituted diarylmethylnapthoxy ethylamines 33a-e, 35a-e and 37a-e were more active than their *para-* substituted counterparts 34a-e, 36a-e and 38a-e. Among the *ortho*-substituted diarylmethylnapthoxy ethylamines, 33a-e, 37b and 37d showed promising activity *in vitro*. It is conceivable that these triaryl methane derivatives
containing naphthalene ring might act as a lead for optimizing antitubercular activity. It would be interesting to prepare new analogues of the most active compounds, which might be nontoxic with significant anti-tubercular activity.

4.8 Experimental Section

4.8.1 General Remarks:

Same as that described in the Section A of Chapter 2.

4.8.2 Preparation Benzhydrols (29a-c):

**Diphenylmethanol (29a):**

This compound is commercially available but it was prepared by the following method. Sodium borohydride (1.24 g, 32.77 mmol) was added to a stirring solution of benzophenone 28a (5.0 g, 27.43 mmol) in methanol (75 mL) at 0°C over a period of 10 min and the mixture was stirred at room temperature for 2 h. After removing methanol under reduced pressure, diethyl ether (100 mL) and water (100 mL) were added to the resulting residue. The aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO4 and concentrated under reduced pressure. The crude product was obtained as an oil which was recrystallized in a hexane and ethyl acetate mixture to give 29a (4.8 g, 95%) as a white solid. Mp: 65-66°C. This compound was used for the next step without recording any spectral data.

**OH

(4-Chlorophenyl)phenylmethanol (29b):**

As described for 29a, compound 29b was prepared by the reduction of 4-chlorobenzophenone 28b (5.0 g, 23.07 mmol) with sodium borohydride (1.04 g, 27.68 mmol). The crude product was recrystallized in a hexane and ethyl acetate mixture to give 29b (4.84 g, 96%) as a white solid. Mp: 56-57°C (literature mp: 54-55°C). Rf 0.43 (20% ethyl acetate in hexane). IR (KBr): 3355, 1500, 1229, 1020, 698, 560 cm⁻¹. ^1H NMR (200 MHz, CDCl₃): δ 7.39-7.28 (m, 9H), 5.79 (s, 1H), 2.36 (s, 1H). ^13C NMR (50 MHz, CDCl₃): δ 143.5, 142.2, 133.3, 128.7, 128.6, 128.0, 127.9, 126.5, 75.6. MS (ESI): m/z 219 [M]^+ 202 [M-OH]^+. Anal. Caled for C₁₃H₁₀ClO: C, 71.40; H, 5.07. Found: C, 71.57; H, 5.37. The above physical and spectroscopic data were in agreement with the literature data.

**OH

(4-Fluorophenyl)phenylmethanol (29c):**
As described for 29a, compound 29c was prepared by the reduction of 28c (5.0 g, 24.97 mmol) with sodium borohydride (1.13 g, 29.96 mmol). The product 28c (4.8 g, 95%) was obtained as a colorless oil with sufficient purity. \( R_f \ 0.43 \) (20% ethyl acetate in hexane). IR (neat): 3371, 1507, 1224, 1020, 559 cm\(^{-1}\). \( \text{IH NMR (CDCl} \_3\ 200 \text{MHz):} \ 7.36-7.29 \text{ (m, 7H), 7.05-6.96 \ (m, 2H), 5.80 \ (s, 1H), 2.34 \ (s, 1H).} \ ^{13}\text{C NMR (50 MHz, CDCl} \_3\): \ \delta \ 162.1, 143.6, 139.5, 128.5, 128.2, 127.6, 126.3, 115.1, 75.6. \text{MS (ESI):} \ m/z \ 202 \ [M]^+, \ 183 \ [M-OH]^+. \text{Anal. Calcd for C}_{13}\text{H}_{11}\text{FO: C, 77.21; H, 5.48. Found: C, 77.39; H, 5.70.} \text{The above physical and spectroscopic data were in agreement with the literature data.} ^{34}

### 4.8.3 Preparation Diarylmethylnapthols (30a-b, 31a-b and 32a-b):

#### 1-Benzhydrylnaphthalen-2-ol (30a):

To a solution of 29a (4.0 g, 21.71 mmol) and 2-naphthol (3.44 g, 23.88 mmol) in dry benzene (80 mL) was added a catalytic amount of conc. H\(_2\)SO\(_4\) and the reaction mixture was refluxed at 80\(^\circ\)C for 2h. It was then cooled to room temperature, treated with a saturated aq. NaHCO\(_3\) solution (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 30a (5.99 g, 89%) as a light yellow semi-solid. \( R_f \ 0.39 \) (20% ethyl acetate in hexane). IR (KBr): 3480, 1600, 1509, 1228, 1158, 812, 745 cm\(^{-1}\). \text{IH NMR (200 MHz, CDCl} \_3\): \ \delta \ 7.91 \ (m, 1H), 7.85-7.75 \ (m, 2H), 7.34-7.22 \ (m, 13H), 6.43 \ (s, 1H), 5.12 \ (s, 1H). \text{MS (ESI):} \ m/z \ 309 \ [M-I]^+. \text{Anal. Calcd for C}_{23}\text{H}_{18}\text{O: C, 89.00; H, 5.85. Found: C, 89.12; H, 5.93.}

#### 4-Benzhydrylnaphthalen-1-ol (30b):

As described for 30a, compound 30b was synthesized from 29a (4.0 g, 21.71 mmol) and 1-naphthol (3.44 g, 23.88 mmol). The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 30b (4.91 g, 73%) as a colorless gum. \( R_f \ 0.39 \) (20% ethyl acetate in hexane). IR (KBr): 3492, 2361, 1622, 1450, 1253, 1205, 702
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1-[4-Chlorophenyl]phenylmethyl]naphthalen-2-ol (31a):

As described for 30a, compound 31a was synthesized from 29b (4.0 g, 18.29 mmol) and 2-naphthol (2.9 g, 20.12 mmol). The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 31a (5.29 g, 84%) as a light yellow semi-solid. Rf 0.39 (20% ethyl acetate in hexane). IR (KBr): 3488, 1607, 1511, 1220, 1158, 817, 745 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.08 (m, 1H), 7.76-7.74 (m, 1H), 7.47-7.37 (m, 3H), 7.34-7.16 (m, 10H), 6.98 (d, 1H, J = 8.5), 5.83 (s, 1H), 5.16 (s, 1H). MS (ESI): m/z 309 [M-1]⁺. Anal. Calcd for C₂₃H₁₉ClO: C, 89.00; H, 5.85. Found: C, 89.30; H, 5.70.

1-[4-Fluorophenyl]phenylmethyl]naphthalen-2-ol (32a):

As described for 30a, compound 32a was synthesized from 29c (4.0 g, 19.78 mmol) and 2-naphthol (3.13 g, 21.75 mmol). The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 32a (5.52 g, 85%) as a light yellow semi-solid. Rf 0.43 (20% ethyl acetate in hexane). IR (KBr): 3497, 1602, 1471 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.02 (m, 1H), 7.71 (m, 1H), 7.45-7.40 (m, 3H), 7.35-7.24 (m, 4H), 7.15-7.10 (m, 4H), 7.06-6.93 (m, 2H), 5.79 (s, 1H), 5.01 (s, 1H). MS (ESI): m/z 344 [M-1]⁺. Anal. Calcd for C₂₃H₁₇FClO: C, 80.11; H, 4.97. Found: C, 80.23; H, 5.15.

4-[4-Chlorophenyl]phenylmethyl]naphthalen-1-ol (31b):

As described for 30a, compound 31b was synthesized from 29b (4.0 g, 18.29 mmol) and 1-naphthol (2.9 g, 20.12 mmol). The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 31b (4.40 g, 70%) as a colorless semi-solid. Rf 0.39 (20% ethyl acetate in hexane). IR (KBr): 3469, 2925, 1660, 1488, 1382, 1087, 751 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.02 (m, 1H), 7.71 (m, 1H), 7.45-7.40 (m, 3H), 7.35-7.24 (m, 4H), 7.15-7.10 (m, 4H), 7.06-6.93 (m, 2H), 5.79 (s, 1H), 5.01 (s, 1H). MS (ESI): m/z 344 [M-1]⁺. Anal. Calcd for C₂₃H₁₇ClO: C, 80.11; H, 4.97. Found: C, 80.23; H, 5.15.
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1506, 1224, 1158, 812, 745 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.93 (d, 1H, \(J = 8.3\)), 7.73-7.69 (m, 2H), 7.34-7.17 (m, 9H), 7.06-6.93 (m, 3H), 6.36 (s, 1H), 5.13 (s, 1H). MS (ESI): \(m/z\) 327 [M-1]. Anal. Calcd for C\(_{23}\)H\(_{17}\)FO: C, 84.12; H, 5.22. Found: C, 84.01; H, 5.37.

4-[(4-Fluorophenyl)phenylmethyl]naphthalen-1-ol (32b):

As described for 30a, compound 32b was synthesized from 29c (4.0 g, 19.78 mmol) and 1-naphthol (3.13 g, 21.75 mmol). The crude product was purified by silica gel column chromatography (eluent: 4% ethyl acetate/hexanes) to give 32b (4.41 g, 68%) as a colorless gum. \(R_f\) 0.43 (20% ethyl acetate in hexane).

IR (KBr): 3508, 1661, 1504, 1227, 810, 746 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.06 (m, 1H), 7.74 (m, 1H), 7.47-7.42 (m, 3H), 7.34-7.27 (m, 4H), 7.17-7.09 (m, 4H), 7.03-6.93 (m, 2H), 5.82 (s, 1H), 5.14 (s, 1H). MS (ESI): \(m/z\) 327 [M-1]. Anal. Calcd for C\(_{23}\)H\(_{17}\)FO: C, 84.12; H, 5.22. Found: C, 84.31; H, 5.44.

4.8.4 Synthesis of Diarylmethylnaphthoxy Ethylamines (33a-e, 34a-e, 35a-e, 36a-e, 37a-e and 38a-e):

[2-(1-Benzhydrylnaphthalen-2-yloxy)ethyl]dimethylamine (33a):

A mixture of compound 30a (0.5 g, 1.61 mmol), anhyd. K\(_2\)CO\(_3\) (0.55 g, 4.02 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.25 g, 1.73 mmol) in dry acetone (20 mL) was refluxed for 8 h. After removing acetone under reduced pressure, water (30 mL) and ethyl acetate (60 mL) were added to the residue. The aqueous layer was extracted with ethyl acetate (30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 33a (0.43 g, 70%) as a colorless solid. Mp: 94-95°C. \(R_f\) 0.56 (10% methanol in dichloromethane). IR (KBr): 2945, 1596, 1455, 1254, 1031, 739 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.87 (m, 1H), 7.81-7.74 (m, 2H), 7.32-7.15 (m, 13H), 6.55 (s, 1H), 3.93 (t, 2H, \(J = 6.2\)), 2.34 (t, 2H, \(J = 6.2\)), 2.2 (s, 6H). \(^13\)C NMR (50 MHz, CDCl\(_3\)): \(\delta\) 155.1, 144.0, 133.8, 130.4, 129.6, 129.0, 128.5, 126.5, 126.2, 125.3, 123.7, 116.2, 68.5, 58.5, 48.3, 46.3. MS
[(1-Benzhydrylnaphthalen-2-yloxy)ethyl]diethylamine (33b):

As described for 33a, compound 33b was prepared from compound 30a (0.5 g, 1.61 mmol), anhyd. K$_2$CO$_3$ (0.55 g, 4.02 mmol) and 2-diethylaminoethyl chloride hydrochloride (0.3 g, 1.74 mmol). Silica gel column chromatography (elucent: 2% methanol in dichloromethane) of the crude product furnished 33b (0.43 g, 67%) as a colorless solid. Mp: 92-93°C. R$_f$: 0.56 (10% methanol in dichloromethane). IR (KBr): 2966, 1597, 1451, 1260, 1071, 1032, 717 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): δ 7.94-7.89 (m, 1H), 7.83-7.76 (m, 2H), 7.35-7.17 (m, 13H), 6.56 (s, 1H), 3.94 (t, 2H, $J = 6.7$), 2.57 (m, 6H), 0.98 (t, 6H, $J = 7.1$). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 155.0, 144.0, 133.8, 130.3, 129.6, 129.1, 128.5, 126.6, 126.2, 125.9, 125.2, 123.7, 116.0, 68.5, 52.2, 48.2, 12.2. MS (ESI): $m/z$ 410 [M+H]$^+$. Anal. Cacld for C$_{29}$H$_{31}$NO: C, 85.04; H, 7.63; N, 3.42. Found: C, 85.41; H, 7.76; N, 3.61.

1-(2-(1-Benzhydrylnaphthalen-2-yloxy)ethyl)pyrrolidine (33c):

As described for 33a, compound 33c was prepared from compound 30a (0.5 g, 1.61 mmol), anhyd. K$_2$CO$_3$ (0.55 g, 4.02 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (0.3 g, 1.76 mmol). Silica gel column chromatography (elucent: 2% methanol in dichloromethane) of the crude product furnished 33c (0.53 g, 80%) as a brown solid. Mp: 93-94°C. R$_f$: 0.59 (10% methanol in dichloromethane). IR (KBr): 2956, 2793, 2374, 1594, 1455, 1258, 1083, 1032, 717 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): δ 7.90 (m, 1H), 7.83-7.76 (m, 2H), 7.33-7.21 (m, 13H), 6.57 (s, 1H), 4.01 (t, 2H, $J = 6.2$), 2.57-2.51 (m, 6H), 1.72 (m, 4H). $^{13}$C NMR (50 MHz, CDCl$_3$): δ 155.0, 144.0, 133.8, 130.4, 129.6, 129.0, 128.4, 126.5, 126.2, 126.0, 125.3, 123.7, 116.0, 69.1, 55.1, 55.0, 48.1, 23.9. MS (ESI): $m/z$ 408 [M+H]$^+$. Anal. Cacld for C$_{29}$H$_{29}$NO: C, 85.47; H, 7.17; N, 3.44. Found: C, 85.29; H, 7.33; N, 3.55.

1-(2-(1-Benzhydrylnaphthalen-2-yloxy)ethyl)piperidine (33d):
As described for 33a, compound 33d was prepared from compound 30a (0.5 g, 1.61 mmol), anhyd. K₂CO₃ (0.55 g, 4.02 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.32 g, 1.73 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 16d (0.55 g, 81%) as an orange gum. Rf: 0.59 (10% methanol in dichloromethane). IR (KBr): 2937, 1597, 1446, 1257, 1030, 698 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 7.91-7.86 (m, 1H), 7.79-7.73 (m, 2H), 7.31-7.17 (m, 13H), 6.56 (s, 1H), 4.00 (t, 2H, J = 6.2), 2.42-2.33 (m, 6H), 1.51-1.49 (m, 4H), 1.39-1.36 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): δ 155.1, 144.1, 133.9, 129.7, 129.6, 129.1, 128.5, 126.5, 126.3, 125.9, 125.3, 123.7, 115.9, 68.0, 58.2, 55.4, 48.2, 26.4, 24.6. MS (ESI): m/z 422 [M+H]⁺. Anal. Cacld for C₃₀H₃₁NO: C, 85.47; H, 7.41; N, 3.32. Found: C, 85.29; H, 7.33; N, 3.55.

1-[2-(1-Benzhydrylnaphthalen-2-yloxy)ethyl]azepane (33e):

As described for 30a, compound 33e was prepared from compound 30a (0.5 g, 1.61 mmol), anhyd. K₂CO₃ (0.55 g, 4.02 mmol) and 2-(hexamethyleneimino)ethyl chloride hydrochloride (0.34 g, 1.73 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 33e (0.483 g, 69%) as an orange gum. Rf: 0.59 (10% methanol in dichloromethane). IR (KBr): 2926, 1446, 1254, 1079, 1028, 701 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 7.93-7.88 (m, 1H), 7.81-7.76 (m, 2H), 7.33-7.21 (m, 13H), 6.53 (s, 1H), 3.98 (t, 2H, J = 6.1), 2.65 (m, 4H), 2.55 (t, 2H, J = 6.1), 1.55 (m, 8H). ¹³C NMR (50 MHz, CDCl₃): 155.1, 144.1, 133.9, 129.7, 129.6, 129.1, 128.5, 126.5, 126.3, 125.9, 125.3, 123.7, 116.04, 68.4, 57.0, 56.4, 48.3, 28.4, 27.5. MS (ESI): m/z 436 [M+H]⁺. Anal. Cacld for C₃₁H₃₃NO: C, 85.48; H, 7.64; N, 3.22. Found: C, 85.52; H, 7.71; N, 3.36.

[2-(4-Benzhydrylnaphthalen-1-yloxy)ethyl]dimethylamine (34a):

As described for 33a, compound 34a was prepared compound 30b (0.5 g, 1.61 mmol), anhyd. K₂CO₃ (0.55 g, 4.02 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.25 g, 1.73 mmol). Silica gel column chromatography (eluent: 2%
methanol in dichloromethane) of the crude product furnished 34a (0.545 g, 78%) as a colorless solid. Mp: 111-112°C. Rf 0.55 (10% methanol in dichloromethane). IR (KBr): 2940, 1596, 1450, 1353, 1273, 1085, 1025, 697 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.14 (d, 1H, J = 8.8), 7.79 (m, 1H), 7.51-7.47 (m, 3H), 7.30-7.21 (m, 6H), 7.19-7.11 (m, 5H), 6.29 (s, 1H), 3.82 (t, 2H, J = 5.9), 2.72 (t, 2H, J = 5.9), 2.31 (s, 6H). ¹³C NMR (50 MHz, CDCl₃): δ 152.9, 144.4, 134.3, 132.6, 129.9, 129.2, 128.7, 128.4, 127.4, 126.7, 126.4, 126.3, 124.3, 122.9, 72.5, 59.6, 49.6, 46.3. MS (ESI): m/z 382 [M+H⁺]. Anal. Cacld for C₂₇H₂₇NO: C, 85.00; H, 7.13; N, 3.67. Found: C, C, 85.11; H, 7.01; N, 3.55.

2-(4-Benzhydrylnaphthalen-1-yloxy)ethyl]diethylamine (34b):

As described for 33a, compound 34b was prepared from compound 30b (0.5 g, 1.61 mmol), anhyd. K₂CO₃ (0.55 g, 4.02 mmol) and 2-diethylaminoethyl chloride hydrochloride (0.3 g, 1.74 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 34b (0.47 g, 73%) as a brown solid. Mp: 105-106°C. Rf 0.55 (10% methanol in dichloromethane). IR (KBr): 2965, 1596, 1446, 1357, 1077, 1016, 695 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.16 (d, 1H, J = 7.0), 7.78 (m, 1H), 7.55-7.47 (m, 3H), 7.27-7.21 (m, 5H), 7.19-7.11 (m, 6H), 6.28 (s, 1H), 3.82 (t, 2H, J = 6.4), 2.88 (t, 2H, J = 6.4), 2.56 (q, 4H, J = 8.0), 1.01 (t, 6H, J = 7.1). ¹³C NMR (50 MHz, CDCl₃): δ 153.0, 144.5, 134.3, 132.5, 129.9, 128.7, 128.4, 126.6, 126.3, 124.2, 123.0, 73.2, 53.2, 49.6, 47.9, 12.2. MS (ESI): m/z 410 [M+H⁺]. Anal. Cacld for C₂₉H₃₁NO: C, 85.04; H, 7.63; N, 3.42. Found: C, 85.12; H, 7.52; N, 3.74.

1-[2-(4-Benzhydrylnaphthalen-1-yloxy)ethyl]pyrrolidine (34c):

As described for 33a, compound 34c was prepared from compound 30b (0.5 g, 1.61 mmol), anhyd. K₂CO₃ (0.55 g, 4.02 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (0.3 g, 1.76 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 34c (0.45 g, 68%) as a brown solid. Mp: 95-96°C. Rf 0.59 (10% methanol in dichloromethane). IR (KBr): 2931, 2793, 2376, 1595, 1455, 1347, 1274, 1082, 699 cm⁻¹. ¹H NMR (300 MHz,
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CDCl$_3$): $\delta$ 8.19-8.16 (m, 1H), 7.83-7.80 (m, 1H), 7.57-7.43 (m, 3H), 7.36-7.21 (m, 5H), 7.19-7.09 (m, 6H), 6.30 (s, 1H), 3.96 (t, 2H, $J=4.0$), 2.95 (t, 2H, $J=4.0$), 2.65 (m, 4H), 1.89-1.83 (m, 4H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 150.5, 142.1, 131.9, 130.2, 128.1, 127.5, 126.3, 126.0, 124.3, 124.0, 123.9, 121.9, 120.6, 53.9, 52.6, 47.3, 21.5. MS (ESI): $m/z$ 408 [M+1]$^+$. Anal. Calcld for C$_{29}$H$_{29}$NO: C, 85.47; H, 7.17; N, 3.41. Found: C, 85.57; H, 7.27; N, 3.31.

1-(2-(4-Benzhydrylnaphthalen-1-yloxy)ethyl)piperidine (34d):

As described for 33a, compound 34d was prepared from compound 30b (0.5 g, 1.61 mmol), anhyd. K$_2$CO$_3$ (0.55 g, 4.02 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.32 g, 1.73 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 34d (0.427 g, 63%) as a brown solid. Mp: 100-101°C. R$_f$: 0.55 (10% methanol in dichloromethane). IR (KBr): 2935, 2784, 1596, 1455, 1347, 1274, 1082, 699 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.19 (d, 1H, $J=7.6$), 7.79 (d, 1H, $J=8.2$), 7.55-7.40 (m, 3H), 7.30-7.11 (m, 11H), 6.29 (s, 1H), 3.86 (t, 2H, $J=5.7$), 2.75 (t, 2H, $J=5.7$), 2.43 (m, 4H), 1.62-1.60 (m, 4H), 1.46-1.44 (m, 2H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 152.9, 144.5, 134.3, 132.6, 129.9, 128.7, 128.6, 128.4, 126.7, 126.3, 124.3, 123.1, 72.3, 59.3, 55.5, 49.6, 26.3, 24.7. MS (ESI): $m/z$ 422 [M+1]$^+$. Anal. Calcld for C$_{30}$H$_{31}$NO: C, 85.47; H, 7.41; N, 3.32. Found: C, 85.62; H, 7.49; N, 3.42.

1-[2-(4-Benzhydrylnaphthalen-1-yloxy)ethyl]azepane (34e):

As described for 33a, compound 34e was prepared from compound 30b (0.5 g, 1.61 mmol), anhyd. K$_2$CO$_3$ (0.55 g, 4.02 mmol) and 2-(hexamethyleneimino)ethyl chloride hydrochloride (0.34 g, 1.71 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 34e (0.44 g, 63%) as a brown solid. Mp: 103-104°C. R$_f$: 0.56 (10% methanol in dichloromethane). IR (KBr): 2919, 1596, 1450, 1346, 1279.
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1078, 1015, 699 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.18 (d, 1H, \(J = 7.2\)), 7.78 (m, 1H), 7.50-7.46 (m, 3H), 7.27-7.11 (m, 11H), 6.27 (s, 1H), 3.84 (t, 2H, \(J = 6.0\)), 2.94 (t, 2H, \(J = 6.0\)), 2.68-2.66 (m, 4H), 1.60 (m, 8H). MS (ESI): \(m/z\) 436 [M+1]\(^+\). Anal. Calc. for C\(_{31}\)H\(_{33}\)NO: C, 85.48; H, 7.64; N, 3.22. Found: C, 85.70; H, 7.48; N, 3.45.

(2-{1-[(4-Chlorophenyl)phenylmethyl]naphthalen-2-yloxy}ethyl)dimethylamine (35a):

As described for 33a, compound 35a was prepared from compound 31a (0.5 g, 1.45 mmol), anhyd. K\(_2\)CO\(_3\) (0.50 g, 3.62 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.23 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 35a (0.398 g, 66%) as a light yellow semi-solid. R\(_f\) 0.56 (10% methanol in dichloromethane). IR (KBr): 2937, 1624, 1598, 1489, 1248, 1087, 750 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)+CCI\(_4\)): \(\delta\) 7.79-7.75 (m, 3H), 7.30-7.14 (m, 12H), 6.45 (s, 1H), 3.93 (t, 2H, \(J = 6.2\)), 2.33 (t, 2H, \(J = 6.2\)), 2.21 (s, 6H). \(^1\)C NMR (50 MHz, CDCl\(_3\)+CCI\(_4\)): \(\delta\) 154.8, 143.4, 142.5, 133.6, 132.0, 130.9, 130.4, 129.9, 129.4, 129.1, 128.6, 126.8, 126.4, 125.5, 124.8, 123.8, 115.9, 68.1, 58.3, 47.7, 46.2. MS (FAB): \(m/z\) 416 [M]\(^+\). Anal. Calc. for C\(_{27}\)H\(_{26}\)ClNO: C, 77.96; H, 6.30; N, 3.37. Found: C, 78.19; H, 6.35; N, 3.47.

(2-{1-[(4-Chlorophenyl)phenylmethyl]naphthalen-2-yloxy}ethyl)diethylamine (35b):

As described for 33a, compound 35b was prepared from compound 31a (0.5 g, 1.45 mmol), anhyd. K\(_2\)CO\(_3\) (0.50 g, 3.62 mmol) and 2-diethylaminoethyl chloride hydrochloride (0.275 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 35b (0.437 g, 68%) as a light yellow semi-solid. R\(_f\) 0.56 (10% methanol in dichloromethane). IR (KBr): 2968, 1597, 1489, 1256, 1083, 748 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)+CCI\(_4\)): \(\delta\) 7.85-7.73 (m, 3H), 7.30-7.09 (m, 12H), 6.44 (s, 1H), 3.91 (t, 2H, \(J = 6.5\)), 2.62-2.38 (m, 6H), 0.97 (t, 2H, \(J = 7.1\)). \(^1\)C NMR (50 MHz, CDCl\(_3\)+CCI\(_4\)): \(\delta\) 154.9, 143.4, 142.7, 133.7, 132.0, 130.9, 130.3, 129.8, 129.4, 129.1, 128.6, 126.8, 126.4, 125.5, 124.8, 123.8, 115.9, 68.1, 58.3, 47.7, 46.2. MS (FAB): \(m/z\) 416 [M]\(^+\). Anal. Calc. for C\(_{27}\)H\(_{26}\)ClNO: C, 77.96; H, 6.30; N, 3.37. Found: C, 78.19; H, 6.35; N, 3.47.
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129.1, 128.5, 126.8, 126.4, 125.3, 124.7, 123.8, 115.8, 68.5, 52.3, 48.1, 47.7, 12.4.

MS (FAB): m/z 444 [M]⁺. Anal. Calc'd for C₂₉H₃₀ClNO: C, 78.45; H, 6.81; N, 3.15. Found: C, 78.38; H, 7.75; N, 3.43.

1-(2-{1-(4-Chlorophenyl)phenylmethyl}naphthalen-2-yloxy)ethyl)pyrrolidine (35c):

As described for 33a, compound 35c was prepared from compound 31a (0.5 g, 1.45 mmol), anhyd. K₂CO₃ (0.50 g, 3.62 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (0.272 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 35c (0.474 g, 74%) as a brown gum. Rf 0.56 (10% methanol in dichloromethane). IR (KBr): 2956, 1596, 1435, 1243, 1083, 745 cm⁻¹. ¹H NMR (200 MHz, CDCl₃+CCI₄): δ 7.84-7.72 (m, 3H), 7.33-7.09 (m, 12H), 6.44 (s, 1H), 4.01 (t, 2H, J = 5.9), 2.71-2.47 (m, 6H), 1.79-1.76 (m, 4H). ¹³C NMR (50 MHz, CDCl₃+CCI₄): δ 154.4, 143.4, 142.5, 133.6, 132.1, 130.5, 129.3, 129.2, 128.6, 126.9, 126.5, 125.2, 124.6, 124.0, 115.9, 67.4, 54.5, 47.8, 23.7. MS (FAB): m/z 442 [M]⁺. MS (FAB): m/z 442 [M]⁺. Anal. Calc'd for C₂₉H₂₇ClNO: C, 78.80; H, 6.39; N, 3.17. Found: C, 78.97; H, 6.44; N, 3.31.

1-(2-{1-[4-Chlorophenyl]phenylmethyl}naphthalen-2-yloxy)ethyl)piperidine (35d):

As described for 33a, compound 35d was prepared from compound 31a (0.5 g, 1.45 mmol), anhydrous K₂CO₃ (0.50 g, 3.62 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.275 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 35d (0.462 g, 70%) as an orange gum. Rf 0.56 (10% methanol in dichloromethane). IR (KBr): 2932, 1596, 1456, 1257, 1085, 751 cm⁻¹. ¹H NMR (200 MHz, CDCl₃+CCI₄): δ 7.84-7.72 (m, 3H), 7.29-7.10 (m, 12H), 6.45 (s, 1H), 3.99 (t, 2H, J = 6.1), 2.36-2.33 (m, 6H), 1.53-1.39 (m, 4H), 1.28-1.25 (m, 2H). ¹³C NMR (50 MHz, CDCl₃+CCI₄): δ 154.7, 143.4, 142.6, 133.6, 132.2, 130.9, 130.5, 129.4, 128.5, 126.8, 126.5, 125.8, 124.6, 124.0, 115.9, 67.4, 54.5, 47.8, 23.7. MS (FAB): m/z 442 [M]⁺. MS (FAB): m/z 442 [M]⁺. Anal. Calc'd for C₂₉H₂₇ClNO: C, 78.80; H, 6.39; N, 3.17. Found: C, 78.97; H, 6.44; N, 3.31.
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1-(2-\{1-[(4-Chlorophenyl)phenylmethyl]naphthalen-2- yloxy\}ethyl)azepane (35e):

As described for 33a, compound 35e was prepared from compound 31a (0.5 g, 1.45 mmol), anhyd. K$_2$CO$_3$ (0.50 g, 3.62 mmol) and 2-(hexamethylenimino)ethyl chloride hydrochloride (0.294 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 35e (0.470 g, 69%) as an orange gum. R$_f$ 0.56 (10% methanol in dichloromethane). IR (KBr): 2926, 2229, 1596, 1439, 1262, 1084, 744 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$+CCL$_4$): $\delta$ 7.85-7.72 (m, 3H), 7.32-7.08 (m, 12H), 6.42 (s, 1H), 4.03 (t, 2H, $J = 5.5$), 2.77-2.47 (m, 6H), 1.57 (m, 8H). $^{13}$C NMR (50 MHz, CDCl$_3$+CCL$_4$): $\delta$ 154.4, 143.4, 142.6, 133.6, 132.1, 130.8, 130.4, 129.3, 129.1, 128.6, 126.9, 125.1, 124.5, 123.9, 115.8, 67.1, 56.8, 56.0, 47.8, 27.3, 26.9. MS (ESI): \textit{m/z} 470 [M]$^+$. Anal. Cacld for C$_{31}$H$_{32}$CINO: C, 79.21; H, 6.86; N, 2.98. Found: C, 79.38; H, 7.13; N, 3.13.

(2-\{4-[(4-Chlorophenyl)phenylmethyl]naphthalen-1-yloxy\}ethyl)dimethylamine (36a):

As described for 33a, compound 36a was prepared from compound 31b (0.5 g, 1.45 mmol), anhyd. K$_2$CO$_3$ (0.50 g, 3.62 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.23 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 36a (0.475 g, 79%) as a colorless solid. Mp: 120-121°C. R$_f$: 0.56 (10% methanol in dichloromethane). IR (KBr): 3059, 2363, 1596, 1389, 1202, 814, 703 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.11 (m, 1H), 7.56 (m, 1H), 7.51-7.45 (m, 3H), 7.28-7.20 (m, 5H), 7.15-7.05 (m, 5H), 6.26 (s, 1H), 3.82-3.79 (m, 2H), 2.71 (t, 2H, $J = 5.8$), 2.30 (s, 6H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 153.0, 143.9, 143.1, 134.3, 132.5, 132.0, 131.2, 129.8, 128.8, 128.4, 126.9, 126.5, 124.4, 122.9, 72.8, 59.7, 48.9, 46.4. MS (ESI): \textit{m/z} 416 [M]$^+$. Anal. Cacld for C$_{27}$H$_{26}$CINO: C, 77.96; H, 6.30; N, 3.37. Found: C, 78.23; H, 6.58; N, 3.23.
(2-[(4-Chlorophenyl)phenylmethyl]naphthalen-1-yl)ethyldimethylamine (36b):

As described for 33a, compound 36b was prepared from compound 31b (0.5 g, 1.45 mmol), anhydrous K$_2$CO$_3$ (0.50 g, 3.62 mmol) and 2-diethylaminoethy chloride hydrochloride (0.275 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 36b (0.424 g, 67%) as a colorless solid. Mp: 114-115°C. R$_f$: 0.56 (10% methanol in dichloromethane). IR (KBr): 2968, 2369, 1632, 1486, 1362, 1083, 741 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.13 (m, 1H), 7.82-7.78 (m, 1H), 7.51-7.47 (m, 3H), 7.27-7.20 (m, 5H), 7.15-7.05 (m, 5H), 6.25 (s, 1H), 3.85 (t, 2H, $J = 6.1$), 2.90 (t, 2H, $J = 6.1$), 2.59 (q, 4H, $J = 7.1$), 1.03 (t, 6H, $J = 7.1$). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 152.9, 143.9, 143.1, 134.3, 132.5, 131.9, 131.2, 129.8, 128.8, 128.5, 128.4, 128.3, 126.9, 126.5, 124.4, 124.4, 122.9, 73.2, 53.2, 49.0, 48.0, 12.0. MS (ESI): $m/z$ 444 [M$^+$]. Anal. Calcd for C$_{29}$H$_{30}$CINO: C, 78.45; H, 6.81; N, 3.15. Found: C, 78.63; H, 7.95; N, 3.22.

(1-2-[(4-Chlorophenyl)phenylmethyl]naphthalen-1-yl)ethyl)pyrrolidine (36c):

As described for 33a, compound 36c was prepared from compound 31b (0.5 g, 1.45 mmol), anhydrous K$_2$CO$_3$ (0.50 g, 3.62 mmol) and N-(2-chloroethyl)pyrrolidine hydrochloride (0.272 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 36c (0.474 g, 74%) as a brown solid. Mp: 104-105°C. R$_f$: 0.56 (10% methanol in dichloromethane). IR (KBr): 2930, 2376, 1654, 1487, 1355, 1081, 736 cm$^{-1}$. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 8.19-8.16 (m, 1H), 7.85-7.82 (m, 1H), 7.58-7.48 (m, 3H), 7.31-7.24 (m, 5H), 7.18-7.09 (m, 5H), 6.30 (s, 1H), 3.93-3.89 (m, 2H), 2.93 (t, 2H, $J = 5.1$), 2.61-2.59 (m, 4H), 1.87-1.83 (m, 4H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 1523.0, 143.9, 143.1, 134.3, 132.5, 132.1, 131.2, 129.8, 128.8, 128.6, 128.4, 128.3, 126.9, 126.4, 124.4, 122.9, 73.7, 56.4, 55.0.
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1-(2-[(4-Chlorophenyl)phenylmethyl]naphthalen-1-ylxy)ethyl)piperidine (36d):

As described for 33a, compound 36d was prepared from compound 31b (0.5 g, 1.45 mmol), anhydrous K₂CO₃ (0.50 g, 3.62 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.275 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 36d (0.41 g, 63%) as a brown solid. Mp: 96-97°C. Rf: 0.56 (10% methanol in dichloromethane). IR (KBr): 2924, 1489, 1345, 1279, 1083, 1021, 782 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 8.19 (m, 1H), 7.82-7.78 (m, 1H), 7.56-7.47 (m, 3H), 7.28-7.20 (m, 5H), 7.15-7.06 (m, 5H), 6.25 (s, 1H), 3.88 (t, 2H, J = 5.9), 2.76 (t, 2H, J = 5.9), 2.47-2.45 (m, 4H), 1.65-1.60 (m, 4H), 1.47-1.45 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): δ 152.9, 143.9, 143.1, 134.3, 132.5, 132.0, 131.2, 129.8, 128.8, 128.6, 128.4, 128.2, 126.9, 126.5, 124.4, 123.1, 72.4, 59.3, 55.5, 48.9, 26.3, 24.7. MS (ESI): m/z 456 [M]^+. Anal. Calcld for C₃₀H₃₀ClINO: C, 79.01; H, 6.63; N, 3.07. Found: C, 79.36; H, 6.55; N, 3.21.

1-(2-[(4-Chlorophenyl)phenylmethyl]naphthalen-1-ylxy)ethyl)azepane (36e):

As described for 33a, compound 36e was prepared from compound 31b (0.5 g, 1.45 mmol), anhydrous K₂CO₃ (0.50 g, 3.62 mmol) and 2-(hexamethyleneimino)ethyl chloride hydrochloride (0.294 g, 1.6 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 36e (0.470 g, 69%) as a brown solid. Mp: 99-100°C. Rf: 0.56 (10% methanol in dichloromethane). IR (KBr): 2929, 1487, 1355, 1274, 1081, 813 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 8.24-8.21 (m, 1H), 7.85-7.82 (m, 1H), 7.59-7.47 (m, 3H), 7.34-7.24 (m, 5H), 7.19-7.11 (m, 5H), 6.29 (s, 1H), 3.87 (t, 2H, J = 5.2), 2.96 (t, 2H, J = 5.2), 2.72-2.69 (m, 4H), 1.64 (m, 8H). ¹³C NMR (50 MHz, CDCl₃): δ 153.1, 144.0, 143.2, 134.3, 132.5, 132.0, 131.3, 129.8, 128.9, 128.4, 128.3, 126.9, 126.5,
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124.4, 123.2, 73.4, 58.2, 56.6, 49.1, 28.5, 27.5. MS (ESI): m/z 470 [M]+. Anal. Calcd for C_{31}H_{22}ClNO: C, 79.21; H, 6.86; N, 2.98. Found: C, 78.98; H, 7.05; N, 3.29.

(2-{1-[4-(Fluorophenyl)phenylmethyl]naphthalen-2-yl}oxy)ethyl)dimethylamine (37a):

As described for 33a, compound 37a was prepared from compound 32a (0.5 g, 1.52 mmol), anhyd. K_{2}CO_{3} (0.53 g, 3.83 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.240 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 37a (0.42 g, 69%) as a colorless semi-solid. R_{f} 0.56 (10% methanol in dichloromethane). IR (KBr): 2928, 1600, 1466, 1238, 1082, 815, 750 cm\(^{-1}\). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.87-7.78 (m, 3H), 7.33-7.27 (m, 3H), 7.25-7.15 (m, 7H), 6.96-6.87 (m, 2H), 6.49 (s, 1H), 3.99-3.96 (m, 2H), 2.39 (t, 2H, \(J = 6.1\)), 2.25 (s, 6H). MS (ESI): m/z 400 [M+H]^+\]. Anal. Calcd for C_{27}H_{26}NO: C, 81.17; H, 6.56; N, 3.51. Found: C, 81.28; H, 6.88; N, 3.75.

Diethyl-(2-{1-[(4-fluorophenyl)phenylmethyl]naphthalen-2-yl}oxy)ethyl)amine (37b):

As described for 33a, compound 37b was prepared from compound 32a (0.5 g, 1.52 mmol), anhyd. K_{2}CO_{3} (0.53 g, 3.83 mmol) and 2-diethylaminoethyl chloride hydrochloride (0.287 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 37b (0.485 g, 75%) as a colorless semi-solid. R_{f} 0.56 (10% methanol in dichloromethane). IR (KBr): 2928, 1600, 1466, 1238, 1082, 815, 750 cm\(^{-1}\). \(^{1}\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 7.90-7.78 (m, 3H), 7.33-7.27 (m, 3H), 7.20-7.15 (m, 7H), 6.91 (t, 2H, \(J = 8.6\)), 6.49 (s, 1H), 3.97-3.91 (m, 2H), 2.56-2.43 (m, 6H), 1.01-0.94 (t, 4H, \(J = 7.1\)). MS (ESI): m/z 428 [M+H]^+\]. Anal. Calcd for C_{29}H_{30}NO: C, 81.47; H, 6.89; N, 3.57. Found: C, 81.55; H, 6.89; N, 3.57.

1-(2-[1-[(4-Fluorophenyl)phenylmethyl]naphthalen-2-yl}oxy)ethyl)pyrrolidine (37c):
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As described for 33a, compound 37c was prepared from compound 32a (0.5 g, 1.52 mmol), anhyd. K₂CO₃ (0.53 g, 3.83 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (0.284 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 37c (0.51 g, 79%) as a light brown semi-solid. Rf: 0.56 (10% methanol in dichloromethane).

IR (KBr): 2929, 1601, 1507, 1255, 1077, 746 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ 7.89-7.85 (m, 1H), 7.83-7.80 (m, 2H), 7.36-7.29 (m, 3H), 7.28-7.19 (m, 7H), 6.97-6.92 (m, 2H), 6.55 (s, 1H), 4.08-4.03 (m, 2H), 2.62-2.55 (m, 6H), 1.80-1.75 (m, 4H). MS (ESI): m/z 426 [M+H⁺]. Anal. Calcd for C₂₉H₂₆FNO: C, 81.97; H, 6.88; N, 3.19. Found: C, 82.19; H, 7.16; N, 3.40.

1-(2-{1-[4-Fluorophenyl]phenylmethyl}naphthalen-2-yloxy)ethyl)piperidine (37d):

As described for 33a, compound 37d was prepared from compound 32a (0.5 g, 1.52 mmol), anhyd. K₂CO₃ (0.53 g, 3.83 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.307 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 37d (0.55 g, 83%) as an orange semi-solid. Rf: 0.56 (10% methanol in dichloromethane).

IR (KBr): 2932, 1601, 1505, 1226, 1083, 752 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.93-7.89 (m, 1H), 7.85-7.80 (m, 2H), 7.36-7.29 (m, 3H), 7.27-7.20 (m, 7H), 6.98-6.93 (m, 2H), 6.56 (s, 1H), 4.08-4.02 (m, 2H), 2.47-2.38 (m, 6H), 1.60-1.53 (m, 4H), 1.46-1.43 (m, 2H). MS (ESI): m/z 440 [M+H⁺]. Anal. Calcd for C₃₀H₃₀FNO: C, 81.97; H, 6.88; N, 3.19. Found: C, 82.17; H, 6.96; N, 3.42.

1-(2-{1-[4-Fluorophenyl]phenylmethyl}naphthalen-2-yloxy)ethyl)azepane (37e):

As described for 33a, compound 37e was prepared from compound 32a (0.5 g, 1.52 mmol), anhyd. K₂CO₃ (0.53 g, 3.83 mmol) and 2-(hexamethyleneimino)ethyl chloride hydrochloride (0.331 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 37e (0.53 g, 76%) as an orange semi-solid. Rf: 0.56 (10% methanol in dichloromethane). IR (KBr):
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2923, 2365, 1598, 1502, 1220, 1081, 815 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.91-7.88 (m, 1H), 7.84-7.79 (m, 2H), 7.35-7.19 (m, 10H), 6.97-6.91 (m, 2H), 6.53 (s, 1H), 4.01-3.95 (m, 2H), 2.65-2.56 (m, 6H), 1.58 (m, 8H). MS (ESI): \(m/z\) 454 [M+\(^+\)]. Anal. Calcd for C\(_{31}\)H\(_{32}\)FNO: C, 82.09; H, 7.11; N, 3.09. Found: C, 82.15; H, 7.06; N, 3.22.

2-{4-[(4-Fluorophenyl)phenylmethyl]naphthalen-1-yloxy}ethyl)dimethylamine (38a):

As described for 33a, compound 38a was prepared from compound 32b (0.5 g, 1.52 mmol), anhyd. K\(_2\)CO\(_3\) (0.53 g, 3.83 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.240 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 21a (0.45 g, 74%) as a colorless semi-solid. \(R_f\) 0.56 (10% methanol in dichloromethane). IR (KBr): 2928, 1599, 1461, 1235, 1082, 1028, 815, 750 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.14 (d, 1H, \(J = 7.4\)), 7.80 (d, 1H, \(J = 8.2\)), 7.56-7.48 (m, 3H), 7.28-7.20 (m, 3H), 7.15-7.07 (m, 5H), 6.99-6.91 (m, 2H), 6.27 (s, 1H), 3.81 (t, 2H, \(J = 5.8\)), 2.70 (t, 2H, \(J = 5.8\)), 2.29 (s, 6H). MS (ESI): \(m/z\) 400 [M+\(^+\)]. Anal. Calcd for C\(_{27}\)H\(_{26}\)FNO: C, 81.17; H, 6.56; N, 3.51. Found: C, 81.48; H, 6.63; N, 3.55.

Diethyl-(2-{4-[(4-fluorophenyl)phenylmethyl]naphthalen-1-yloxy}ethyl)amine (38b):

As described for 33a, compound 38b was prepared from compound 32b (0.5 g, 1.52 mmol), anhyd. K\(_2\)CO\(_3\) (0.53 g, 3.83 mmol) and 2-diethylaminoethyl chloride hydrochloride (0.287 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 38b (0.477 g, 73%) as a colorless semi-solid. \(R_f\) 0.56 (10% methanol in dichloromethane). IR (KBr): 2925, 1599, 1503, 1359, 1221, 1082, 1021, 815, 738 cm\(^{-1}\). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 8.16 (d, 1H, \(J = 7.7\)), 7.80 (d, 1H, \(J = 7.8\)), 7.56-7.48 (m, 3H), 7.28-7.20 (m, 3H), 7.15-7.07 (m, 5H), 6.99-6.91 (m, 2H), 6.27 (s, 1H), 3.81 (t, 2H, \(J = 5.8\)), 2.70 (t, 2H, \(J = 5.8\)), 2.29 (s, 6H). MS (ESI): \(m/z\) 400 [M+\(^+\)]. Anal. Calcd for C\(_{27}\)H\(_{26}\)FNO: C, 81.17; H, 6.56; N, 3.51. Found: C, 81.48; H, 6.63; N, 3.55.
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7.80 (d, 1H, J = 6.9), 7.56-7.47 (m, 3H), 7.31-7.24 (m, 3H), 7.19-7.07 (m, 5H), 6.99-6.90 (m, 2H), 6.26 (s, 1H), 3.82 (t, 2H, J = 6.3), 2.88 (t, 2H, J = 6.3), 2.56 (q, 4H, J = 7.1), 1.01 (t, 6H, J = 7.1). MS (ESI): m/z 428 [M+1]+. Anal. Calcd for C_{29}H_{30}FNO: C, 81.47; H, 7.07; N, 3.28. Found: C, 81.38; H, 6.99; N, 3.35.

1-(2-{4-[4-(4-Fluorophenyl)phenylmethyl]naphthalen-1-yloxy}ethyl)pyrrolidine (38c):

As described for 33a, compound 38c was prepared from compound 32b (0.5 g, 1.52 mmol), anhyd. K_{2}CO_{3} (0.53 g, 3.83 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (0.284 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 38c (0.446 g, 69%) as an orange semi-solid. R_{f}: 0.56 (10% methanol in dichloromethane). IR (KBr): 2960, 2365, 1624, 1600, 1507, 1230, 1077, 746 cm⁻¹. ^{1}H NMR (200 MHz, CDCl_{3}): δ 8.12 (m, 1H), 7.77 (m, 1H), 7.56-7.47 (m, 3H), 7.28-7.23 (m, 3H), 7.15-7.07 (m, 5H), 6.99-6.95 (m, 2H), 6.27 (s, 1H), 3.88 (t, 2H, J = 5.9), 2.90 (t, 2H, J = 5.9), 2.57 (m, 4H), 1.83-1.80 (m, 4H). MS (ESI): m/z 426 [M+1]+. Anal. Calcd for C_{29}H_{28}FNO: C, 81.97; H, 6.88; N, 3.19. Found: C, 82.01; H, 6.96; N, 3.25.

1-(2-{4-[4-(4-Fluorophenyl)phenylmethyl]naphthalen-1-yloxy}ethyl)piperidine (38d):

As described for 33a, compound 38d was prepared from compound 32b (0.5 g, 1.52 mmol), anhyd. K_{2}CO_{3} (0.53 g, 3.83 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (0.307 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 38d (0.527 g, 79%) as an orange semi-solid. R_{f}: 0.56 (10% methanol in dichloromethane). IR (KBr): 2926, 2365, 1624, 1600, 1507, 1229, 1079, 744 cm⁻¹. ^{1}H NMR (200 MHz, CDCl_{3}): δ 8.18 (d, 1H, J = 7.4), 7.82-7.77 (m, 1H), 7.56-7.41 (m, 3H), 7.31-7.20 (m, 3H), 7.15-7.07 (m, 5H), 6.99-6.91 (m, 2H), 6.26 (s, 1H), 3.89 (t, 2H, J = 5.6), 2.77 (t, 2H, J = 5.6), 2.46 (m, 4H).
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4H), 1.64-1.62 (m, 4H), 1.47-1.45 (m, 2H). MS (ESI): m/z 440 [M+H]^+. Anal. Calcd for C_{30}H_{30}FNO: C, 81.97; H, 6.88; N, 3.19. Found: C, 82.13; H, 7.06; N, 3.32.

1-(2-[(4-Fluorophenyl)phenylmethyl]naphthalen-1-yloxy)ethyl)azepane (38e):

As described for 33a, compound 38e was prepared from compound 32b (0.5 g, 1.52 mmol), anhyd. K_{2}CO_{3} (0.53 g, 3.83 mmol) and 2-(hexamethyleneimino)ethyl chloride hydrochloride (0.331 g, 1.67 mmol). Silica gel column chromatography (eluent: 2% methanol in dichloromethane) of the crude product furnished 38e (0.44 g, 63%) as an orange semi-solid. Rf 0.56 (10% methanol in dichloromethane). IR (KBBr): 2925, 1599, 1507, 1228, 1079, 744 cm^-1. 'H NMR (200 MHz, CDCl3): δ 8.18 (d, 1H, J = 7.4), 7.81-7.77 (m, 1H), 7.55-7.45 (m, 3H), 7.28-7.19 (m, 3H), 7.15-7.07 (m, 5H), 6.99-6.90 (m, 2H), 6.26 (s, 1H), 3.85 (t, 2H, J = 5.9), 2.94 (t, 2H, J = 5.9), 2.69-2.66 (m, 4H), 1.60 (m, 8H). MS (ESI): m/z 454 [M+H]^+. Anal. Calcd for C_{31}H_{32}FNO: C, 82.09; H, 7.11; N, 3.09. Found: C, 82.38; H, 7.26; N, 3.12.

4.8.5 Biological Activity

4.8.5.1 Micro Almar Blue Assay (MABA):

All the synthesized final molecules (33-38)a-e were evaluated against M. tuberculosis H_{37}Rv strains following micro almar blue assay.\textsuperscript{31} Briefly, two hundred microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates to minimize evaporation of the medium in the test wells during incubation. The 96-well plates received 100 μL of the Middlebrook 7H9 broth and a serial dilution of the compounds (33-38) a-e was made directly on the plate. The final drug concentrations tested were 0.01-10.0 μL/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for 5 days. After this time, 25 mL of a freshly prepared 1:1 mixture of Alamar blue reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC (Minimal Inhibition Concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink.
4.8.5.2 Agar Micro Dilution Method:

Drug susceptibility and determination of MIC of the test compounds/drugs against *M. tuberculosis* H₃₇Rᵥ were performed by agar micro dilution method where serial two fold dilutions of each test compound were added into 7H10 agar and *M. tuberculosis* H₃₇Rᵥ was used as test organism. MIC was the concentration of the compound that completely inhibited the growth and colony forming ability of *M. tuberculosis*.

In 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 25, 12.5, 6.25, 3.125 and 1.56 μg/mL respectively. The known CFU of H₃₇Rᵥ culture was dispensed on top of agar in each well in negative pressure biosafety hood. The plates are then incubated at 37°C/5% CO₂ incubator. The concentration at which complete inhibition of colonies was observed was taken as MIC of test drug.

4.8.5.3 Cytotoxicity of Selected Compounds:

Cytotoxicity of the selected compounds 33a-e, 37b and 37d was checked by cell proliferation assay using VERO cells. In the assay numbers of viable cells were determined colorimetrically with a reagent containing a tetrazolium compound (MTS, Owen’s reagent) and an electron-coupling reagent (PES, phenazine ethosulphate). The MTS was bioreduced (by NADPH or NADH produced by dehydrogenase enzyme in live cells) into a coloured formazen that was soluble in tissue culture medium. VERO cells (104 cells/well/0.1 mL MEM containing antibiotics and 10% FBS) were seeded in 96-well tissue culture plate. After 24 h incubation (37°C, 5% CO₂) medium was replaced with fresh medium (5% FBS and no antibiotic) containing different concentrations of test compound/known toxic compound/DMSO. After 24 h incubation (37°C, 5% CO₂) 20 mL MTS reagent (Promega Kit) was added and absorbance was read after 2 h at 490 nm. Absorbance shown by DMSO containing wells was taken as 100% survivors. A compound was considered toxic if it caused 50% inhibition at concentration 10-fold higher than its MIC.
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4.9 References


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4.10 Spectra

Figure 4.5 $^1$H NMR (200 MHz, CDCl$_3$) spectrum of 33a

Figure 4.6 $^{13}$C NMR (50 MHz, CDCl$_3$) spectrum of 33a
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Figure 4.7 $^1$H NMR (200 MHz, CDCl$_3$) spectrum of 33b

Figure 4.8 $^{13}$C NMR (50 MHz, CDCl$_3$) spectrum of 33b
Figure 4.9 $^1$H NMR (200 MHz, CDCl$_3$+CCl$_4$) spectrum of 35a

Figure 4.10 $^{13}$C NMR (50 MHz, CDCl$_3$+CCl$_4$) spectrum of 35a
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Figure 4.11 $^1$H NMR (200 MHz, CDCl$_3$) spectrum of 36a

Figure 4.12 $^{13}$C NMR (50 MHz, CDCl$_3$) spectrum of 36a
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Figure 4.13 $^1$H NMR (300 MHz, CDCl$_3$) spectrum of 36c

Figure 4.14 $^{13}$C NMR (50 MHz, CDCl$_3$) spectrum of 36c
Figure 4.15 $^1$H NMR (200 MHz, CDCl$_3$) spectrum of 37b

Figure 4.16 $^1$H NMR (200 MHz, CDCl$_3$) spectrum of 38a