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Substituted 1, 2, 3, 4-Tetrahydroquinolin-6-yloxypropanes as β_3-adrenergic receptor agonists: Design, synthesis, biological evaluation and pharmacophore modeling

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Abstract

In search of potent β_3-adrenergic receptor agonists, a series of novel substituted 1,2,3,4-tetrahydroquinolin-6-yloxypropanes has been synthesized and evaluated for their β_3-adrenergic receptor agonistic activity (ranging from -17.73% to 90.64% inhibition at 10 μM) using well established Human SK-N-MC neuroblastoma cells model. Four molecules *viz.* **11, 15, 22** and **23** showed β_3-AR agonistic IC_{50} value of 0.55 μM, 0.59 μM, 1.18 μM and 1.76 μM respectively. These four candidates have been identified as possible leads for further development of β_3-adrenergic receptor agonists for obesity and Type-II diabetes pharmacotherapy. The free OH and NH functions are found to be essential for β_3-adrenergic receptor agonistic activity. Among the synthesized β_3-adrenergic receptor agonists having 1,2,3,4-tetrahydroquinoline scaffold, the N-benzyl group is found to be superior over N-arylsulphonyl group. A putative pharmacophore model has been modeled considering the above four active molecules which distinguishes well between the active and inactive molecules.

Keywords: 1,2,3,4-Tetrahydroquinolin-6-yloxypropanes, β_3-adrenergic receptor agonist, Obesity, Type-II Diabetes, Putative Pharmacophore, HipHop, Catalyst

1. Introduction

The β_3–adrenergic receptors (β_3-AR), belonging to G-protein coupled receptor (GPCR) family, are found to mediate various pharmacological and physiological effects such as lipolysis in white adipocytes and thermogenesis (energy expenditure) in brown tissue adipocytes and intestinal smooth muscle relaxation in rodents.[1] Recent studies have indicated that, in addition to adipocytes, the β_3-AR is also distributed in human urinary bladder detrusor tissue and its relaxation occurs mainly *via* β_3-AR[2] and hence β_3–AR has been an important target for obesity and exploration of molecules with β_3–AR agonistic activity may provide potential anti-obesity agents with a potential for the treatment of non insulin dependent diabetes mellitus (NIDDM) or Type-II diabetes.[3] On the other hand, the simultaneous activation of β_1- or β_2-ARs would lead to undesirable side effects such as increased heart rate and/or muscle tremors. Therefore, β_3-AR selectivity over β_1-AR and β_2-AR has been required for development of novel therapeutic agents.[4]

In the past decades, the drug discovery efforts have shifted towards the design of selective β_3-AR agonists. Furthermore, a number of potent and selective human β_3-AR chemotypes (Figure 1) have been reported by several groups, but unfortunately, these are still not sufficient in terms of the pharmacokinetic properties.[5]

Please insert Figure 1

These reported β_3-AR agonists suffer from lack of selectivity, tissue specificity, full agonistic activity and short plasma half life as well as drug toxicity.[16, 17] In view of above and in order to meet the need of a potent and efficient drug for obesity, NIDDM and related disorders, attempts have been made to rationalize the Structure Activity Relationship (SAR) in terms of identification of the essential structural features (pharmacophore) for β_3-AR agonistic activity.[18] In this study, the role of the secondary amino (NH) group in the side chain has been shown to be essential while the role of hydroxyl group has been shown to be of lesser importance for β_3-AR agonistic activity. In order to validate these observations and to increase our understanding about the important interactions of the ligand with β_3-AR, the molecules with OH (**9-38**), without OH (**40-45**), with tertiary amines (**17-21, 23-38, 45, 47-52**) and those where NH and OH are part of the ring (morpholine) (**61-63**) have been synthesized and evaluated for their β_3-agonistic activity. These studies along with the development of a putative pharmacophoric model distinguishing well the active and inactive molecules are reported in this manuscript.

2. Results and Discussion

2.1. Chemistry

The synthetic strategy adopted for the synthesis of the title compounds has been outlined in scheme-1 where p-anisidine (**1**) on reaction with glycerol (**2**) and conc. sulphuric acid yielded 6-methoxyquinoline (**3**) (Skraup synthesis).[19, 20] Skraup synthesis was carried out with variation in reaction temperature ranging from 120-180^{o}C. The most efficient output

was achieved when the reaction was carried out at 140°C. The hydrogenation of 6-methoxyquinoline by PtO_2, $NaBH_4$, $NaCNBH_4$ was not successful, and resulted in either the recovery of starting material or a complex mixture of 5-6 products. Ultimately the reduction of 6-methoxyquinoline by Ni-Al alloy in ethanol gave desired product 6-methoxy-1,2,3,4-tetrahydroquinoline (**4**).[21] The N-benzylation of compound **4** using benzyl chloride in the presence of Na_2CO_3 (or K_2CO_3) and NaI (or KI) afforded 1-benzyl-1,2,3,4-tetrahydro-6-methoxyquinoline (**5**). The demethylation of compound **5** with 47% HBr in water gave 1-benzyl-1,2,3,4-tetrahydro-6-hydroxyquinoline (**6**). The compound **6** on condensation with epichlorohydrin in the presence of base like NaOH or NaH, in THF at 100°C gave 1-benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**) along with **7** (a side product). This side product showed almost similar signals in PMR spectra but had molecular ion peak (M^+) at 534 in mass spectrum. A careful analysis of its PMR indicated that signal for O*C*H*C*H_2 appeared at 4.13-4.28 in **7** as compared to its appearance at 4.05-4.12 in **8** as broad signal (bs) and based on its mass and PMR spectra the structure of the side product confirmed as **7**, where it is formed by the condensation of two molecules of 1,2,3,4- tetrahydro-6-hydroxyquinoline (**6**) with one molecule of epichlorohydrin. In order to improve the yield of the desired compound **8,** this reaction was tried at room temperature whereby the yield of the desired product (**8**) was increased to 51% from 34% without accounting the recovery of the unreacted **6** in the latter case. The yield of **8** was further improved to 73% using NaH (at -10°C) instead of NaOH as a base (at room temperature).

Please insert Scheme 1

The substituted 1,2,3,4-tetrahydroquinoline **8** on reaction with (un)substituted amines, piperidines, piperazines yielded the corresponding substituted 3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ols (**9-38**) as the title compounds. The compound **6** was also subjected to react with 1-bromo-3-chloropropane to afford 1-benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**). The compound **39** on condensation with various amines, piperidines, piperazines afforded the corresponding substituted 1-benzyl-6-[3-propoxy]-1,2,3,4-tetrahydroquinolines (**40-45)** as the title compounds (Scheme-1).

In order to investigate the importance of the side chain free NH function and the benzyl group at position 1 of the 1,2,3,4-tetrahydroquinoline, the compound **11**, which was found to be the most active compound in the series, was targeted for further modification. (Scheme-2)

Please Insert Scheme 2

The compound **11** was debenzylated to yield the corresponding debenzylated derivative, **46**. The compound **46** was selectively mono N-protected with Boc group to give compound **47**. The compound **47** was alternatively obtained by N-Boc protection of compound **11** followed by debenzylation of compound **48** thus obtained. The latter approach was found to be better than the former one in terms of the yield value. The reaction of compound **47** with various sulfonyl chlorides yielded the corresponding Boc

protected quinolinyl sulphonyl derivatives (**49-52**). These compounds were then Boc-deprotected to afford the desired quinolinyl derivatives (**53-56**) (Scheme-2).

Synthesis of substituted 4-(1-methyl-2-phenylethyl)-2-phenylmorpholines

The synthetic strategy for the titled compounds which may be considered as semi-rigid analogues of arylethanolamine where the rigidity has been introduced in the side chain between hydroxyl and amino function as outlined in scheme 3 and has essentially similar steps as represented by Bettoni *et.al.*[22]

Please Insert Scheme 3

The synthesis of the 1-(4-hydroxyphenyl)propan-2-one (**59**) was done using procedure reported by Koremura *et.al.*[23] The reaction of 4-hydroxy-benzaldehyde **(57)** with nitroethane led to 4-(2-Nitropropenyl)phenol (**58)** which on treatment with iron powder in the presence of ferric chloride and HCl afforded 1-(4-Hydroxyphenyl)propan-2-one (**59)**. The compound **59** was then used for reductive alkylation of **60** which afforded 4-[2-(2-phenylmorpholin-4-yl)propyl]-phenol (**61)**. The compound **61** was esterified with ethylbromoacetate to afford {4-[2-(2-phenyl-morpholin-4-yl)-propyl]-phenoxy}acetic acid ethyl ester (**62**) which on hydrolysis afforded the desired compound {4-[2-(2-phenyl-morpholin-4-yl)-propyl]-phenoxy}acetic acid (**63**).

2.2. Structure Activity Relationship (SAR):

The ayloxypropanolamine analogs **9-38** were evaluated for their β_3-adrenergic receptor agonistic activity at 1 μM and 10 μM concentrations (Table 1).

Please Insert Table 1

Among these, the compound **11** (IC_{50} = 0.55 μM) with 72.79% inhibition at 1 μM and 90.64% inhibition at 10 μM concentration showed highest β_3-AR agonistic activity. It was followed by the compound **15** (IC_{50} = 0.59 μM), which had isopropyl group in side chain in place of the 3,4-dimethoxyphenethyl group, showed 59.69% inhibition at 1 μM and 83.17% inhibition at 10 μM concentrations. The compound **22,** with only one methoxy group on phenyl ring in side chain instead of two methoxy groups present in compound **11,** also showed good activity (IC_{50} = 1.18 μM) with 56.22% inhibition at 1 μM and 76.50% inhibition at 10 μM concentrations. The replacement of isopropyl group in the compound **15** by propyl group resulted in compound **14** with decrease in activity (66.27% inhibition at 10 μM; IC_{50}>1μM). The replacement of 3,4-dimethoxyphenethyl group in compound **11** by 4-chlorophenethyl group resulted in the compound **12** with decrease in activity (55.79% inhibition at 1 μM and 63.08% inhibition at 10 μM). These results indicate that steric factor at side chain NH functionality is not so important rather electronic effects which seem to be important for the β_3-AR agonistic

activity, where the electron donating groups substituted on the phenyl ring play favorable role for enhancement of activity.

In order to examine the effect of free OH group in the side chain (at the position 6 of 1,2,3,4-tetrahydroquinoline nucleus) on β_3-AR agonistic activity, we synthesized compounds **40**-**45**. As expected, it was found that the deletion of OH group from side chain of **11**, **12**, **14** and **27** led to the corresponding compounds **40**, **41**, **44** and **45**, respectively with considerable decrease in activity (Table 1) suggesting the favorable role of the side chain free OH (hydroxyl) group towards β_3-AR agonistic activity.

Further, in order to examine the importance of the free NH function in the side chain and N-benzyl group at position 1 of the 1,2,3,4-tetrahydroquinoline nucleus, the most active compound **11** was further targeted for modification as shown in scheme 2.

The N-protection with Boc group at the side chain in compound **11** led to the compound **48** with considerable decrease in activity (46.66% inhibition at 10 μM concentration). Therefore, it may be inferred from the above studies that the amino function in the side chain must be free (secondary) for better agonistic activity. In order to strengthen this observation that the free NH and OH groups in the side chain are necessary for β_3-AR agonistic activity, we also synthesized rigid analogues of reported arylethanolamines **61**, **62** and **63** (Scheme 3)[11, 24-26] where both secondary amino (NH) and hydroxyl (OH) function in the side chain have been changed to tertiary amine (N) and ether (O) respectively by incorporating a morpholine nucleus. The synthesis of these molecules involved essentially the similar steps as reported by Bettoni *et al*.[22]

These compounds showed very poor activity, thus strengthening the view that the free OH and free NH groups are essential requirement for better β_3-AR agonistic activity. The importance of free NH group was also substantiated by the fact that among the synthesized compounds with piperazine or piperidine moiety (for example compounds **20**, **23-38**, **42**, **45** instead of secondary amine), none of them showed good β_3 agonistic activity. Therefore, it may be concluded that the NH function here is more prone to act as hydrogen bond donor (HBD) rather than as positively ionizable because of the fact that piperazine, piperidine and trisubstituted nitrogen (tertiary N) may act as positively ionizable function whereas the secondary amino (NH) may act as both positively ionizable as well as HBD. Since, the compounds with tertiary N was found to be less active than the corresponding compounds with secondary NH function, it become evident that the essential secondary amino (NH) function may possibly be acting as HBD function rather than positively ionizable in the active site gorge of β_3-AR.

We also synthesized few compounds with an aim to establish the contribution of the N-benzyl group present in these 1,2,3,4-tetrahydroquinoline moiety towards their β_3-AR agonism. The debenzylation of the compound **48** led to **47** with decrease in activity (28.14% inhibition at 10 μM). Therefore, it appeared that the benzyl group at this position may have important contribution for the activity which was also substantiated by the fact that debenzylation of the most active compound **11** of the series afforded **46** (56.45% inhibition at 10 μM) with considerable decrease in β_3-AR agonistic activity. It may be due to the fact that the phenyl residue of the benzyl group may be involved in π-π interaction (hydrophobic) with hydrophobic residues like tryptophan (Trp), phenylalanine (Phe), leucine (Leu), isoleucine (Ile), tyrosine (Tyr), valine (Val) *etc* in the lipophilic (hydrophobic) pocket of the β_3-adrenergic receptor.

In order to further establish the importance of benzyl function, we synthesized four selected compounds **53-56**. The compound **53** (with benzenesulphonyl group instead of benzyl group at 1,2,3,4-tetrahydrquinolinyl nitrogen; 38.92% inhibition at 10 μM; IC_{50} >10 μM) was found to be much less activity in comparison to the most active compound **11**. Thus, in 1,2,3,4-tetrahydroquinoline nucleus, N-benzyl group is more favorable substituent over N-benzenesulphonyl group for β_3-AR agonistic activity. Here this may be explained on the basis that the benzenesulphonyl group may render these compounds (**53-56**) to acquire unfavourable conformation in the active site which may not be favourable for the phenyl residue of the benzenesulphonyl group to reach or attain the position to show π-π interaction (hydrophobic) with hydrophobic residues in the lipophilic (hydrophobic) pocket of the β_3-AR. In addition, the $–SO_2$ group in the benzenesulphonyl group is a strong HBA with the ability to show two HBA interaction simultaneously may have strong interaction with the residues in the active site which may render the molecules to attain an unfavourable binding pose, overall shape etc in the active pocket of the β_3-AR.

Two compounds **15** and **22** were assayed for their selectivity towards β_3-AR over β_1- and β_2-ARs. The compound **15** was found to be 1.31 fold selective for β_3-AR over β_1-AR and 2,3 fold selective for β_3 AR over β_1-AR. The compound **22** was found to be 1.2 fold selective for β_3-AR over β_1-AR and 1.47 fold selective for β_3 AR over β_1-AR. The selectivity data for these two compounds is illustrated in table 2.

Please Insert Table 2 here

An in brief SAR of few selected compounds, covering all modulations exercised in the present study, has been illustrated diagrammatically (Figure 2).

Please Insert Figure 2

The effects of changes at different positions like presence or absence of free OH and/or free NH, substituents at N in the side chain and the effects of the substitution with benzenesulphonyl in place of benzyl and also the effects of unsubstituted N (NH) of the 1,2,3,4-tetrahydroquinoline on the β_3-adrenergic receptor agonistic activity have been illustrated.

2.3. Putative β_3-AR Pharmacophore Model:

In order to correlate the β_3-AR agonistic activity to the structures and to gain better insight and understanding of the possible shape and size of the β_3-adrenergic receptor active site, four active molecules *viz.* **11**, **15**, **22, 23** were modeled using HipHop algorithm in Catalyst molecular modeling software.

All molecules were minimized to their closest local minimum using the CHARMm force field. The diverse conformations for these molecules were generated using the option best conformation generation method with 20 kcal/mol energy cutoff beyond the calculated potential energy minimum and 250 as maximum number of the possible conformers. All other parameters used were kept at their default settings.

The best putative pharmacophore (Hypo-01), with the highest rank value of 67.261,

based on four active candidates (**11**, **15**, **22, 23),** comprised of the following six features (Figure 3A): (i) a hydrogen bond donor (HBD) features mapped for free NH function in the side chain, (ii) two hydrogen bond acceptor (HBA) features, one mapped for m-methoxy oxygen of the 3,4-dimethoxyphenethyl group of the most active compound **11** and other mapped for free hydroxyl group in the side chain, (iii) one ring aromatic (RA) feature mapped for phenyl residue of the benzyl group, (iv) one hydrophobic aliphatic (HpAl) feature mapped for alicyclic ring of the 1,2,3,4-tetrahydroquinoline and (v) one hydrophobic aromatic (HpAr) feature mapped for aromatic ring of the 1,2,3,4-tetrahydroquinoline core. The fit values, relative energies and actual β_3-AR agonistic activity of the active candidates (**11**, **15**, **22, and 23)** with the best putative pharmacophore (Hypo-01) have been provided in the supplementary information.

Please Insert Figure 3

The possible bioactive conformation and shape of the most active molecule **11** is shown in figure 3A which mapped well to the modeled putative pharmacophore. The overall shape (Electrostatic surface) of the bioactive conformation of compound **11** (Figure 3B) provides a clue for the possible shape and size of the binding site in the β_3-AR where the active candidates fit well for the β_3-AR agonistic activity.
This putative model maps well the four most active compounds (**11**, **15**, **22** & **23)** as shown in figure 4A whereas the mapping of inactive compounds (**32, 34** & **36**) is shown in figure 4B. These inactive compounds miss to map three features *viz.* two HBA and one HBD of the best hypothesis (Hypo-01).

Please Insert Figure 4

3. Conclusion

We have described here the design, synthesis and in-vitro biological evaluation of substituted 1,2,3,4-tetrahydroquinolin-6-yloxypropanes incorporating essential pharmacophoric requirements as a novel class of β_3-adrenergic receptor agonists. Four candidates *viz.* compound **11** (IC_{50} = 0.55 μM), **15** (IC_{50} = 0.59 μM), **22** (IC_{50} = 1.18μM) and **23** (IC_{50} = 1.76μM) have shown good β_3-adrenergic receptor agonistic activity. SAR analysis of structure and in-vitro activity data have shown that: (i) the benzyl group as a substituent at position 1 of 1,2,3,4-tetrahydroquinoline is favourable for activity, and (ii) the free NH and OH group present in the side chain at position 6 of 1,2,3,4-tetrahydroquinoline are essential for β_3-adrenergic receptor agonistic activity. The putative pharmacophore model based on the four active molecules **11**, **15**, **22** and **23** substantiates the above observations and provides an insight into the essential structural requirements. The putative pharmacophore model provides important clue about the possible shape and size of the β_3-adrenergic receptor active site as well as the possible bioactive conformation of the active molecules. It also distinguishes well among the active and inactive candidates where the active candidates map all the features i.e two HBA, one HBD, one hydrophobic aromatic (HpAr), one hydrophobic aliphatic (HpAl), and one ring aromatic (RA) features, whereas the inactive molecules miss to map three features *viz.* two HBA and one HBD of the best putative pharmacophore. In addition, the

putative pharmacophore gives an insight about the nature of the free NH function in the side chain where it appears to be more prone to act as HBD rather than as positively ionizable group while the free OH function in the side chain appears to be more prone to act as HBA rather than as HBD group.

4. Experimental Section

4.1. 6-Methoxy quinoline (3)

A mixture of p-anisidine (**1**; 10.0g, 0.08 mol), glycerol (**2**; 35 mL, 0.48 mol), conc. sulphuric acid (20 mL, 0.37 mol) and iodine (4.0g, 0.016 mol) was refluxed at 140-170^{o}C for 14 hours. After completion of the reaction, followed by thin layer chromatography (TLC), sufficient amount of water was added to the reaction mixture and then basified with 10% NaOH solution followed by extraction with ethyl acetate (10x30 mL). The ethyl acetate layer was washed with water (3x30 mL) and dried over Na_2SO_4. Finally concentrated under vacuum to give crude 6-methoxyquinoline (**3**) which was purified by vacuum distillation at 125/2mm or alternatively through column chromatography on 60-120 mesh silica gel using chloroform as an eluent to give **3** as reddish brown viscous oil. Yield: 5.5g (42.5%); b.p.: 125-127^{o}C/2mm; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.93 (s, 3H, CH_3), 7.07 (d, *J*=2.7 Hz, 1H) 7.27-7.40 9 (m, 2H, Ar), 8.12 (t, 2H, Ar), 8.76 (m, 1H, Ar); FTIR (Neat): cm^{-1} 810, 1015, 1100, 1115, 1225, 1320, 1342, 1372, 1430, 1460, 1495, 1575, 1592, 1620, 2832, 2960, 3010. EIMS: m/z 159 (M^+); Anal. calcd. for $C_{10}H_9NO$: C, 75.47; H, 5.66; N, 8.80%; Found: C, 75.61; H, 5.42; N, 8.62%.

4.2. 6-Methoxy-1,2,3,4-tetrahydroquinoline (4)

Nickel-aluminium alloy (42 g) was added portion wise during 1 hour to a continuously stirred mixture of 6-methoxyquinoline (**3**; 25g, 0.157 mol), and potassium hydroxide (or sodium hydroxide) solution (750 mL; 10% in water, w/v) in ethanol (350 mL) at a 50^{o}C. The reaction mixture was stirred further for an additional 1 hour after complete addition of Ni-Al alloy. After the completion of the reaction, the reaction mixture was filtered and the ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate (2x5 mL), and the combined ethyl acetate fractions were dried over Na_2SO_4 and concentrated under vacuum to give crude product of **4** which was purified by vacuum distillation or alternatively by column chromatography on silica gel using chloroform: hexane (60:40) as eluent to give **4** as oil. Yield: 15g, (58.5%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.83-1.91 (m, 2H), 2.68 (t, *J*=6.47 Hz, 2H), 3.18 (t, *J*=5.48 Hz, 2H), 3.65 (s, 3H), 6.38 (d, *J*=8.32 Hz, 1H), 6.49-6.54 (m, 2H); FTIR (Neat): cm^{-1} 494, 669, 760, 926, 1040, 1094, 1155, 1217, 1258, 1442, 1467, 1506, 2364, 2402, 2847, 2957, 3020, 3422; EIMS: m/z 163 (M^+); Anal calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%; Found: C, 73.75; H, 8.24; N, 8.72%.

4.3. 1-Benzyl-1,2,3,4-tetrahydro-6-methoxyquinoline (5)

A mixture of 1,2,3,4-tetrahydro-6-methoxyquinoline (**4**; 16.3g, 0.1 mol), benzyl chloride (11.7 mL, 0.22 mol), baked Na_2CO_3 (2.65 g, 0.22 mol) and NaI (0.34 g, 0.22 mol) in DMF was heated at 80^{o}C for 1 hour. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (5x20 mL). The combined ethyl acetate fractions were concentrated under vacuum. The crude so obtained

was crystallized with ether or alternatively chromatographed on silica gel (60-120 mesh) using chloroform:hexane (50:50) as eluent to give **5** as white solid. Yield: 20.9 g (82.5%); m.p.: 181-183^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97-2.03 (m, 2H), 2.80 (t, *J*=6.33 Hz, 2H), 3.29 (t, *J*=5.60 Hz, 2H), 3.71 (s, 3H), 4.41 (s, 2H), 6.45 (d, *J*=8.44 Hz, 1H), 6.56-6.61 (m, 2H), 7.23-7.37 (m, 5H); FTIR (KBr): cm^{-1} 548, 669, 759, 929, 976, 1059, 1121, 1157, 1216, 1268, 1298, 1352, 1431, 1452, 1508, 1602, 1672, 1723, 1953, 2402, 2837, 2939, 3017, 3408, 3679; EIMS: m/z 253 $(M)^{+}$; Anal. calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53%; Found: C, 80.72; H, 7.77; N, 5.69%.

4.4. 1-Benzyl-1,2,3,4-tetrahydroquinolin-6-ol (6)

A mixture of 1,2,3,4-tetrahydro-6-methoxyquinoline (**5**; 2.53 g, 0.01 mol) and 47% HBr (70 mL) was refluxed at 110^{o}C for 5 hours. The reaction mixture was cooled to 19^{o}C and filtered. The residue was stirred with triethylamine (1.01 mL) in dry ether (10 mL) for 3 hours at 19^{o}C. The reaction mixture was filtered and the filtrate was concentrated to give crude **6** which was column chromatographed using 60-120 mesh silica gel as adsorbent and methnol:chloroform (2:98) as eluent to give pure **6** as solid. Yield: 1.12 g (46.8%); m.p.: 106-108^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.99 (bs, 2H), 2.77-2.87 (bs, 2H), 3.29-3.41 (bs, 2H), 4.40 (s, 2H), 6.43-6.52 (m, 3H), 7.16-7.38 (m, 5H); FTIR (KBr): cm^{-1} 458, 340, 561, 600, 629, 695, 728, 795, 853, 909, 937, 979, 1027, 1054, 1073, 1160, 1197, 1241, 1350, 1451, 1510, 1597, 1810, 2342, 2373, 2836, 2949, 3027, 3275, 3754, 3856; EIMS m/z: 239 $(M)^{+}$; Anal calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85%; Found: C, 80.65; H, 7.28; N, 5.96%.

4.5. 1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (8) and 1,3-bis-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ol (7)

1-Benzyl-1,2,3,4-tetrahydroquinolin-6-ol (**6**, 0.478 g, 2 mmol) was added to a stirred solution of NaOH (0.080 g, 2 mmol) in water (0.1 mL) and ethanol (10 mL). The reaction mixture was stirred further for 15 minutes at 33^{o}C. Epichlorohydrin (0.170 mL, 2.2 mmol) was added to the stirring reaction mixture at 33^{o}C and then the reaction mixture was heated at 100^{o}C (or alternatively stirred at 33^{o}C) for three hours. The ethanol was removed under vacuum and the residue was extracted with chloroform (3x5 mL). The chloroform fractions were combined and dried over Na_2SO_4. The combined fractions of chloroform were concentrated under vacuum and the crude concentrate was then chromatographed on silica gel using chloroform: hexane (50:50) as eluent to give **8** as oil and chloroform: hexane (75:25) as eluent to give **7** as oil.
Yield of **8**: (0.20 g, 33.9%) (at 100^{o}C); 0.3 g (50.8%) (at 33^{o}C).
Yield of **7**: 0.30 g (27.2%) (at 100^{o}C) while ~0.02 g, (7.14%) (at 33^{o}C).
(Product **8**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.69-2.88 (m, 5H), 3.29 (t, *J*=5.6 Hz, 2H), 3.84-3.92 (m, 1H), 4.05-4.12 (m, 1H), 4.41 (s, 2H), 6.42 (d, *J*=5.72 Hz, 1H), 6.56-6.63 (m, 2H), 7.22-7.35 (m, 5H); FTIR (Neat): cm^{-1} 561, 636, 753, 799, 855, 910, 976, 1034, 1112, 1162, 1203, 1269, 1348, 1447, 1506, 1600, 1714, 1956, 2370, 2852, 2929, 3024, 3402, 3761; FAB-MS: m/z 295 $(M)^{+}$; Anal. calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74%; Found: C, 77.38; H, 7.28; N, 4.66%.

(Product **7**): Molecular Formula: $C_{35}H_{38}N_2O_3$; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93-2.05 (m, 4H), 2.78 (t, *J*=6.34 Hz, 4H), 3.29 (t, *J*=5.60 Hz, 4H), 3.99-4.05 (m, 4H), 4.26 (bs, 1H), 4.41 (s, 4H), 6.42 (d, *J*=8.62 Hz, 2H), 6.56-6.62 (m, 4H), 7.19-7.35 (m, 10H); FTIR (Neat): cm^{-1} 762, 879, 1058, 1121, 1161, 1210, 1347, 1443, 1506, 1605, 1750, 1954, 2339, 2376, 2930, 3016, 3404, 3654, 3687, 3762; FAB- MS: m/z 534 $(M)^+$.

4.6. General Procedure 1 for the synthesis of substituted 1-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)aminopropan-2-ol (9-38)

A mixture of 1-benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) and appropriate amine/piperidine/piperazine (1 mmol) in ethanol (10 mL) was stirred at 27^{o}C for 5 hours. The ethanol was evaporated under reduced pressure and the residue was washed with cold ether (5 mL) followed by acetone (1 mL) to give the products **9-38 (**which were finally crystallized with ether-acetone mixture in case of solids.

4.6.1. 1-Benzylamino-3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ol (9)

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with benzylamine (0.11 mL, 1 mmol) using general procedure 1 to afford the title compound **9** as solid. Yield: 0.30 g (74.6%); m.p: 109-111^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93-2.50 (m, 2H), 2.70-2.89 (m, 4H), 3.29 (t, *J*=5.63 Hz, 2H), 3.81-4.05 (m, 4H), 3.96-4.75 (m, 1H), 4.41 (s, 2H), 6.42 (d, *J*=8.64, Hz, 1H), 6.54-6.61 (m, 2H), 7.20-7.31 (m, 10H); FTIR (Neat): cm^{-1} 486, 562, 596, 696.4, 788, 828, 884, 914, 969, 1037, 1068, 1152, 1200,1238, 1270, 1294, 1341, 1453, 1509, 1633, 1743, 1802, 2371, 2928, 3028, 3271, 3426, 3754, 3824, 3909; FAB-MS: m/z 403 $(M+1)^+$; Anal. calcd. for $C_{26}H_{30}N_2O_2$: C, 77.58; H, 7.51; N, 6.96%; Found: C, 77.76; H, 7.85; N, 6.45%.

4.6.2. 1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(4-methoxybenzylamino)-propan-2-ol (10)

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.590g, 2 mmol) was coupled with 4-methoxybenzylamine (0.27 mL, 2 mmol) using general procedure 1 to afford the title compound **10** as solid. Yield: 0.60 g (69.4%); m.p: 111-114^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.88-1.99 (m, 2H), 2.78-2.87 (m, 4H), 3.29 (t, *J*=5.63 Hz, 2H), 3.76 (bs, 2H), 3.80 (s, 3H), 3.88 (d, *J*=3.14, 2H), 4.08-4.20 (m, 1H), 4.41 (s, 2H), 6.42 (d, *J*=8.64 Hz, 1H), 6.55-6.61 (m, 2H), 6.84-6.88 (m, 2H), 7.21-7.26 (m, 7H); FTIR (Neat): cm^{-1} 520, 568, 699, 736, 806, 890, 972, 1034, 1067, 1117, 1201, 1249, 1342, 1458, 1512, 1616, 2247, 2930, 3449, 3751; FAB-MS: m/z 433 $(M+1)^+$; Anal. calcd. for $C_{27}H_{32}N_2O_3$: C, 74.97; H, 7.46; N, 6.48%; Found: C, 74.82; H, 7.32; N, 6.31%.

4.6.3. 1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(3,4-dimethoxyphenyl) ethylamino]propan-2-ol (11)

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with 3,4-dimethoxyphenylethylamine (0.18 mL, 1 mmol) using general procedure 1 to afford the title compound **11** as solid. Yield: 0.60 g (63.0%); m.p:75-77^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93-2.05 (m, 2H), 2.75-2.96 (m, 8H), 3.26-3.42 (m, 2H), 3.84-3.86 (m, 8H), 3.96-4.00 (m, 1H), 4.41 (s, 2H), 6.42 (d, *J*=8.70 Hz, 1H), 6.52-6.60 (m, 2H), 6.73-6.82 (m, 3H), 7.22-7.35 (m, 5H); FTIR (Neat): cm^{-1} 634, 753, 802, 856, 1029, 1052, 1203, 1242, 1349, 1455, 1510, 1600, 1735, 2062, 2276, 2375, 2933, 3408, 3757, 3906; FAB-MS: m/z 477 $(M+1)^{+}$; Anal. calcd. for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61; N, 5.88 %; Found: C, 73.24; H, 7.52; N, 5.95%.

4.6.4. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(4-chlorophenyl)ethyl-amino]-propan-2-ol (12)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with 4-chlorophenylethyl amine (0.14 mL, 1 mmol) using general procedure 1 to afford the title compound **12** as solid. Yield: 0.32 g (71.1%); m.p: 89-91^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.95-2.04 (m, 2H), 2.74-2.80 (m, 8H), 3.28 (t, *J*=5.32 Hz, 2H), 3.82 (bs, 2H), 3.99 (bs, 1H), 4.40 (s, 2H), 6.41 (d, *J*=8.66 Hz, 1H), 6.53-6.59 (m, 2H), 7.04-7.34 (m, 9H); FTIR (Neat): cm^{-1} 520, 754, 806, 972, 1088, 1159, 1202, 1241, 1267, 1295, 1352, 1452, 1506, 1655, 2372, 2853, 2927, 3029, 3406, 3754; FAB-MS: 450 $(M)^{+}$; Anal. calcd. for $C_{27}H_{31}ClN_2O_2$: C, 71.90; H, 6.93; N, 6.21%; Found: C, 72.19; H, 7.12; N, 6.57%.

4.6.5. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(2-p-tolylethylamino)-propan-2-ol (13)**

1-benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with 2-p-tolylethylamine (0.135g, 1 mmol) using general procedure 1 to afford the title compound **13** as oil. Yield: 0.32 g (71.1%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.01 (m, 2H), 2.30 (s, 3H), 2.74-2.93 (m, 8H), 3.29 (t, *J*=5.47 Hz, 2H), 3.85-3.87 (m, 2H), 4.03-4.05 (m, 1H), 4.40 (s, 2H), 6.40 (d, *J*=8.73 Hz,1H), 6.51-6.59 (m, 2H), 7.09 (bs, 5H), 7.25-7.35 (m, 4H); FTIR (Neat): cm^{-1} 497, 556, 668, 764, 881, 973, 1057, 1120, 1216, 1268, 1355, 1454, 1509, 1657, 2342, 2366, 2403, 2859, 2929, 3017, 3406, 3677, 3754, 4213; FAB-MS: m/z 430 $(M)^{+}$; Anal. calcd. for $C_{28}H_{34}N_2O_2$: C, 78.10; H, 7.96; N, 6.51%; Found: C, 78.35; H, 7.83; N, 6.32%.

4.6.6. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-propylaminopropan-2-ol (14)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with propylamine (0.026g, 1 mmol) using general procedure 1 to afford the title compound **14** as solid. Yield: 0.11 g (31.1%), m.p.: 80-83^{o}C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.90-0.98 (m, 3H), 1.56-1.71 (m, 2H), 1.96-2.00 (m, 2H), 2.74-3.04 (m, 6H), 3.26-3.30 (m, 2H), 3.95-4.01 (m, 2H), 4.18-4.20 (m, 1H), 4.40 (s, 2H), 6.40 (d, *J*=5.8 Hz,1H), 6.47-6.83 (m, 2H), 7.26 (bs, 5H); FTIR (KBr): cm^{-1} 668, 762, 976, 1060, 1158,

1218, 1268, 1353, 1456, 1508, 1621, 2340, 2364, 2337, 3012, 3399; FAB-MS: m/z 354 $(M)^+$; Anal. calcd. for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90%; Found: C, 74.32; H, 8.67; N, 7.94%.

4.6.7. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-isopropylaminopropan-2-ol (15)**

1-benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with isopropylamine (0.026g, 1 mmol) using general procedure 1 to afford the title compound **15** as oil. Yield: 0.13 g (42.3%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20-1.33 (m, 6H), 1.96-2.00 (m, 2H), 2.76 (t, *J*=5.87 Hz., 2H), 2.86-3.09 (m, 2H), 3.28 (t, *J*=4.96 Hz., 2H), 3.80-3.94 (m, 2H), 4.18 (bs, 1H), 4.4 (s, 2H), 4.73 (bs, 1H), 6.40 (d, *J*=8.56 Hz., 1H), 6.53-6.60 (m, 2H), 7.27 (bs, 5H); FTIR (Neat): cm^{-1} 668, 766, 1060, 1217, 1351,1454, 1508, 1639, 2341, 2367, 2932, 3015, 3436, 3754, 3806, 3906; FAB-MS: m/z 354 $(M+1)^+$; Anal. calcd. for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90%; Found: C, 74.78; H, 8.76; N, 8.05%.

4.6.8. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(1-phenylethylamino)-propan-2-ol (16)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 0.01 mol) was coupled with 1-phenylethylamine (0.121g, 1 mmol) using general procedure 1 to afford the title compound **16** as oil. Yield: 0.15 g (36.0%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (d, *J*=3.23 Hz., 3H), 1.85-1.94 (m, 2H), 2.47-2.72 (m, 5H), 3.21 (t, *J*=5.41 Hz, 2H), 3.78 (bs, 2H), 3.95 (bs, 1H), 4.33 (s, 1H), 4.40 (s, 2H), 6.32 (d, *J*=8.68 Hz, 1H), 6.70 (d, *J*=12.42 Hz, 2H), 7.23 (bs, 10H); FTIR (Neat): cm^{-1} 667, 699, 760, 847, 974, 1061, 1115, 1158, 1217, 1240, 1268, 1296, 1353, 1453, 1508, 1646, 2363, 2931, 3011, 3419; FAB-MS: m/z 416 (M^+); Anal. calcd. for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73 %; Found: C, 77.62; H, 7.95; N, 7.02 %.

4.6.9. **1-(Benzylmethylamino)-3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ol (17)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295 g, 1 mmol) was coupled with benzylmethylamine (0.12 g, 1 mmol) using general procedure 1; oil; Yield: 0.15 g (37.3%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.01(m, 2H), 2.26 (s, 3H), 2.53-2.62 (m, 2H), 2.78 (t, *J*=6.34 Hz, 2H), 3.28 (t, *J*=5.61 Hz, 2H), 3.87 (d, *J*=5.06 Hz, 2H), 4.05-4.15 (m, 1H), 4.40 (s, 2H), 5.28 (s, 2H), 6.42 (d, *J*=8.67 Hz, 1H), 6.54-6.62 (m, 2H), 7.21-7.31 (m, 10H); FTIR (Neat): cm^{-1} 626, 700, 740, 798, 869, 975, 1027, 1157, 1201, 1241, 1268, 1350, 1451, 1506, 1601, 1661, 1812, 1954, 2372, 1843, 2929, 3028, 3427, 3778; FAB-MS: 416 $(M)^+$; Anal. calcd. for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 7.68 %; Found: C, 77.35; H, 8.07; N, 7.89 %.

4.6.10. **1-(4-Benzylpiperazin-1-yl)-3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-propan-2-ol (18)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.20g, 0.67 mmol) was coupled with 1-benzylpiperazine (0.13g, 0.67 mmol) using general procedure 1 to afford the title compound **18** as oil. Yield: 0.18 g (56.3%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26-2.04 (m, 2H), 2.48-2.68 (m, 10H), 2.78 (t, *J*=6.31 Hz, 2H), 3.28 (t, *J*=5.56 Hz, 2H), 3.87 (d, *J*=4.86 Hz, 2H), 4.00-4.02 (m, 1H), 4.40 (s, 2H), 5.27 (m, 2H), 6.42 (d, *J*=8.70 Hz, 1H), 6.55-6.62 (m, 2H), 7.21-7.30 (m, 10H); FTIR (Neat): cm^{-1} 467, 607, 700, 742, 799, 828, 877, 940, 1010, 1059, 1155, 1202, 1241, 1269, 2347, 1452, 1506, 1601, 1661, 1746, 1811, 1952, 2340, 2373, 2815, 2932, 3028, 3404, 3780; FAB-MS: 472$(M+1)^+$; Anal. calcd. for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91 %; Found: C, 76.77; H, 7.83; N, 8.73 %.

4.6.11. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-dibutylaminopropan-2-ol (19)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.20g, 0.67 mmol) was coupled with dibutylamine (0.09g, 0.67 mmol) using general procedure 1 to afford the title compound **19** as oil. Yield: 0.17 g (59.1%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87-0.94 (m, 6H), 1.28-1.47 (m, 8H), 1.92-2.09 (m, 2H), 2.35-2.56 (m, 6H), 2.76 (t, *J*=6.38 Hz, 2H), 3.28 (t, *J*=5.61 Hz, 2H), 3.80-4.01 (m, 3H), 4.40 (s, 2H), 6.43 (d, *J*=8.67 Hz, 1H), 6.56-6.64 (m, 2H), 7.21-7.30 (m, 5H); FTIR (Neat): cm^{-1} 667, 698, 757, 867, 940, 1060, 1162, 1203, 1240, 1268, 1295, 1351, 1455, 1508, 1603, 2370, 2866, 2932, 3010, 3406, 3657, 3782; FAB-MS: m/z 424 $(M+1)^+$; Anal. calcd. for $C_{27}H_{40}N_2O_2$: C, 76.37; H, 9.50; N, 6.60; %; Found: C, 76.56; H, 9.68; N, 6.35 %.

4.6.12. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(4-nitrophenyl)piperazin-1-yl]propan-2-ol (20)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.20g, 0.67 mmol) was coupled with 1-(4-nitrophenyl)piperazine (0.14 g, 0.67 mmol) using general procedure 1 to afford the title compound **20** as oil. Yield: 0.18 g (52.8%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97-2.06 (m, 2H), 2.60-2.70 (m, 4H), 2.76-7.82 (m, 4H), 3.30 (t, *J*=5.50 Hz, 2H), 3.41-3.46 (m, 4H), 3.90-3.93 (m, 2H), 4.07-4.11 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.68 Hz, 1H), 6.56-6.63 (m, 2H), 6.80-6.84 (m, 2H), 7.22-7.35 (m, 5H), 8.10-8.19 (m, 2H); FTIR (Neat): cm^{-1} 501, 538, 668, 694, 746, 797, 828, 921, 1000, 1061, 1110, 1164, 1199, 1242, 1265, 1324, 1452, 1493, 1597, 2341, 2367, 2832, 2940, 3431, 3753, 3823; FAB-MS: m/z 503 $(M+1)^+$; Anal. calcd for $C_{29}H_{34}N_4O_4$: C, 69.30; H, 6.82; N, 11.15 %; Found: C, 69.62; H, 6.96; N, 10.98%.

4.6.13. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-diethylaminopropan-2-ol (21)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.20g, 0.67 mmol) was coupled with diethylamine (0.05g, 0.67 mmol) using general procedure 1 to afford the title compound **21** as oil. Yield: 0.14 g (58.3%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.01-1.08 (m, 6H), 1.96-2.01 (m, 2H), 2.52-2.62 (m, 6H), 2.78 (t, *J*=6.23 Hz, 2H), 3.28 (t, *J*=5.55 Hz, 2H), 3.88-3.95 (m, 3H), 4.40 (s, 2H), 6.43 (d, *J*=8.60 Hz, 1H), 6.56-6.63 (m, 2H), 7.22-7.34 (m, 5H); FTIR (Neat): cm^{-1} 667, 759, 866, 908, 939, 977, 1060, 1170, 1204, 1240, 1268, 1294, 1348, 1453, 1508, 1655, 1802, 2144, 2342, 2373, 2841, 2931, 2970, 3012, 3429, 3754,3906; FAB-MS: m/z 368 $(M)^+$; Anal. calcd. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60%; Found: C, 74.58; H, 8.89; N, 7.59%.

4.6.14. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(4-methoxyphenyl)ethyl amino]-propan-2-ol (22)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.295g, 1 mmol) was coupled with 2-(4-methoxyphenyl)ethylamine (0.16g, 1 mmol) using general procedure 1 to afford the title compound **22** as oil. Yield: 0.21 g (39.4%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.88-1.97 (m, 2H), 2.67-2.84 (m, 8H), 3.21 (t, *J*=5.60 Hz, 2H), 3.70 (s, 3H), 3.77-3.91 (m, 3H), 4.33 (s, 2H), 6.34 (d, *J*=8.68 Hz, 1H), 6.45-6.52 (m, 2H), 7.14-7.23 (m, 5H), 6.75 (d, *J*=8.58 Hz, 2H), 7.04 (d, *J*=8.53 Hz, 2H); FTIR (Neat): cm^{-1} 526, 565, 759, 936, 1036, 1120, 1178, 1217, 1245, 1298, 1351, 1455, 1510, 1612, 1878, 2403, 2840, 2933, 3014, 3410, 3754; FAB-MS: m/z 446 $(M)^+$; Anal. calcd for $C_{28}H_{34}N_2O_3$: C, 75.31; H, 7.67; N, 6.27%; Found: C, 75.55; H, 7.85; N, 6.19%.

4.6.15. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(4-fluorophenyl)piperazin-1-yl] propan-2-ol (23)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 4-(4-fluorophenyl)piperazine (0.04g, 0.27 mmol) using general procedure 1 to afford the title compound **23** as oil. Yield: 0.10 g (77.6%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02(m, 2H), 2.57-2.67 (m, 4H), 2.76-2.81 (m, 4H), 3.10-3.15 (m, 4H), 3.29 (t, *J*=5.60 Hz, 2H), 3.90-3.92 (m, 2H), 4.10-4.25 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.68 Hz, 1H), 6.56-6.64 (m, 2H), 6.85-7.00 (m, 4H), 7.22-7.31 (m, 5H); FTIR (Neat): cm^{-1} 531, 734, 801, 875, 921, 1000, 1062, 1148, 1203, 1236, 1269, 1302, 1350, 1441, 1510, 1595, 2372, 2827, 2930, 3420, 3759; FAB-MS: m/z 476 $(M+1)^+$; HRMS: m/z 475.2618

4.6.16. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(2-methoxyphenyl)-piperazin-1-yl]propan-2-ol (24)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.17g, 0.58 mmol) was coupled with 4-(2-methoxyphenyl)piperazine (0.11g, 0.58 mmol) using general procedure 1 to afford the title compound **24** as oil. Yield: 0.12 g (42.7%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.58-2.86 (m, 8H), 3.08-3.11 (m, 4H), 3.29 (t, *J*=5.62 Hz, 2H), 3.86 (s, 3H), 3.90-3.92 (m, 2H), 4.09-4.21 (m, 1H), 4.41 (s, 2H), 6.44 (d, *J*=8.68 Hz, 1H), 6.58-6.66 (m, 2H), 6.88-6.96 (m, 4H), 7.26-7.31 (m, 5H); FTIR (Neat):

cm^{-1} 525, 609, 724, 738, 822, 876, 925, 1033, 1074, 1146, 1198, 1243, 1350, 1384, 1447, 1511, 1597, 2367, 2822, 2939, 3433, 3780; FAB-MS: m/z 487 $(M)^+$; Anal. calcd. for $C_{30}H_{37}N_3O_3$: C, 73.89; H, 7.65; N, 8.62; %; Found: C, 74.03; H, 7.78; N, 8.73%.

4.6.17. **1-[3-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl]-4-phenylpiperidin-4-ol (25)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.17g, 0.58 mmol) was coupled with 1-phenylpiperidine (0.10 g, 0.58 mmol) using general procedure 1 to afford the title compound **25** as oil. Yield: 0.12 g (44.1%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93-2.21 (m, 6H), 2.56-2.63 (m, 4H), 2.79-2.82 (m, 4H), 3.29 (t, *J*=5.62 Hz, 2H), 3.91 (d, *J*=4.93 Hz, 2H), 4.08-4.20 (m, 1H), 4.41 (s, 2H), 6.44 (d, *J*=8.60 Hz, 1H), 6.57-6.64 (m, 2H), 7.26-7.53 (m, 10H); FTIR (Neat): cm^{-1} 542, 700, 761, 840, 881, 992, 1044, 1104, 1199, 1241, 1351, 1384, 1450, 1507, 1506, 2363, 2826, 2929, 3404; FAB-MS: m/z 472 $(M)^+$; Anal calcd. for $C_{30}H_{36}N_2O_3$: C, 76.24; H, 7.68; N, 5.93%; Found: C, 76.20; H, 8.02%.

4.6.18. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol (26)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.10g, 0.34 mmol) was coupled with 4-phenylpiperazine (0.05g, 0.34 mmol) using general procedure 1 to afford the title compound **26** as solid. Yield: 0.10 g (64.6%); m.p.:115-118^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.93-2.02 (m, 2H), 2.58-2.69 (m, 4H), 2.76-2.82 (m, 4H), 3.19-3.32 (m, 6H), 3.90-3.92 (m, 2H), 4.09-4.22 (m, 1H), 4.41 (s, 1H), 6.43 (d, *J*=8.63 Hz, 1H), 6.57-6.64 (m, 2H), 6.86-6.95 (m, 5H), 7.22-7.30 (m, 5H); FTIR (KBr): cm^{-1} 694, 757, 872, 931, 1054, 1150, 1236, 1342, 1452, 1504, 1598, 1656, 2365, 2824, 2928, 3029, 3400, 3626, 3684, 3753, 3865; FAB-MS: m/z 458 $(M+1)^+$; Anal. calcd for $C_{29}H_{35}N_3O_2$: C, 76.12; H, 7.71; N, 9.18%; Found: C, 76.25; H, 7.85; N, 9.24%.

4.6.19. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(4-methoxyphenyl)-piperazin-1-yl]propan-2-ol (27)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.1g, 0.34 mmol) was coupled with 1-(4-methoxyphenyl)piperazine (0.065g, 0.34 mmol) using general procedure 1 yielded the title comound **27** as cream coloured solid. Yield: 0.10 g (60.6%); m.p.:126-128^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.57-2.68 (m, 4H), 2.76-2.82 (m, 4H), 3.08-3.13 (m, 4H), 3.29 (t, *J*=5.62 Hz, 2H), 3.77 (s, 3H), 3.91 (d, *J*=5.02 Hz, 2H), 4.08-4.19 (m, 1H), 4.41 (s, 2H), 6.44 (d, *J*=8.60 Hz, 1H), 6.58-6.64 (m, 2H), 6.81-6.93 m, 4H), 7.26-7.31 (m, 5H); FTIR (KBr): cm^{-1} 529, 607, 726, 875, 924, 1035, 1147, 1199, 1244, 1348, 1385, 1451, 1510, 1597, 2371, 2826, 2942, 3426, 3754, 3908; FAB-MS: m/z 487 (M^+); Anal. calcd for $C_{30}H_{37}N_3O_3$: C, 73.89; H, 7.65; N, 8.62; %; Found: C, 73.65; H, 7.73; N, 8.52%.

4.6.20. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-piperidin-1-ylpropan-2-ol (28)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with piperidine (0.023g, 0.27 mmol) using general procedure 1 to afford the title compound **28** as oil. Yield: 0.05 g (48.5%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.18-1.51 (m, 6H), 1.92-2.03 (m, 2H), 2.27-2.78 (m, 8H), 3.21 (t, *J*=5.72 Hz, 2H), 3.78-3.82 (m, 2H), 4.07-419 (m, 1H), 4.34 (s, 2H), 6.36 (d, *J*=8.60 Hz, 1H), 6.49-6.65 (m, 2H), 7.15-7.28 (m, 5H); FTIR (Neat): cm^{-1} 469, 769, 1037, 1120, 1157, 1219, 1350, 1448, 1508, 1638, 2146, 2374, 2934, 3433, 3755, 3907; FAB-MS: m/z 380 $(M)^+$; Anal calcd. for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36%; Found: C, 75.67; H, 8.50; N, 7.28%.

4.6.21. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(4-pyridin-2-yl-piperazin-1-yl)-propan-2-ol (29)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 1-pyridin-2-ylpiperazine (0.04g, 0.27 mmol) using general procedure 1 to afford the title compound **29** as white solid.Yield: 0.06g (48.3%); m.p.:98-101^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.90-2.52 (m, 2H), 2.02-2.62 (m, 4H), 2.68-2.82 (m, 4H), 3.29 (t, *J*=5.58 Hz, 2H), 3.56 (t, *J*=4.88 Hz, 4H), 3.91 (d, *J*=4.93 Hz, 2H), 4.08-4.21 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.69 Hz, 1H), 6.56-6.66 (m, 2H), 7.22-7.31 (m, 6H), 7.44-7.48 (m, 2H), 8.18-8.20 (m, 1H); FTIR (KBr): cm^{-1} 528, 667, 761, 870, 942, 981, 1006, 1058, 1156, 1218, 1242, 1311, 1383, 1438, 1508, 1596, 2838, 2932, 3012, 3425, 3655, 3755; FAB-MS: m/z 458 (M^+); Anal. calcd for $C_{28}H_{34}N_4O_2$: C, 73.33; H, 7.47; N, 12.22 %; Found: N, 11.99 %.

4.6.22. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(2-fluorophenyl)piperazin-1-yl] -propan-2-ol (30)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 1-(2-fluorophenyl)piperazine (0.048g, 0.27 mmol) using general procedure 1 to afford the title compound **30** as white solid. Yield: 0.05 g (38.8%); m.p.:96-98^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.58-2.70 (m, 4H), 2.76-2.84 (m, 4H), 3.10-3.15 (m, 4H), 3.29 (t, *J*=5.57 Hz, 2H), 3.91 (d, *J*=4.91 Hz, 2H), 4.07-4.20 (m, 1H), 4.40 (s, 2H), 6.37 (d, *J*=8.60 Hz, 1H), 6.41-6.61 (m, 2H), 6.97-7.07 (m, 5H), 7.25-7.30 (m, 5H); FTIR (KBr): cm^{-1} 460, 545, 611, 644, 742, 792, 875, 925, 1001, 1076, 1145, 1202, 1237, 1297, 1348, 1384, 1450, 1505, 1605, 1664, 2826, 2927, 3030, 3069, 3424, 3760, 3836, 3930; FAB-MS: m/z 475 $(M)^+$; HRMS: 475.2628.

4.6.23. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(3-chlorophenyl)piperazin-1-yl]propan-2-ol (31)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 1-(3-chlorophenyl)piperazine (0.05g, 0.27 mmol) using general procedure 1 to afford the title compound **31** as white solid.. Yield: 0.09 g (67.5%); m.p.:112-114^{o}C;

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.57-2.66 (m, 4H), 2.76-2.82 (m, 4H), 3.18-3.32 (m, 6H), 3.91 (d, *J*=5.43 Hz, 2H), 4.08-4.20 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.70 Hz, 1H), 6.58-6.64 (m, 2H), 6.80-6.86 (m, 3H), 7.12-7.31 (m, 6H); FTIR (KBr): cm^{-1} 459, 537, 612, 648, 685, 738, 765, 790, 814, 846, 876, 907, 946, 997, 1080, 1149, 1202, 1239, 1302, 1352, 1385, 1453, 1507, 1595, 1810, 2365, 2825, 2924, 3030, 3418, 3754; FAB-MS: m/z 492 $(M)^+$; Anal calcd. for $C_{29}H_{34}ClN_3O_2$: C, 70.79; H, 6.96; N, 8.54%; Found: N, 8.39%.

4.6.24. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(3,4-dichlorophenyl)-piperazin-1-yl]propan-2-ol (32)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 1-(3,4-dichlorophenyl)piperazine (0.062g, 0.27 mmol) using general procedure 1 to afford the title compound **32** as white solid. Yield: 0.09 g (63.1%); m.p.:118-120^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.58-2.66 (m, 4H), 2.79-2.82 (m, 4H), 3.18 (t, *J*=4.94 Hz, 4H), 3.29 (t, *J*=5.62 Hz, 2H), 3.91 (d, *J*=4.99 Hz, 2H), 4.07-4.19 (m, 1H), 4.41 (s, 2H), 6.43(d, *J*=8.68 Hz, 1H), 6.57-6.76 (m, 3H), 6.94-6.96 (m, 1H), 7.24-7.31 (m, 6H); FAB-MS: m/z 526 $(M)^+$; Anal calcd. for $C_{29}H_{33}Cl_2N_3O_2$: C, 66.16; H, 6.32; N, 7.98%; Found: C, 66.42; H, 6.55; N, 8.02%.

4.6.25. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(4-methylpiperazin-1-yl)-propan-2-ol (33)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 4-methylpiperazine (0.027g, 0.27 mmol) using general procedure 1 to afford the title compound **33** as oil**.** Yield: 0.05 g (46.7%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96-2.02 (m, 2H), 2.30-2.76 (m, 9H), 2.78 (t, *J*=6.35 Hz, 2H), 3.29 (t, *J*=5.57 Hz, 2H), 3.39 (t, *J*=5.58 Hz, 2H), 3.59 (t, *J*=4.94 Hz, 2H), 3.88 (d, *J*=4.94 Hz, 2H), 4.08-4.20 (m, 1H), 4.41 (s, 2H), 6.43 (d, 1H), 6.55-6.63 (m, 2H), 7.22-7.31 (m, 5H); FTIR (Neat): cm^{-1} 735, 803, 870, 1013, 1055, 1160, 1202, 1242, 1290, 1351, 1454, 1507, 1658, 2145, 2340, 2374, 2810, 2934, 3422, 3679, 3756; FAB-MS: m/z 396 $(M+1)^+$; Anal calcd. for $C_{24}H_{33}N_3O_2$: C, 72.88; H, 8.41; N, 10.62%; Found: C, 72.79; H, 8.32; N, 10.58%.

4.6.26. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[4-(4-chlorophenyl)-2-methylpiperazin-1-yl]propan-2-ol (34)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 1-(4-chlorophenyl)-3-methylpiperazine (0.057g, 0.27 mmol) using general procedure 1 to afford the title compound **34** as yellowish solid. Yield: 0.09 g (65.7%); m.p:123-124^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.06 (d, *J*=6.44 Hz, 3H), 1.96-2.02 (m, 2H), 2.45-2.62 (m, 4H), 2.76-2.82 (m, 4H), 3.13-3.15 (m, 2H), 3.29 (t, *J*=5.55 Hz, 2H), 3.91 (d, *J*=4.75 Hz, 2H), 3.85-3.89 (m, 2H), 4.08-4.20 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.66 Hz, 1H), 6.57-6.64 (m, 2H), 6.82 (d, *J*=8.84 Hz, 2H), 7.20 (d, *J*=8.75 Hz, 2H), 7.26-7.31 (m, 5H); FTIR (Neat): cm^{-1} 735, 869, 1025, 1068, 1154, 1199, 1352, 1442, 1506, 1595, 2365, 2827, 2934, 3428, 3753, 3860, 3968; FAB-MS: m/z 506 (M^+); Anal calcd. for $C_{30}H_{36}ClN_3O_2$: C, 71.20; H, 7.17; N, 8.30; Found: C, 71.02; H, 7.32; N, 8.47%.

4.6.27. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(2-methyl-4-p-tolylpiperazin-1-yl)propan-2-ol (35)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 3-methyl-1-p-tolylpiperazine (0.05g, 0.27 mmol) using general procedure 1 to afford the title compound **35** as oil. Yield: 0.08 g (60.8%); m.p.:119-122^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (d, *J*=6.38 Hz, 3H), 1.90-1.94 (m, 2H), 2.20 (s, 3H), 2.45-2.75 (m, 10H), 3.02-3.07 (m, 2H), 3.21(t, *J*=5.58 Hz, 2H), 3.62-3.73 (m, 1H), 3.84 (d, *J*=4.50 Hz, 2H), 4.08-4.19 (m, 1H), 6.36 (d, *J*=8.70 Hz, 1H), 6.50-6.57 (m, 2H), 6.77 (d, *J*=8.40 Hz, 2H), 7.00 (d, *J*=8.33 Hz, 2H), 7.16-7.23 (m, 5H); FTIR (KBr): cm^{-1} 557, 669, 762, 930, 1048, 1159, 1216, 1268, 1649, 1450, 1510, 1615, 2368, 2402, 2828, 2936, 3017, 3425, 3695, 3782; FAB-MS: m/z 486 $(M+1)^{+}$; Anal. calcd. for $C_{31}H_{39}N_3O_2$: C, 76.67; H, 8.09; N, 8.65%; Found: C, 76.35; H, 7.89; N, 8.99%.

4.6.28. **1-(4-Benzo[1,3]dioxol-5-ylmethylpiperazin-1-yl)-3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ol (36)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 4-benzo[1,3]dioxol-5-ylmethylpiperazine (0.055g, 0.27 mmol) using general procedure 1 to afford the title compound **36** as oil. Yield: 0.10 g (71.6%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92-2.04 (m, 2H), 2.40-2.68 (m, 8H), 2.78 (t, *J*=6.35 Hz, 2H), 3.28 (t, *J*=5.62 Hz, 2H), 3.42 (s, 2H), 3.87 (d, *J*=5.02 Hz, 2H), 3.92-4.08 (m, 1H), 4.40 (s, 2H), 5.29 (s, 2H), 5.93 (s, 2H), 6.42 (d, *J*=8.66 Hz, 1H), 6.55-6.63 (m, 2H), 6.74 (s, 2H), 6.84 (s, 1H), 7.21-7.30 (m, 5H); FTIR (Neat): cm^{-1} 738, 806, 868, 1039, 1155, 1202, 12444, 1341, 1443, 1503, 1580, 658, 1806, 1848, 2143, 2340, 2376, 2817, 2931, 3404, 3627, 3684, 3758, 3876, 3907; FAB-MS: m/z 516 $(M+1)^{+}$; Anal. calcd for $C_{31}H_{37}N_3O_4$: C, 72.21; H, 7.23; N, 8.15%; Found: C, 71.72; H, 6.77; N, 8.32%.

4.6.29. **1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-(4-methylpiperidin-1-yl)-propan-2-ol (37)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 4-methylpiperidine (0.04g, 0.27 mmol) using general procedure 1 to afford the title compound **37** as oil. Yield: 0.08 g (74.8%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93 (d, *J*=5.96 Hz, 3H), 1.23-1.59 (m, 4H), 1.59-1.65 (m, 2H), 1.96-2.02 (m, 4H), 2.46-2.50 (m, 2H), 2.75-2.82 (m, 3H), 3.28 (t, *J*=5.61 Hz, 2H), 3.85-3.88 (m, 2H), 4.01-4.19 (m, 1H), 4.41 (s, 2H), 6.43 (d, *J*=8.69 Hz, 1H), 6.56-6.64 (m, 2H), 7.26-7.32 (m, 5H); FTIR (Neat): cm^{-1} 636, 698, 735, 798, 876, 976, 1059, 11230, 1157, 1202, 1241, 1268, 1332, 452, 1508, 1603, 2866, 2923, 3029, 3402, 3754; FAB-MS: m/z 394 (M^{+}); Anal. calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10%; Found: C, 75.86; H, 8.99%.

4.6.30. **1-(4-Benzylpiperidin-1-yl)-3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy) propan-2-ol (38)**

1-Benzyl-6-oxiranylmethoxy-1,2,3,4-tetrahydroquinoline (**8**; 0.08g, 0.27 mmol) was coupled with 4-benzylpiperidine (0.047g, 0.27 mmol) using general procedure 1 to afford the title compound **38** as oil. Yield: 0.08 g (62.8%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26-1.30 (m, 2H), 1.61-1.68 (m, 2H), 1.96-2.01 (m, 6H), 2.47-2.55 (m, 4H), 2.78 (t, *J*=6.33 Hz, 2H), 3.28 (t, *J*=5.60 Hz, 2H), 3.84-3.88 (m, 2H), 4.03-4.20 (m, 1H), 4.40 (s, 2H), 6.42 (d, *J*=8.69 Hz, 1H), 6.56-6.62 (m, 2H), 7.12-7.31 (m, 10H); FTIR (Neat): cm^{-1} 591,

700, 742, 796, 874, 974, 1059, 1155, 1059, 1155, 1202, 1241, 1269, 1347, 1450, 1506, 1602, 1951, 2340, 2375, 2849, 2924, 3027, 3397, 3757; FAB-MS: m/z 478 $(M+1)^+$; Anal. calcd. for $C_{31}H_{38}N_2O_2$: C, 79.11; H, 8.14; N, 5.95%; Found: C, 79.25; H, 8.26; N, 6.02%.

4.7. 1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (39)

A solution of 1-benzyl-1,2,3,4-tetrahydroquinolin-6-ol (**6**, 2.39 g, 10 mmol) in dry THF was added to a cold (-10^{o}C) and stirred suspension of NaH (0.24 g, 10 mmol) in dry THF (10 mL) and continued the stirring for next 20 minutes. 1-Bromo-3-chloropropane (1.6 mL, 10 mmol) was then added to the reaction mixture under stirring which was stirred for an additional ½ hour. The THF was evaporated; ethyl acetate (10 mL) was added and washed with water, dried over sodium sulphate and concentrated under vacuum to get **39** as oil. Yield: 1.91g (60.5%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.87-2.04 (m, 6H), 2.75-2.91 (m, 6H), 4.40 (s, 2H), 6.42 (s, 1H), 6.51(d, *J*=8.58, 2H), 7.21-7.30 (m, 5H); FTIR (Neat): cm^{-1} 636, 759, 803, 853, 964, 1029, 1151, 1202, 1239, 1264, 1342, 1460, 1511, 1590, 1656, 2342, 2370, 2836, 2933, 3400; FAB-MS: m/z 315 (M^+); Anal. calcd. for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; N, 4.43; Found: C, 72.18; H, 7.22; N, 4.59%.

4.8. General Procedure 2 for the synthesis of compounds (40-45)

A mixture of 1-benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.20g, 1.2 mmol), appropriate amine/piperidine/piperazine (1.2 mmol), Na_2CO_3 (0.168 g, 1.2 mmol) and NaI (0.18g, 1.2 mmol) in dry DMF (2 mL) was heated at 80^{o}C overnight. The reaction mixture was diluted with water (5 mL), extracted with ethyl acetate (3x5 mL). The combined ethyl acetate fractions were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on neutral alumina using methanol:chloroform (1:99) as eluent to give the desired product (**40**-**45**).

4.8.1. 3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-N-(3,4-dimethoxyphenethyl)-propan-1-amine (40)

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.40g, 2.4 mmol) was coupled with 2-(3,4-dimethoxyphenyl)ethylamine (0.225 g, 1.2 mmol) using general procedure 2 to afford the title compound **40** as oil. Yield: 0.12 g (41.2%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.87-2.04 (m, 4H), 2.75-2.91 (m, 8H), 3.28 (t, *J*=5.65 Hz, 2H), 3.83-3.93 (m, 8H), 4.40 (s, 2H), 6.42 (d, *J*=8.60 Hz, 1H), 6.49-6.56 (m, 2H), 6.74-6.76 (m, 3H), 7.21-7.30 (m, 5H); FTIR (Neat): cm^{-1} 636, 759, 803, 853, 964, 1029, 1151, 1202, 1239, 1264, 1342, 1460, 1511, 1590, 1656, 2342, 2370, 2836, 2933, 3400; FAB-MS: m/z 461$(M+1)^+$; Anal. calcd. for $C_{29}H_{36}N_2O_3$: C, 75.62; H, 7.88; N, 6.08; Found: C, 75.58; H, 7.78; N, 5.59 %.

4.8.2. [3-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl][2-(4-chlorophenyl)-ethyl]amine (41)

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.20g, 1.2 mmol) was coupled with 2-(4-chlorophenyl)ethyl]-amine (0.225 g, 1.2 mmol) using general procedure 2 to afford the title compound **41** as oil. Yield: 0.13 g (47.2%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.89-2.02 (m, 6H), 2.75-2.88 (m, 6H), 3.29 (t, *J*=5.49 Hz, 2H), 3.90 (t, *J*=5.91 Hz, 2H), 4.41 (s, 2H), 6.39-6.54 (m, 3H), 7.02-7.28 (m, 9H); FTIR (Neat): cm^{-1} 459, 527, 632, 731, 806, 967, 1021, 1086, 1158, 1201, 1240, 1266, 1352, 1387, 1506,

1667, 1896, 2340, 2372, 2858, 2931, 3029, 3404; FAB-MS: m/z 435 $(M)^+$; Anal calcd. for $C_{27}H_{31}ClN_2O$: C, 74.55; H, 7.18; N, 6.44%; Found: C, 74.68; H, 7.28; N, 6.53%.

4.8.3. **1-Benzyl-6-{3-[4-(4-fluorophenyl)piperazin-1-yl]propoxy}-1,2,3,4-tetrahydro quinoline (42)**

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.10g, 0.62 mmol) was coupled with 4-fluorophenylpiperazine (0.057g, 0.34 mmol) using general procedure 2 to afford the title compound **42** as oil. Yield: 0.10 g (68.7%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.95-2.02 (m, 4H), 2.53-2.65 (m, 6 H), 2.82 (t, *J*=6.20 Hz, 2H), 3.10-3.15 (m, 4H), 3.28 (t, *J*=5.60 Hz, 2H), 3.94 (t, *J*=6.30 Hz, 2H), 4.41 (s, 2H), 6.46-6.61 (m, 3H), 6.88-6.95 (m, 4H), 7.26-7.31 (m, 5H); FTIR (Neat): cm^{-1} 523, 734, 820, 1000, 1062, 1155, 12000, 1240, 1293, 1350, 1388, 1441, 1511, 1593, 2272, 2341, 2375, 2833, 2952, 3433, 3756; FAB-MS: 460 $(M+1)^+$; HRMS: 459.2698

4.8.4. **1-Benzyl-6-[3-(4-phenylpiperazin-1-yl)-propoxy]-1,2,3,4-tetrahydroquinoline (43)**

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.10g, 0.62 mmol) was coupled with 4-phenylpiperazine (0.05g, 0.34 mmol) using general procedure 2 to afford the title compound **43** as oil. Yield: 0.06 g (42.9%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92-2.05 (m, 4H), 2.52-2.65 (m, 6H), 2.79 (t, *J*=6.32 Hz, 2H), 3.18-3.23 (m, 4H), 3.28 (t, *J*=5.64 Hz, 2H), 3.94 (t, *J*=6.29 Hz, 2H), 4.40 (s, 2H), 6.44 (d, *J*=8.59 Hz, 1H), 6.55-6.61 (m, 2H), 6.84-7.30 (m, 10H); FTIR (Neat): cm^{-1} 522, 642, 691, 735, 799, 859, 922, 998, 1060, 1150, 1198, 1240, 1291, 1348, 1389, 1442, 1504, 1596, 1818, 2272, 2341, 2372, 2831, 2951, 3052, 3429, 3681; FAB-MS: 441$(M)^+$; Anal. calcd for $C_{29}H_{35}N_3O$: C, 78.87; H, 7.99; N, 9.52%; Found: C, 78.72; H, 7.89; N, 9.43%.

4.8.5. **[3-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]propylamine (44)**

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.10g, 0.62 mmol) was coupled with propylamine (0.02g, 0.34 mmol) using general procedure 2 to afford the title compound **44** as oil. Yield: 0.09 g (42.9%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.92-2.05 (m, 4H), 2.52-2.65 (m, 6H), 2.79 (t, *J*=6.86 Hz, 2H), 3.18-3.23 (m, 4H), 3.28 (t, *J*=5.61 Hz, 2H), 3.94 (t, *J*=6.08 Hz, 2H), 4.40 (s, 2H), 6.44 (d, *J*=8.58 Hz, 1H), 6.55-6.61 (m, 2H), 6.84-7.30 (m, 5H); FTIR (Neat): cm^{-1} 522, 642, 691, 735, 799, 859, 922, 998, 1060, 1150, 1198, 1240, 1291, 1348, 1389, 1442, 1504, 1596, 1818, 2272, 2341, 2372, 2831, 2951, 3052, 3429, 3681, 3759, 3908; FAB-MS: m/z 339 $(M+1)^+$**;** Anal calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 7.16; N, 8.93%; Found: C, 78.23; H, 6.97%.N, 8.88%.

4.8.6. **1-Benzyl-6-{3-[4-(4-methoxyphenyl)piperazin-1-yl]propoxy}-1,2,3,4-tetra-hydroquinoline (45)**

1-Benzyl-6-(3-chloropropoxy)-1,2,3,4-tetrahydroquinoline (**39**; 0.08g, 0.5 mmol) was coupled with 1-(4-methoxyphenyl)piperazine (0.049 g, 0.5 mmol) using general procedure 2 to afford the title compound **45** as white solid. Yield: 0.06 g (50.2%); m.p.:112-113^oC; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.91-2.02 (m, 4H), 2.52-2.65 (m, 6H), 2.79 (t, *J*=6.37 Hz, 2H), 3.07-3.12 (m, 4H), 3.29 (t, *J*=5.59 Hz, 2H), 3.76 (s, 3H), 3.93 (t, *J*=6.31 Hz, 2H), 4.41 (s, 2H), 6.44 (d, *J*=8.68 Hz, 1H), 6.56-6.61 (m, 2H), 6.80-6.93 (m, 4H), 7.26-7.31 (m, 5H); FTIR (KBr): cm^{-1} 523, 696, 731, 771, 817, 855, 882, 924, 1002,

1035, 1062, 1152, 1200, 1244, 1351, 1386, 1444, 1511, 1597, 1847, 2341, 2368, 2825, ,2949, 3424, 3676, 3754; FAB-MS: m/z 472 $(M+1)^+$; Anal. calcd. for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91%; Found: C, 76.52; H, 8.14; N, 9.03%.

4.9. General Procedure 3 for the synthesis of compounds 46 and 47 (from 48)

A mixture of appropiate propan-2-ol (**11** or **48**) (10.5 mmol) and 5% Pd-C (1g) in absolute ethanol (20 mL) was shaken in a par apparatus at 38°C under 50 psi pressure of hydrogen for 5 hours. Pd-C was then discarded through filtration. The reaction mixture was concentrated under vacuum and the residue so obtained was chromatographed on silica gel using methanol:dichloromethane (5:95) as eluent to give the desired compounds.

4.9.1. 1-[2-(3,4-Dimethoxyphenyl)ethylamino]-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)propan-2-ol (46)

1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(3,4-dimethoxyphenyl)ethylamino] -propan-2-ol (**11**; 5.0 g, 10.5 mmol) was debenzylated using general procedure 3 to afford the title compound **46** as oil. Yield: 3.0 g (74 %); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.11-2.16 (m, 2H), 2.91-3.20 (m, 4H), 3.25-3.35 (m, 4H), 3.80 (s, 3H), 3.84 (s, 3H), 4.04-4.06 (m, 2H), 4.12-4.31 (m, 1H), 6.83-6.97 (m, 6H); FTIR (Neat): cm^{-1} 472, 667, 759, 809, 851, 883, 936, 1029, 1153, 1192, 1259, 1462, 1511, 1592, 2342, 2371, 2838, 2931, 3006, 3374, 3672, 3753; FAB-MS: m/z 487 $(M+1)^+$; Anal. calcd. for $C_{22}H_{30}N_2O_4$: C, 68.37 H, 7.82; N, 7.25%; Found: C, 68.54; H, 7.68; N, 6.99%.

4.10. General Procedure 4 for the synthesis of compounds 47 (from 46) and 48

A solution of di-tert-butyloxydicarbonate (1.8g) in THF (1 mL) was added to a cold (0°C) solution of appropriate substituted propan-2-ol (**11** or **46**; 6.3 mmol), Na_2CO_3 (3.53 g, 25.2 mmol) [in water (20 mL)] in THF (20 mL). The reaction mixture was stirred overnight during which temperature of the reaction mixture was allowed to rise to 30°C. The THF was evaporated completely under vacuum and the residue was extracted with ethyl acetate (4x5 mL) and then, the combined ethyl acetate fractions were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on neutral alumina using dichloromethane:hexane (9:1) as eluent to give the desired products**.**

4.10.1. [2-(3,4-Dimethoxyphenyl)ethyl]-[2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy) propyl]carbamic acid tert-butyl ester (47)

1-[2-(3,4-Dimethoxyphenyl)ethylamino]-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)-propan-2-ol (**46**; 3.0 g, 6.3 mmol) was protected with Boc-group using general procedure 4 to afford the title compound **47** as oil. Yield: 2.0 g (52.9%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.18 (s, 3H), 1.43 (s, 3H), 1.81-1.87 (m, 2H), 2.62-2.73 (m, 4H), 3.15-3.25 (m, 2H), 3.35-3.38 (m, 4H), 3.78 (bs, 8H), 3.98-4.03 (m, 1H), 6.37-6.74 (m, 6H); FTIR (Neat): cm^{-1} 556, 667, 759, 808, 853, 887, 938, 1031, 1160, 1236, 1258, 1366, 1418, 1466, 1511, 1592, 1683, 2341, 2360, 2838, 2933, 3385, 3655, 3753; FAB-MS: m/z 487 $(M)^+$; Anal. calcd. for $C_{27}H_{38}N_2O_6$: C, 66.64; H, 7.87; N, 5.76%; Found: C, 66.78; H, 7.78; N, 5.96%.

Alternately, a mixture of [3-(1-benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl][2-(3,4-dimethoxyphenyl)ethyl]-carbamic acid tert-butyl ester (**48**; 5.0 g,

10.2 mmol) was debenzylated using general procedure 3 to afford the title compound **47** as oil. Yield: 2.5 g (59.2%).

4.10.2. **[3-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl][2-(3,4-dimethoxyphenyl)ethyl]-carbamic acid tert-butyl ester (48)**

1-(1-Benzyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(3,4-dimethoxyphenyl)ethylamino] propan-2-ol (**11**; 0.476 g, 1 mmol) was protected with Boc group using the general procedure 4 to get the title compound **48** as oil. Yield: 0.5 g (86.8%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44 (s, 9H), 1.93-2.05 (m, 2H), 2.78-2.81 (m, 4H), 3.29 (t, *J*=5.48 Hz, 2H), 3.41-3.46 (m, 4H), 3.86 (bs, 8H), 4.07 (bs, 1H), 4.41 (s, 2H), 6.42 (d, *J*=8.64 Hz, 1H), 6.55-6.81 (m, 5H), 7.22-7.35 (m, 5H); FTIR (Neat): cm^{-1} 635, 699, 758, 803, 856, 887, 941, 974, 1031, 1161, 1201, 1240, 1264, 1364, 1418, 1461, 1511, 1592, 1688, 2372, 2931, 3429, 3754; FAB-MS: m/z 577 $(M+1)^+$; Anal. calcd for $C_{34}H_{44}N_2O_6$: C, 70.81; H, 7.69; N, 4.86%; Found: N, 4.92%.

4.11. General Procedure 5 for the synthesis of compounds 49-52

A mixture of [2-(3,4-dimethoxyphenyl)ethyl][2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-carbamic acid tert-butyl ester (**47**; 0.2 g, 0.41 mmol), appropriate sulfonyl chloride, Na_2CO_3 (0.11 g, 0.80 mmol) in dry acetone (10 mL) was stirred for 12-16 hrs. The reaction mixture was filtered, filtrate was concentrated under vacuum and the residue was chromatographed on silica gel using dichloromethane as eluent to get compounds **49-52.**

4.11.1. **[3-(1-Benzenesulfonyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl] [2-(3,4-dimethoxyphenyl)ethyl]-carbamic acid tert-butyl ester (49)**

[2-(3,4-Dimethoxyphenyl)ethyl][2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-carbamic acid tert-butyl ester (**47**; 0.2 g, 0.41 mmol) was coupled with benzenesulfonyl chloride (0.072 g), using general procedure 5 to give **49** as oil. Yield: 0.14 g (62.0%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46-1.60 (m, 9H), 1.90-2.05 (m, 2H), 2.30-2.37 (m, 2H), 2.79-2.84 (m, 2H), 3.34-3.46 (m, 4H), 3.76 (t, *J*=6.08 Hz, 2H), 3.85 (bs, 8H), 4.09-4.11 (m, 1H), 6.53-6.82 (m, 4H), 7.38-7.73 (m, 7H); FTIR (Neat): cm^{-1} 232: 588, 668, 691, 727, 759, 810, 939, 974, 1029, 1090, 1163, 1236, 1262, 1344, 1418, 1466, 1498, 1662, 2144, 2365, 2936, 3436, 3781; FAB-MS: m/z 627 $(M+1)^+$; Anal. calcd. for $C_{33}H_{42}N_2O_8S$: C, 63.24; H, 6.75; N, 4.47%; Found: C, 63.53; H, 6.69; N, 4.72%.

4.11.2. **[2-(3,4-Dimethoxyphenyl)ethyl]-{3-[1-(4-fluorobenzenesulfonyl)-1,2,3,4-tetra-hydro-quinolin-6-yloxy]-2-hydroxypropyl}carbamic acid tert-butyl ester (50)**

[2-(3,4-Dimethoxyphenyl)ethyl][2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-carbamic acid tert-butyl ester (**47**; 0.486g, 1 mmol) was coupled with 4-fluorobenzenesulfonyl chloride (0.195 g, 1 mmol) using general procedure 5 to give **50** as oil. Yield: 0.38 g (66.0%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46 (s, 6H), 1.51 (s, 3H), 1.84-1.93 (m, 2H), 2.33 (t, *J*=6.53 Hz, 2H), 2.63-2.78 (m, 2H), 3.43-3.46 (m, 4H), 3.64-3.85 (m, 10H), 4.11 (bs, 1H), 6.54-6.82 (m, 5H), 7.01-7.09 (m, 2H), 7.53-7.72 (m, 3H); FTIR (Neat): cm^{-1} 550, 684, 759, 839, 940, 974, 1031, 1090, 1163, 1238, 1365, 1417, 1465, 1501, 1593, 1688, 2370, 2937, 3439, 3756; FAB-MS: m/z 645 $(M+1)^+$; Anal.

calcd. for $C_{33}H_{41}FN_2O_8S$: C, 61.47; H, 6.41; N, 4.34%; Found: C, 61.67; H, 6.68; N, 4.48%.

4.11.3. **[2-(3,4-Dimethoxyphenyl)ethyl]-{2-hydroxy-3-[1-(naphthalene-2-sulfonyl)1,2,3,4-tetrahydroquinolin-6-yloxy]propyl}-carbamic acid tert-butyl ester (51)**

[2-(3,4-Dimethoxyphenyl)ethyl][2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)-propyl]-carbamic acid tert-butyl ester (**47**; 0.486 g, 1 mmol) was coupled with naphthalene-2-sulfonyl chloride (0.23 g, 1 mmol) using general procedure 5 to afford **51** as oil. Yield: 0.41 g (60.7%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 6H), 1.46 (s, 3H), 1.51-1.64 (m, 2H), 2.28 (t, *J*=6.69 Hz, 2H), 2.79-2.84 (m, 2H), 3.43-3.47 (m, 4H), 3.78-3.86 (m, 10H), 4.05-4.21 (m, 1H), 6.51-6.82 (m, 5H), 7.43-7.88 (m, 7H), 8.23 (bs, 1H); FTIR (Neat): cm^{-1} 479, 549, 616, 650, 685, 765, 814, 856, ,974, 1029, 1080, 1160, 1263, 1351, 1463, 1513, 1596, 2341, 2369, 2855, 2927, 3436, 3753, 4003, 4190; FAB-MS: m/z 577 $(M\text{-}Boc)^+$; Anal. calcd. for $C_{37}H_{44}N_2O_8S$: C, 65.66; H, 6.55; N, 4.14%; Found: C, 65.43; H, 6.76; N, 4.34%.

4.11.4. **[2-(3,4-Dimethoxyphenyl)ethyl]-{2-hydroxy-3-[1-(2,4,6-triisopropylbenzene-sulfonyl)-1,2,3,4-tetrahydroquinolin-6-yloxy]propyl}carbamic acid tert-butyl ester (52)**

[2-(3,4-Dimethoxyphenyl)ethyl][2-hydroxy-3-(1,2,3,4-tetrahydroquinolin-6-yloxy)propyl]-carbamic acid tert-butyl ester (**47**; 0.486 g, 1 mmol) was coupled with 2,4,6-triisopropylbenzenesulfonyl chloride (0.363 g, 1.2 mmol) using general procedure 5 to give **52** as oil. Yield: 0.38 g (50.5%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.92-1.31 (m, 21H), 1.37-1.44 (m, 9H), 1.91 (d, *J*=5.26 Hz, 2H), 2.65-2.73 (m, 4H), 3.31-3.37 (m, 4H), 3.63-3.68 (m, 2H), 3.78-3.93 (m, 8H), 4.01 (s, 1H), 6.51-7.19 (m, 8H); FTIR (Neat): cm^{-1} 579, 667, 691, 759, 807, 849, 884, 938, 970, 1032, 1080, 1160, 1223, 1260, 1319, 1367, 1421, 1464, 1499, 1600, 1683, 2872, 2932, 2963, 3016, 3430; FAB-MS: m/z 752 $(M)^+$; Anal. calcd. for $C_{42}H_{60}N_2O_8S$: C, 66.99; H, 8.03; N, 3.72%; Found: C, 66.85; H, 8.23; N, 3.59%.

4.12. General Procedure 6 for the synthesis of compounds 53-56

A solution of acetic acid (TFA): dichloromethane (40:60 v/v; 5 mL) was added to the cold (-10^{o}C) and stirring solution of appropriate substituted 1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl][2-(3,4-dimethoxyphenyl)ethyl]-carbamic acid tert-butyl ester (**49-52**; 0.018 mmol) in dichloromethane. The reaction mixture was stirred for an additional 2 hours while temperature of the reaction mixture was allowed to rise to 31^{o}C. The reaction mixture was concentrated at under reduced pressure, neutralized with $NaHCO_3$ (10% in water w/v), extracted with ethyl acetate (3x5 mL) and dried over sodium sulphate. The combined fractions of ethyl acetate were concentrated under vacuum and the residue was chromatographed on neutral alumina using methanol: dichloromethane (1:99) as eluent to give **53-56**.

4.12.1. **1-(1-Benzenesulfonyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-3-[2-(3,4-dimeth-oxyphenyl)ethylamino]propan-2-ol (53)**

[3-(1-Benzenesulfonyl-1,2,3,4-tetrahydroquinolin-6-yloxy)-2-hydroxypropyl][2-(3,4-di-methoxyphenyl)ethyl]-carbamic acid tert-butyl ester (**49**; 0.10 g, 0.018 mmol) was

subjected to Boc group deprotection using general procedure 6 to give **53** as oil. Yield: 0.04 g (48.9%).^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.51-1.57 (m, 2H), 2.30 (t, *J*=6.68 Hz, 2H), 2.77-2.91 (m, 6H), 3.76 (t, *J*=6.59 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.92-3.94 (m, 2H), 3.99-4.01 (m, 1H), 6.52-6.53 (m, 1H), 6.74-6.79 (m, 2H), 7.27-7.72 (m, 8H); FTIR (Neat): cm^{-1} 567, 614, 693, 730, 761, 821, 1022, 1127, 1164, 1337, 1450, 1514, 1613, 2367, 2955, 3064, 3428, 3752, 3859; FAB-MS: m/z 526 $(M)^+$; Anal. calcd. for $C_{28}H_{34}N_2O_6S$: C, 63.86; H, 6.51; N, 5.32%; Found: C, 63.65; H, 6.43; N, 5.46 %.

4.12.2. **1-[2-(3,4-Dimethoxyphenyl)ethylamino]-3-[1-(4-fluorobenzenesulfonyl)-1,2,3, 4-tetrahydroquinolin-6-yloxy]propan-2-ol (54)**

[2-(3,4-Dimethoxyphenyl)ethyl]-{3-[1-(4-fluorobenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-6-yloxy]-2-hydroxypropyl}-carbamic acid tert-butyl ester (**50**; 0.30 g, 0.465 mmol) was subjected to Boc group deprotection using general procedure 6 to give **54** as oil. Yield: 0.18 g (71.0%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52-2.29 (m, 2H), 2.32 (t, *J*=6.60 Hz, 2H), 2.80-3.18 (m, 6H), 3.75 (t, *J*=6.01 Hz, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.94 (d, *J*=4.92 Hz, 2H), 4.08-4.20 (m, 1H), 6.51-6.53 (m, 1H), 6.75-6.83 (m, 4H), 7.02-7.11 (m, 2H), 7.50-7.70 (m, 3H); FTIR (Neat): cm^{-1} 550, 687, 716, 758, 836, 971, 1028, 1088, 1160, 1197, 1236, 1346, 1461, 1497, 1346, 1461, 1497, 1592, 1680, 2273, 2340, 2374, 2853, 2929, 3317, 3681, 3757, 3908; FAB-MS: m/z 544 $(M)^+$; Anal. calcd. for $C_{28}H_{33}FN_2O_6S$: C, 61.75; H, 6.11; N, 5.14%; Found: C, 61.56; H, 6.33; N, 4.95%.

4.12.3. **1-[2-(3,4-Dimethoxyphenyl)ethylamino]-3-[1-(naphthalene-2-sulfonyl)-1,2,3, 4-tetra-hydroquinolin-6-yloxy]propan-2-ol (55)**

[2-(3,4-Dimethoxyphenyl)ethyl]-{2-hydroxy-3-[1-(naphthalene-2-sulfonyl)-1,2,3,4-tetrahydroquinolin-6-yloxy]propyl}-carbamic acid tert-butyl ester (**51**; 0.30 g, 0.44 mmol) was subjected to Boc group deprotection using general procedure 6 to give **55** as oil. Yield: 0.15 g (58.7%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.52-1.45 (m, 2H), 2.28 (t, *J*=6.69 Hz, 2H), 2.80-3.14 (m, 6H), 3.76-3.96 (m, 11H), 6.47 (bs, 1H), 6.65-6.69 (m, 4H), 7.11-7.16 (m, 3H), 7.35-7.51 (m, 1H), 7.53-7.66 (m, 2H), 7.72-7.87 (m, 3H), 8.24 (m, 1H); FTIR (Neat): cm^{-1} 479, 549, 651, 686, 760, 816, 967, 1027, 1079, 1159, 1195, 1264, 1351, 1462, 1497, 1595, 2367, 2855, 2926, 3420, 3752; FAB-MS: m/z 577 $(M+1)^+$; Anal. calcd. for $C_{32}H_{36}N_2O_6S$: C, 66.64; H, 6.29; N, 4.86%; Found: C, 66.78; H, 6.57; N, 4.95%.

4.12.4. **1-[2-(3,4-Dimethoxyphenyl)ethylamino]-3-[1-(2,4,6-triisopropylbenzenesulfonyl)-1,2,3,4-tetrahydroquinolin-6-yloxy]propan-2-ol (56)**

[2-(3,4-Dimethoxyphenyl)ethyl]-{2-hydroxy-3-[1-(2,4,6-triisopropylbenzene-sulfonyl)-1,2,3,4-tetrahydroquinolin-6-yloxy]propyl}-carbamic acid tert-butyl ester (**52**; 0.25 g, 0.33 mmol) was subjected to Boc group deprotection using general procedure 6 to give **56** as oil. Yield: 0.10 g (46.1%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05-1.18 (m, 21H), 1.98-2.10 (m, 2H), 2.66-2.84 (m, 4H), 3.31-3.37 (m, 4H), 3.63-3.69 (m, 2H), 3.79-3.94 (m, 8H), 4.01 (m, 1H), 6.52-7.19 (m, 8H); FTIR (Neat): cm^{-1} 570, 679, 768, 882, 1014, 1082, 1158, 1220, 1260, 1364, 1461, 1513, 1657, 2342, 2373, 2869, 2960, 3402; FAB-MS: m/z 653 $(M+1)^+$; Anal. calcd. for $C_{37}H_{52}N_2O_6S$: C, 68.07; H, 8.03; N, 4.29%; Found: C, 67.98; H, 8.26; N, 4.42%.

4.13. 4-(2-Nitropropenyl)phenol (58)

A mixture of 4-hydroxy-benzaldehyde (**57**, 1.22 g, 10 mmol), nitroethane (0.69 mL, 10 mmol), ammonium acetate (0.77 g, 10 mmol), and acetic acid (0.6 g, 10 mmol) in dry methanol (10 mL) was stirred for 50 hours at 34^{o}C. The reaction mixture was concentrated under vacuum, diluted with water (10 mL), neutralized with ammonia and extracted with ethyl acetate (5x10 mL). The combined fractions of ethyl acetate were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on silica gel using dichloromethane as eluent to afford **58** as yellow solid. Yield: 0.80 g (44.7%); m.p.:123-124^{o}C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.47 (s, 3H), 6.91-6.97 (m, 2H), 7.34-7.40 (m, 2H), 8.07 (s, 1H), FTIR (KBr): cm^{-1} 523, 671, 834, 982, 1171, 1287, 1361, 1434, 1517, 1603, 1642, 2362, 3382, 3754; FAB-MS: m/z 180 $(M+1)^{+}$; Anal. calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82%; Found: C, 60.53; H, 5.25; N, 7.69%.

4.14. 1-(4-Hydroxyphenyl)propan-2-one (59)

A mixture of 4-(2-nitropropenyl) phenol (**58**; 4.8 g, 37.3 mmol), iron powder (10.66 g), $FeCl_3$ (0.42 g), conc. HCl (5.3 mL), water (133.3 mL) in ethanol (53.3 mL) was heated at 110^{o}C for 5 hours. The reaction mixture was cooled to 33^{o}C and filtered. The filtrate was neutralized with ammonia and extracted with ethyl acetate (5x10 mL). The combined fractions of ethyl acetate were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on silica gel using dichloromethane as eluent to give **59** as oil. Yield: 2.5 g (62.15%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15 (s, 3H), 3.62 (s, 2H), 6.77-6.81 (m, 2H), 7.04-7.08 (m, 2H), FTIR (Neat): cm^{-1} 531, 607, 840, 1016, 1167, 1235, 1360, 1447, 1515, 1612, 1704, 2363, 3374, 3781, FAB-MS: m/z 151$(M+1)^{+}$; Anal. calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71%; Found: C, 71.86; H, 6.85%.

4.15. 2-Phenylmorpholine (60)

Pieces of sodium metal (0.23 g, 10 mmol) were added portion wise to the stirring solution of 2-phenyl-4-(toluene-4-sulfonyl)morpholine (**8** in the supplementary Information; 0.317 g, 1 mmol) in amyl alcohol (5 mL) at 100^{o}C during 3 hours. The reaction mixture was cooled to 34^{o}C, diluted with water (5 mL). The two layers of water and amyl alcohol were separated; alcoholic layer was extracted with 2N HCl (4x2 mL) and the aqueous layer was first extracted with ethyl acetate (5x2 mL) then this combined ethyl acetate fraction with 2N HCl (5x2 mL). The 2N HCl extracts were combined and neutralized with liquid ammonia and finally extracted with ethyl acetate (5x5 mL). The combined fractions of ethyl acetate were dried over Na_2SO_4 and concentrated under vacuum. The residue was chromatographed on silica gel using methanol:dichloromethane (4:96) as eluent to give **60** as oil. Yield: 0.11 g (67.5%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.79-3.05 (m, 2H), 3.78-4.07 (m, 4H), 4.47-4.53 (m, 1H), FTIR (Neat): cm^{-1} 527, 562, 701, 759, 811, 886, 914, 1029, 1096, 1220, 1274, 1352, 1387, 1452, 1541, 1603, 1723, 1815, 1977, 2364, 2467, 2925, 3418, 3694, 3782, FAB-MS: 164 $(M+1)^{+}$; Anal. calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58%; Found: C, 73.65; H, 7.92; N, 8.35%.

4.16. 4-[2-(2-Phenylmorpholin-4-yl)propyl]phenol (61)

$NaCNBH_3$ (0.13g, 2 mmol) was added to a stirring and cooled (-10^{o}C) solution of 2-phenylmorpholine (**60**, 0.33 g, 2 mmol) and 1-(4-hydroxyphenyl)propan-2-one (**59**, 0.30

g, 2 mmol) in dry methanol (10 mL). Glacial acetic acid (0.5 mL, pH 5-6) was added to the reaction mixture and stirred the same overnight during which temperature of the reaction mixture was allowed to rise to 34°C. The reaction mixture was quenched with water (0.2 mL), concentrated under vacuum, neutralized with ammonia and extracted with ethyl acetate (4x3 mL). The combined fractions of ethyl acetate were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on silica gel using methanol:dichloromethane (2:98) as eluent to give **61** as oil. Yield: 0.32 g (53.9%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (d, *J*=6.48 Hz, 3H), 2.34-2.48 (m, 2H), 2.62-2.98 (m, 5H), 3.85-4.10 (m, 2H), 4.58 (d, *J*=10.10 Hz, 1H), 6.74 (d, *J*=7.90 Hz, 2H), 7.01 (d, *J*=8.32 Hz, 2H), 7.26-7.37 (m, 5H), FTIR (Neat): cm^{-1} 560, 772, 815, 937, 1191, 1236, 1352, 1442, 1598, 1664, 1726, 1814, 2365, 2926, 2971, 3347, 3634, 3660, 3698, 3782, FAB-MS: 298 $(M+1)^+$; Anal. calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71 %, Found: N, 5.12%.

4.17. {4-[2-(2-Phenylmorpholin-4-yl)propyl]phenoxy}acetic acid ethyl ester (62)

A mixture of 4-[2-(2-phenylmorpholin-4-yl)propyl]phenol (**61**, 0.297 g, 1 mmol), ethylbromoacetate (0.50 g, 3 mmol), K_2CO_3 (0.40 g, 3 mmol) in acetone (20 mL) was heated at 55°C overnight. The reaction mixture was cooled to 37°C and filtered. The filtrate was concentrated under vacuum and the residue was chromatographed on silica gel using dichloromethane as eluent to give **62** as oil. Yield: 0.34 g (88.7%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93-0.96 (m, 3H), 1.26-1.33 (m, 3H), 2.36-2.46 (m, 2H), 2.62-2.92 (m, 5H), 3.70-3.82 (m, 1H), 4.04-4.09 (m, 1H), 4.21-4.32 (m, 2H), 4.32-4.59 (m, 3H), 6.80-6.84 (m, 2H), 7.06-7.10 (m, 2H), 7.26-7.37 (m, 5H), FTIR (Neat): cm^{-1} 525, 560, 608, 652, 700, 756, 825, 917, 980, 1039, 1110, 1172, 1243, 1354, 1452, 1513, 1609, 1659, 1881, 2277, 2340, 2376, 2861, 2929, 3026, 3344, 3655, 3682, 3757, FAB-MS: 384 $(M+1)^+$; Anal. calcd. for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65 %, Found: C, 72.24; H, 7.49; N, 4.03%.

4.18. {4-[2-(2-Phenylmorpholin-4-yl)propyl]phenoxy}acetic acid (63)

A solution of NaOH (0.04 g, 1 mmol) in methanol (0.5 mL) and water (0.1 mL) was added to the stirring reaction mixture of {4-[2-(2-phenylmorpholin-4-yl)propyl]phenoxy}acetic acid ethyl ester (**62**; 0.38 g, 1 mmol) at 34°C. The stirring was continued for an additional ½ hour. The reaction mixture was concentrated under vacuum, diluted with water (5 mL), neutralized with 2N HCl and extracted with ethyl acetate (3x5 mL). The combined fractions of ethyl acetate were dried over sodium sulphate and concentrated under vacuum. The residue was chromatographed on silica gel using methanol:dichloromethane (7:93) as eluent to give **63** as oil. Yield: 0.3 g (85.1%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91(d, *J*=6.45 Hz, 3H), 2.35-2.50 (m, 2H), 2.62-2.81 (m, 2H), 2.95-3.08 (m, 3H), 4.10-4.24 (m, 2H), 4.50-4.71 (m, 3H), 6.82-6.98 (m, 4H), 7.27-7.41 (m, 5H), FTIR (Neat): cm^{-1} 614, 667, 702, 7058, 831, 949, 1061, 1106, 1184, 1226, 1421, 1512, 1608, 1712, 2371, 1603, 2857, 2927, 3401, 3754, FAB-MS: M/Z 356 $(M+1)^+$; Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94 %, Found: C, 70.78; H, 7.35; N, 4.35%.

4.26. Pharmacology

Human SK-N-MC neuroblastoma cells model was used to evaluate the β_3-AR agonistic activity. This model represents an excellent, non-recombinant model system for evaluating the β_3-AR characteristics of unknown compounds.[27, 28]

Radioligand binding assay

Cell Culture: SK-N-MC cells were maintained in 90% Dulvecco's modified Eagle's medium with 10% fetal calf serum. Upon reaching confluence they were subcultured at a ratio of 1/5 to 1/10 in the same medium. The cells were washed twice in 50mM HEPES (pH 7.5, 4mM $MgCl_2$, 0.04% BSA, 10% sucrose), harvested and homogenized in HEPES. Homogenates were centrifuged at 30000 x g for 10 minutes and pellets are resuspended in HEPES one confluent 10 mm plate/7mm. The final volume of 0.1 mL containing 6.16 μg of membrane (20 μL of a 1:20 dilution), buffer, [^{125}I] iodocyanopindolol (0.46 nM, 2200 Ci/mmol) were incubated in presence or absence of cometing drug for 90 minute at 370^{o}C. Incubations were stopped by filtering over 934 AH (presoaked in 0.5% polyethylanimine) and washed three times with 2 mL ice cold 50mM TRIS-HCl (pH 7.4) containing 4 mM $MgCl_2$. Filters were counted in a gamma-counter. Non-specific binding is defined as binding remaining in the presence of 1 mM alprenolol. The β_3-AR agonistic activity (ranging from -17.73% to 90.64% at 10 μM) was measured as the inhibition of specific binding [^{125}I] Iodocynopindolol to human neuroblastoma (SKN-MC) and CHO cells over- expressing β_3-ARs. Inhibition of binding by various compounds yields IC_{50} values which were transformed to dissociation constants with the dissociation constant for ICYP. Statistical analysis was used for the determination of differences.

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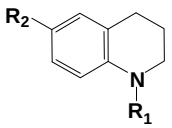
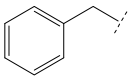
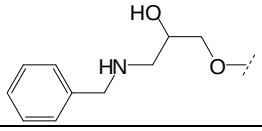
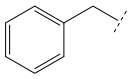
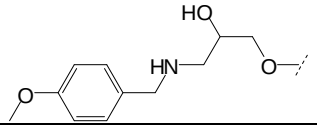
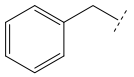
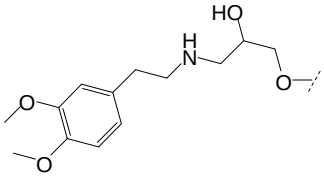
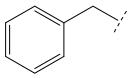
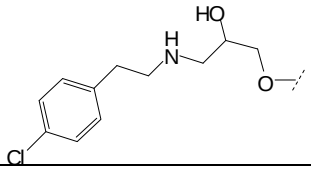
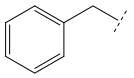
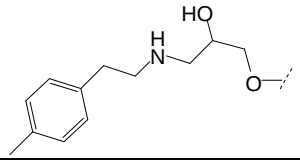
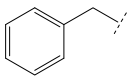
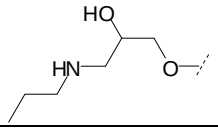
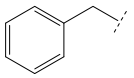
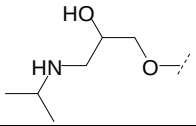
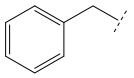
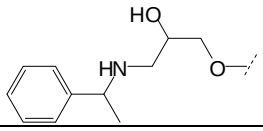
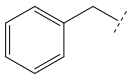
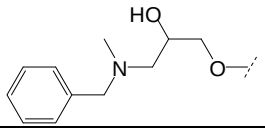
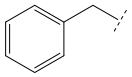
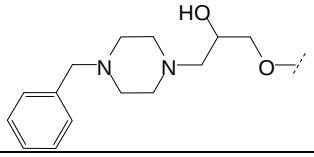
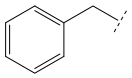
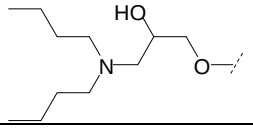
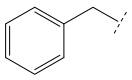
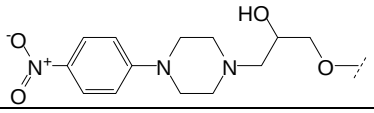
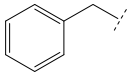
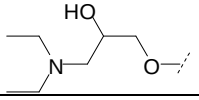
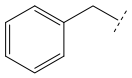
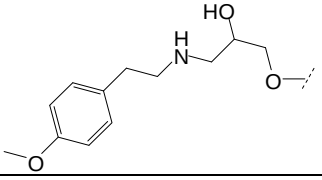
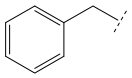
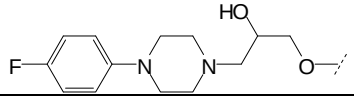
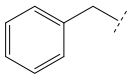
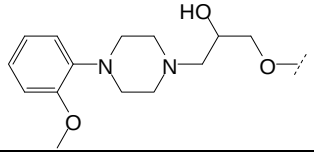
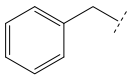
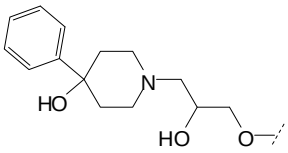
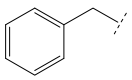
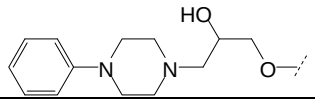
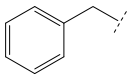
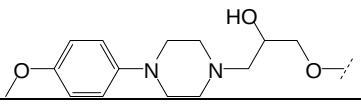
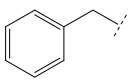
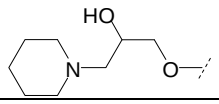
Tables with captions

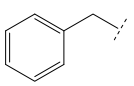
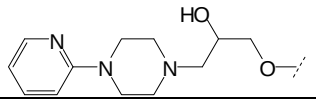
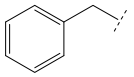
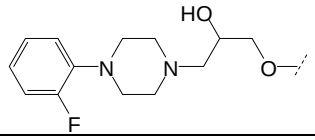
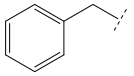
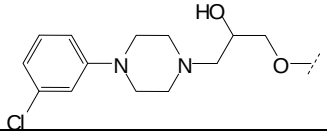
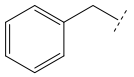
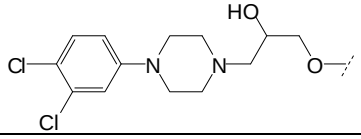
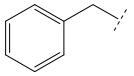
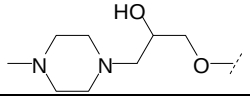
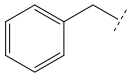
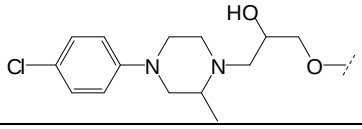
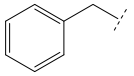
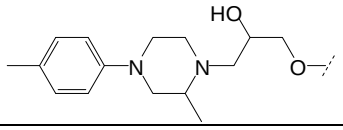
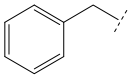
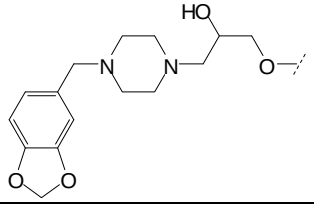
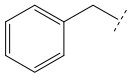
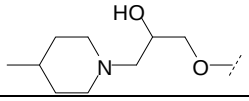
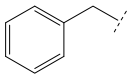
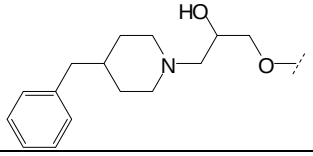
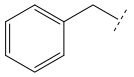
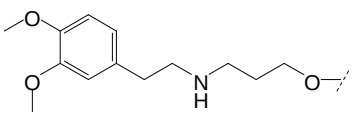
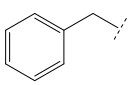
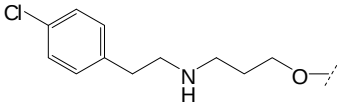
Table 1: Chemical Structures and β_3-AR agonistic activity of the title compounds (**9-56, 61-63**)

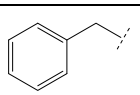
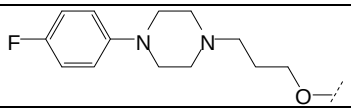
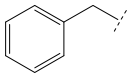
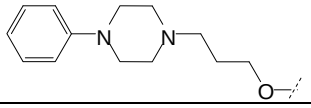
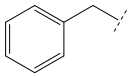
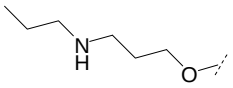
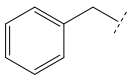
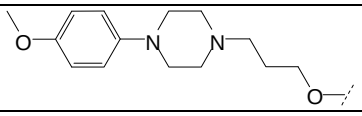
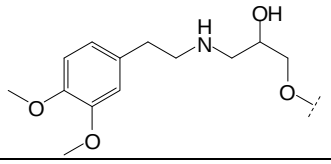
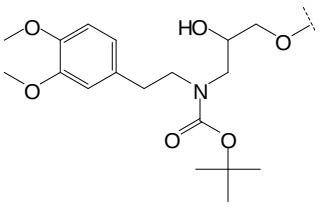
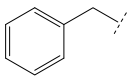
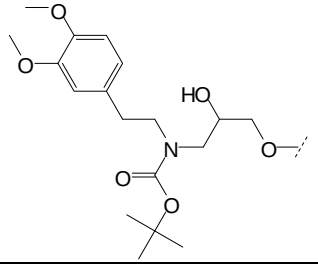
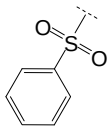
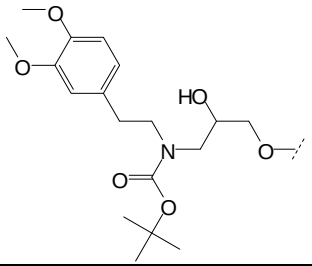


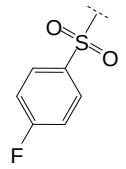
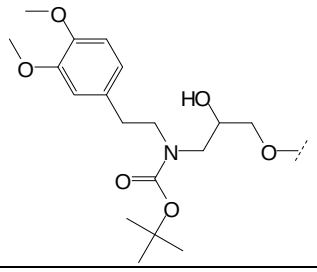
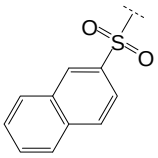
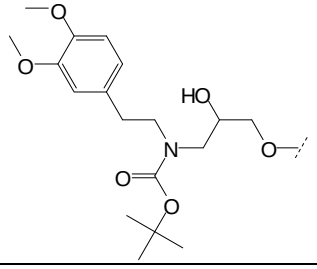
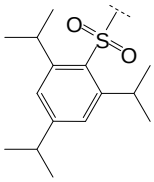
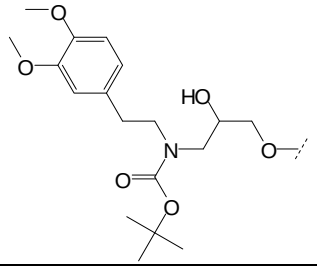
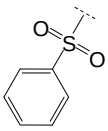
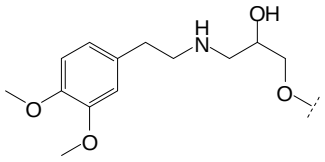
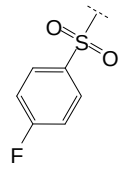
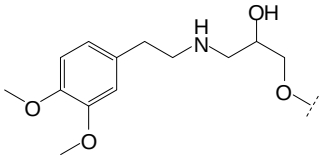
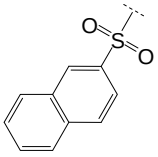
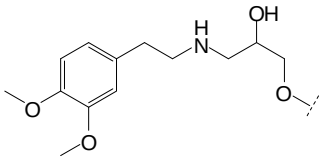
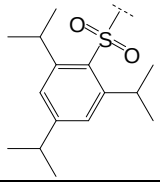
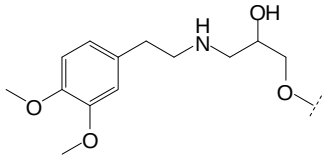
9-39, 41-56

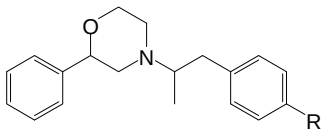
Comp.	R_1	R_2	% inhibition$^{\neq}$ (IC_{50})	
			1μM	10μM
9			1.81	19.02
10			9.26	27.38
11			**72.79**	**90.64 (0.55 μM)**
12			55.79	63.08
13			8.17	18.15
14			19.25	66.27
15			**59.69**	**83.17 (0.59 μM)**
16			7.71	27.54

17			-4.54	2.54
18			-0.84	17.06
19			4.09	14.67
20			6.08	4.13
21			9.18	11.21
22			**56.22**	**76.50 (1.18 μM)**
23			**49.72**	**68.76 (1.76 μM)**
24			12.21	14.53
25			46.35	50.51
26			45.85	52.24
27			45.09	49.84
28			4.27	31.40

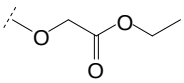
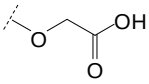
29			5.32	12.69
30			5.50	20.42
31			-2.34	11.35
32			-7.18	-0.28
33			-3.71	-0.18
34			3.61	0.08
35			3.19	11.76
36			-5.28	18.10
37			-1.79	12.85
38			-2.05	23.53
40			-31.8	-17.73
41			42.92	58.68

42			nd†	nd
43			nd	nd
44			5.62	16.18
45			6.72	1.95
46	H		33.08	56.45
47	H		23.17	28.14
48			37.75	46.66
49			nd	nd

50			nd	nd
51			nd	nd
52			nd	nd
53			26.53	38.92
54			nd	nd
55			nd	nd
56			nd	nd



61-63

Comp.	R	% inhibition[≠] (IC_{50})	
		1μM	10μM
61	OH	0.34	0.24
62		-20.93	-1.36
63		-9.63	9.42

[≠] The β_3-AR agonistic activity was measured as the inhibition of specific binding of [^{125}I] Iodocynopindolol to human neuroblastoma (SKN-MC) and CHO cells over-expressing β_3-ARs; [†] Not done due to solubility or other problem

Table 2: Selectivity data (EC_{50}) of the two compounds **15** and **22** for β_3-AR over β_1- and β_2-ARs.

Compd. Name	**β_3-AR (EC_{50})**	**β_2-AR (EC_{50})**	**β_1-AR (EC_{50})**
15	0.883 μM	1.156 μM	2.035 μM
22	4.880 μM	5.895 μM	7.282 μM

Figures with captions

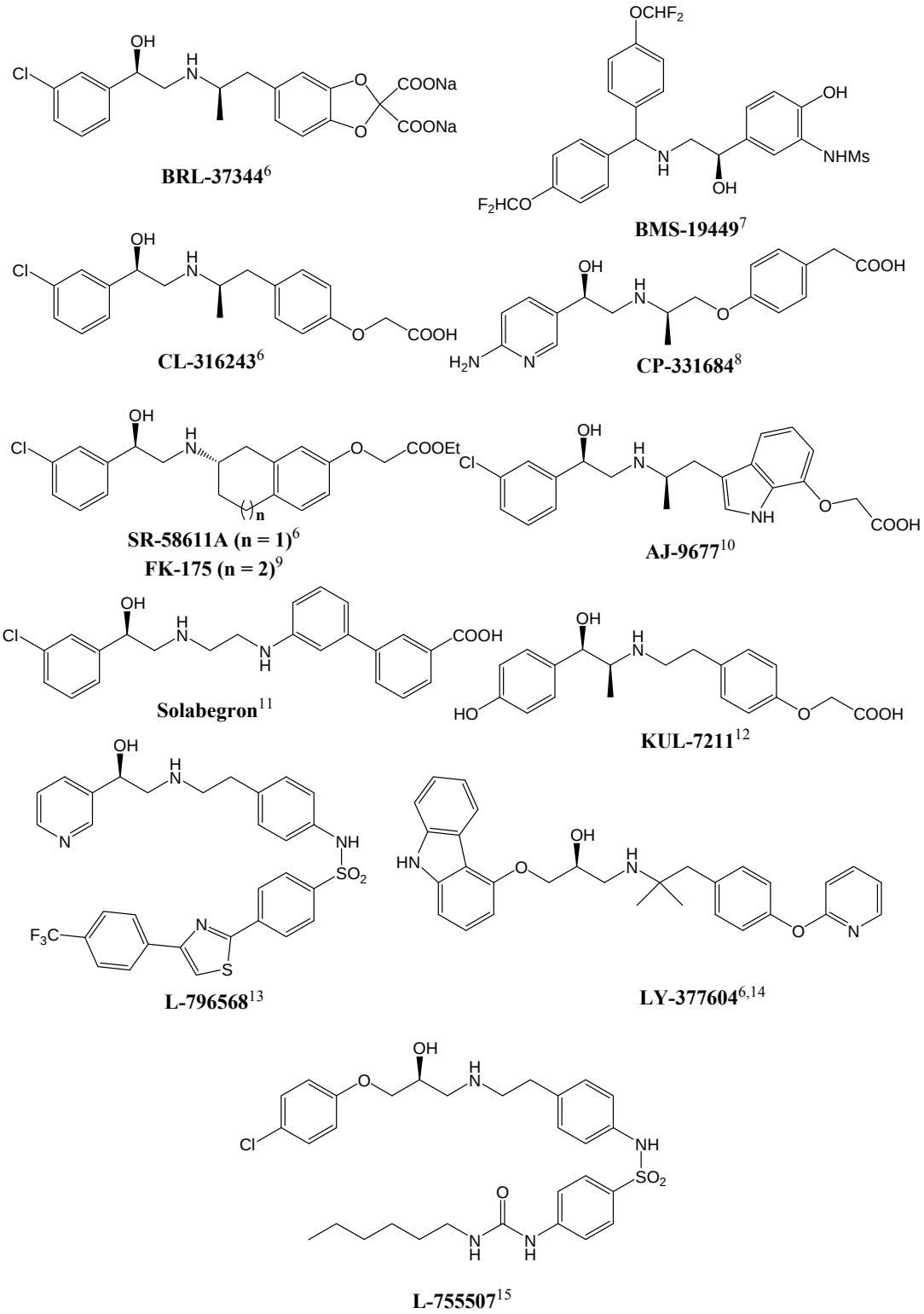
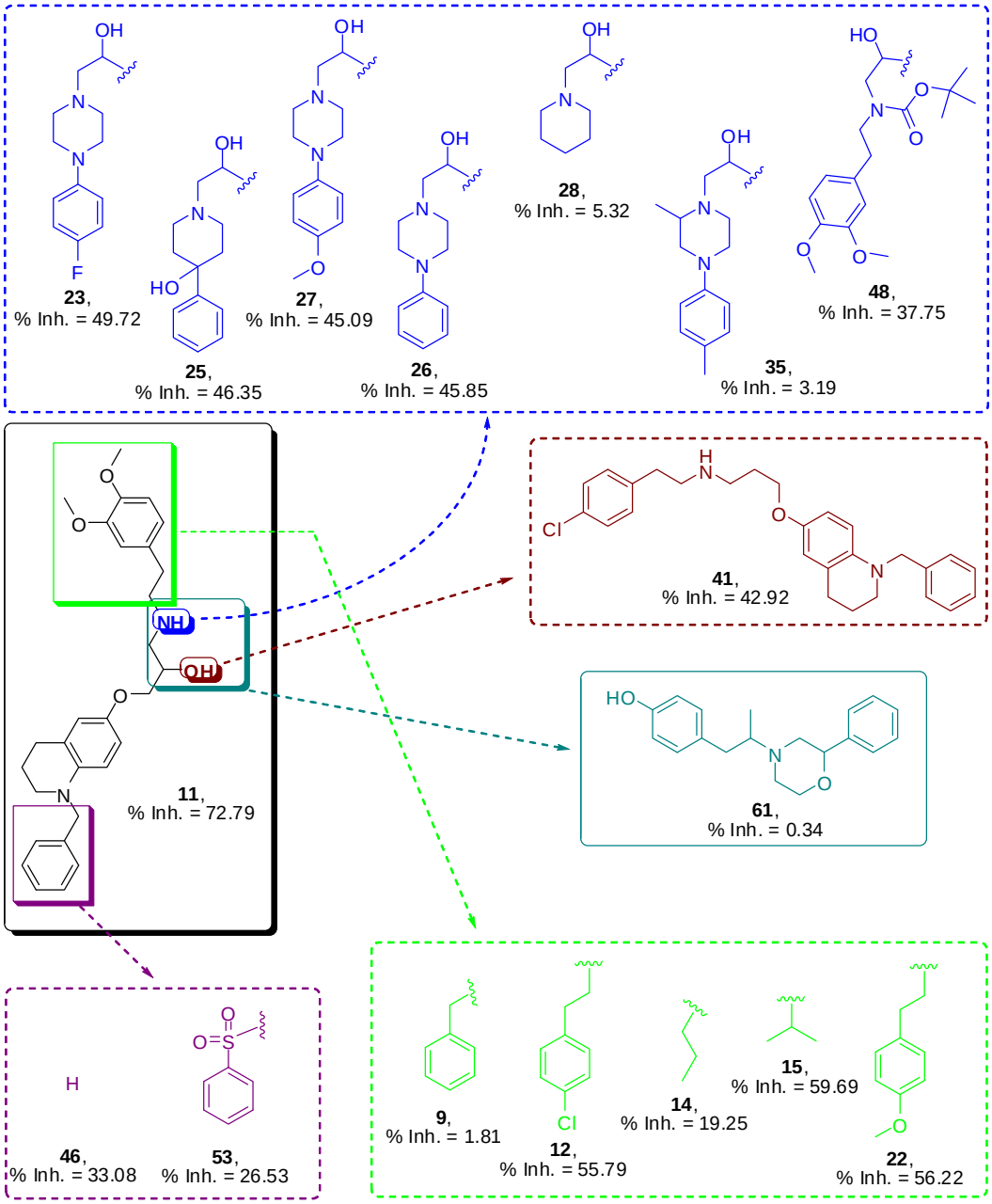


Figure 1: Structures of some β_3 –AR agonists[6-15]



% Inhibition (% Inh.) = Inhibition of specific binding of [^{125}I] iodocynopindolol to human neuroblastoma (SK-N-MC) and CHO cells over-expressing b_3-AR at 1 μM

Figure 2: In brief Structure Activity Relationship (SAR)

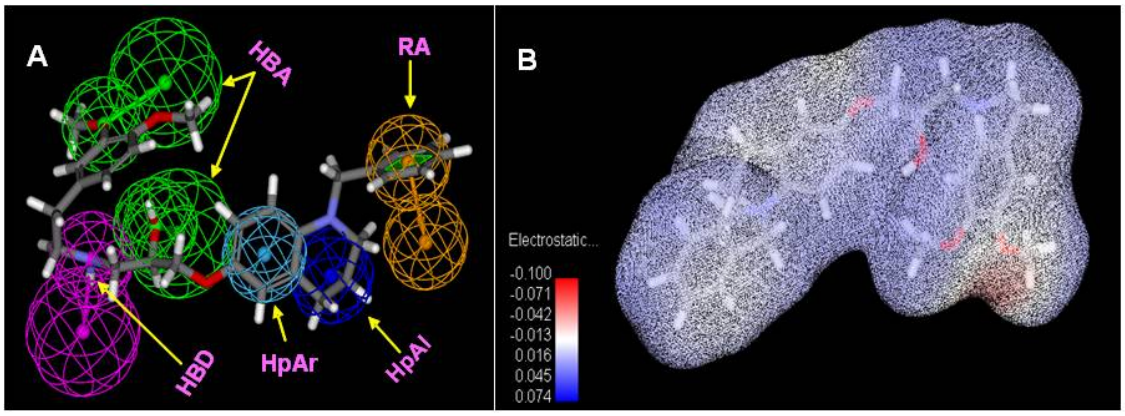


Figure 3: (A) Putative β_3-Adrenergic Receptor pharmacophore (Hypo-01) with mapped compound **11**; **(B)** Overall shape with electrostatic surface of the most active compound 11. [HBA = (green colour); HBD (pink colour); HpAr (light blue); HpAl (dark blue); RA (brown colour)]

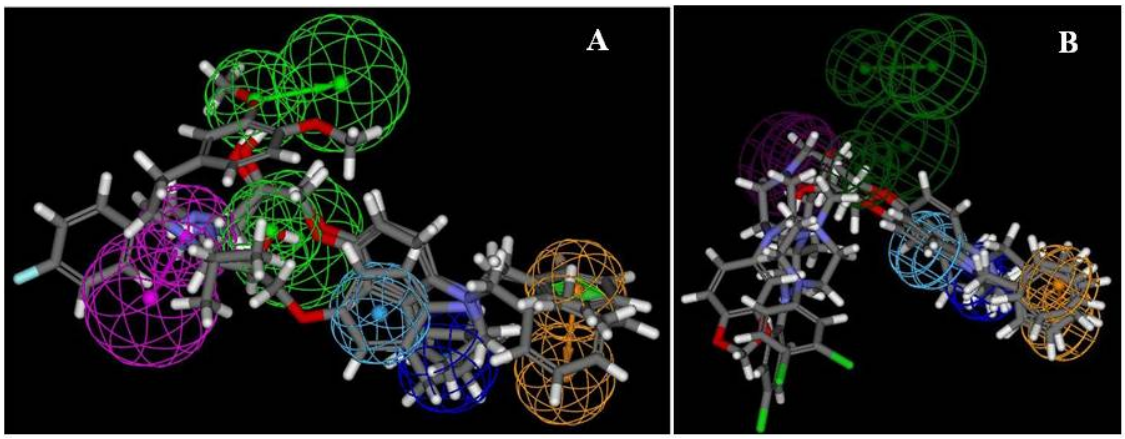
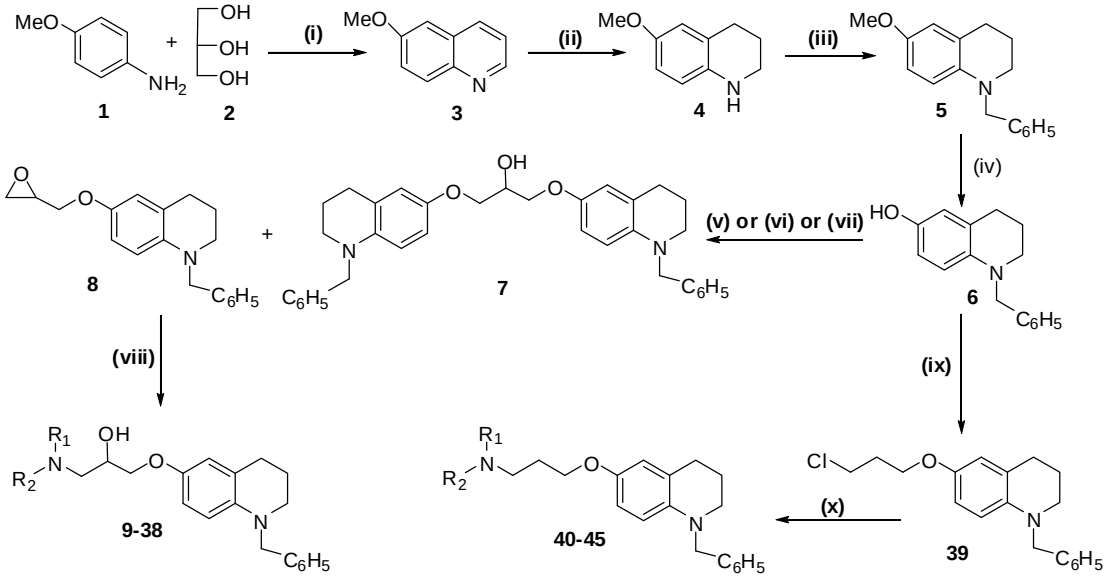


Figure 4: (A) Mapping of the most active compounds **11**, **15**, **22** & **23**; **(B)** Mapping of inactive compounds **32, 34** & **36**. [HBA = (green colour); HBD (pink colour); HpAr (light blue); HpAl (dark blue); RA (brown colour)]

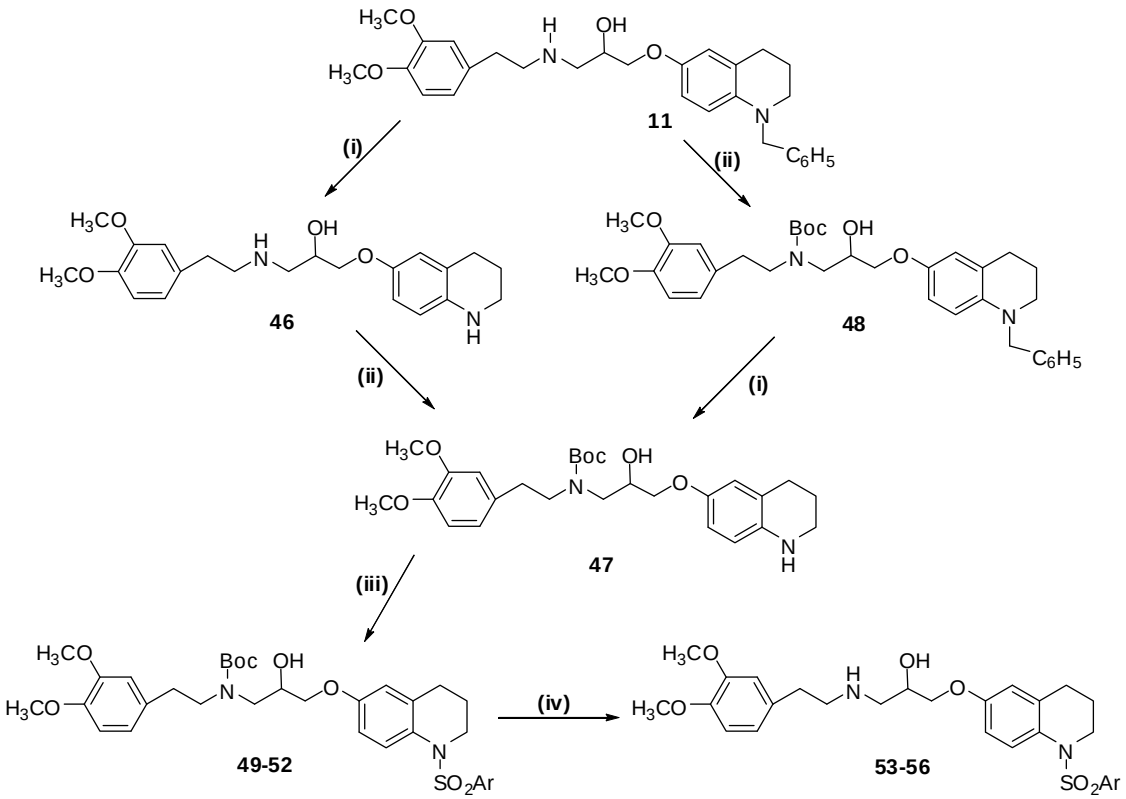
Schemes and captions

Scheme 1: Synthesis of Compounds 9-38 and 40-45.



Reagents and conditions: (i) Conc. H_2SO_4, iodine, 140-170^oC, 16-18 hrs ; (ii) nickel-aluminium alloy, ethanol, 10% NaOH in water (w/v), 50^oC, 2-3 hrs; (iii) benzyl chloride, dry DMF, baked K_2CO_3 (or $NaCO_3$), NaI (or KI), 80^oC, 1 hr; (iv) 47% HBr in water, reflux, 5 hrs; (v) epichlorohydrin, NaOH in water, ethanol, 30^oC; (vi) epichlorohydrin, NaOH in water, tetrabutylammonium iodide, 0-3^oC; (vii) epichlorohydrin, NaH, DMF, NaI, -10 to 30^oC; (viii) ethanol, r.t., various amines; (ix) 1-bromo-3-chloropropane, NaH, dry THF, -10^oC (x) Na_2CO_3, NaI, DMF, 80^oC, (un) substituted amines

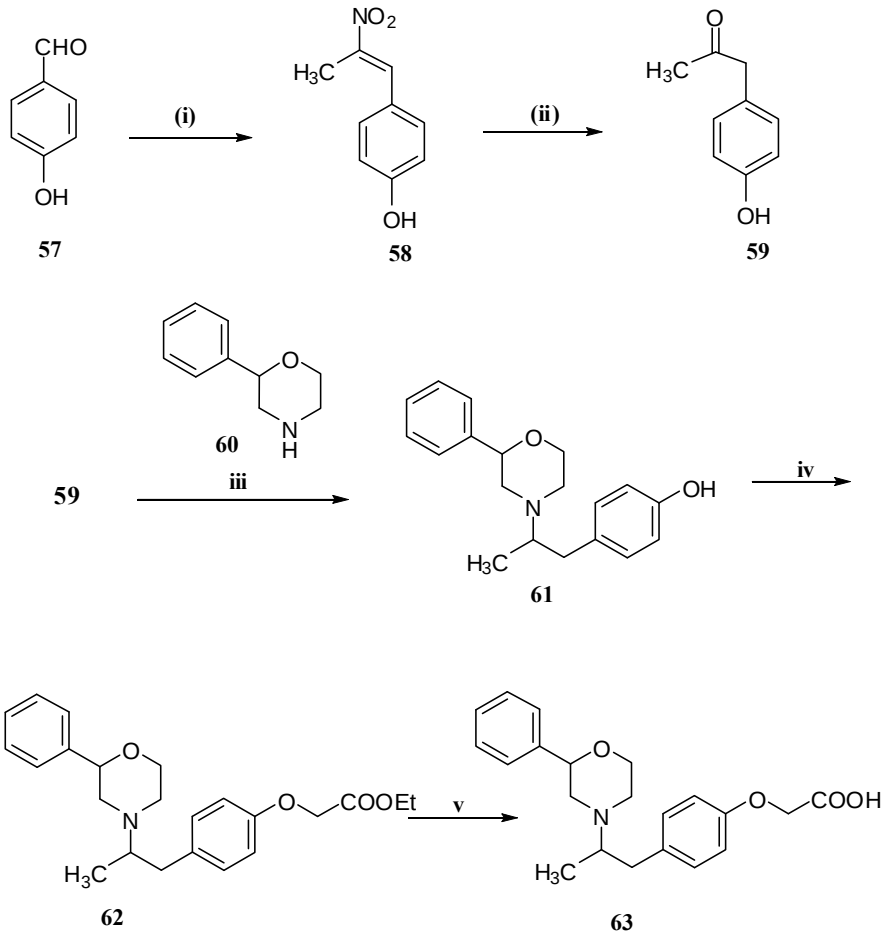
Scheme 2: Modifications and synthesis of the compounds **46-56**



49, 53, Ar = phenyl
50, 54, Ar =4-fluorophenyl
51, 55, Ar = 2-naphthalene
52, 56, Ar = 2, 4, 6-triisopropylphenyl

Reagents and conditions: (i) 5% or 10% Pd-C/H_2 at 50 psi, ethanol at r.t., 5 hrs; (ii) ditertiarybutyloxydicarbonate, Na_2CO_3 in water, THF, 0°C-r.t., 12-16 hrs; (iii) aryl sulfonyl chloride, Na_2CO_3, dry acetone, r.t., 12-16 hrs; (iv) 40% TFA in dichloromethane, -10 to 30°C, ½ hr.

Scheme 3: Synthesis of rigid analogues **61-63**



Reagents and conditions: (i) Nitroethane, acetic acid in excess, ammonium acetate, 110°C, 15 hrs; (ii) $FeCl_3$, HCl, water, ethanol, iron powder, ethanol, 110°C, 5 hrs. (iii) $NaCNBH_3$, acetic acid, methanol, r.t., 14-16 hrs; (iv) ethylbromoacetate, acetone, Na_2CO_3, 55°C; (v) NaOH, methanol, r.t., 14-16 hrs.