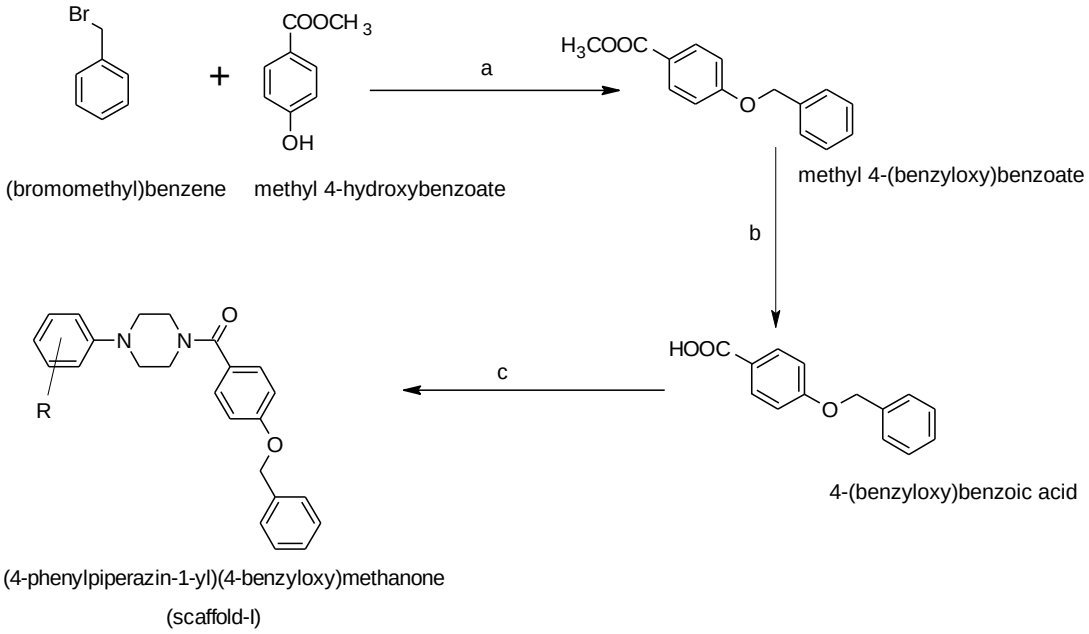
SYNTHESIS AND CHARACTERIZATION

4. Synthesis and Characterization

As has been mentioned in aims and objectives, it was decided to synthesize four series of compounds/seven scaffolds and the synthesized compounds were characterized by standard methods of spectroscopy after purification.

4.1. 4-(benzyloxy)phenyl](4-phenylpiperazin-1-yl)methanone derivatives (scaffold-I)

Synthesis: A data set of 12 compounds was prepared using the following scheme. Pharmacophoric distances were calculated and given in table 4.1



Scheme-1: Reagents and conditions: (a) K_2CO_3, $(CH_3)_2CO$, reflux, 6h; (b) NaOH, H_2O, CH_3OH, reflux, 3h; (c) HOBt, EDC.HCl, THF, TEA, substituted piperazines, 0^0 C, 12h.

Table 4.1: Pharmacophoric distances of 4-(benzyloxy)phenyl](4-phenylpiperazin-1-yl)methanone derivatives

Compound code	R	Distances in angstrom (Å)		
		BM-HA	HA-AM	BM-AM
A-1	2-Cl	6.51	3.71	9.97
A-2	4-Cl	6.48	3.81	9.95

A-3	2-F	6.50	3.83	9.37
A-4	4-F	6.46	3.78	9.92
A-5	2-NO_2	6.51	3.83	9.95
A-6	2-OCH_3	6.50	3.79	9.85
A-7	3-OCH_3	6.49	3.78	9.86
A-8	4-OCH_3	6.55	3.74	9.88
A-9	2,3-diCl	6.47	3.45	9.72
A-10	2-CH_3	6.48	3.55	9.72
A-11	3-CH_3	6.49	3.54	9.71
A-12	4-CH_3	6.42	3.51	9.78

Step-1: Synthesis of methyl 4-(benzyloxy) benzoate: 1 mole of benzyl bromide was dissolved in acetone. 2.5 moles of K_2CO_3 was added to it and stirred for 15 min. Later 1.5 moles of methyl 4-hydroxy benzoate was added and stirred at 55°C for 6 h. Solvent was evaporated to get methyl 4-(benzyloxy)benzoate as oily liquid.

Step-2: Synthesis of 4-(benzyloxy)benzoic acid: Methyl 4-(benzyloxy)benzoate was dissolved in mixture of methanol and 0.5 N aq. NaOH solution (1:1). Mixture was refluxed for 3 h and the hydrolysis was checked by thin layer chromatography. It was neutralized with 1 N HCl on an ice bath. Crystalline precipitate of 4-(benzyloxy)benzoic acid was obtained which was washed with ice cold water to remove excess acid present and dried.

Step-3: Synthesis of final amide product: 1.5 equivalents of synthesized carboxylic acid was dissolved in dichloromethane and to it was added 1.5 equivalents of hydroxy-O-benztriazole (HOBt) and *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbidiimide.HCl (EDC.HCl) and stirred for 15-20 min at ice cold condition. To this solution was added, triethylamine (TEA) and 1.5 equivalent of anilines drop wise. The reaction was run at ice cold condition till completion and worked up by evaporating dichloromethane. The mixture was washed with dil. HCl and sodium bicarbonate ($NaHCO_3$) to remove unreacted amine and acid. Finally extracted with ethyl acetate and the collected layer was evaporated to get solid product.

Spectral data of synthesized compounds:

Methyl 4-(benzyloxy)benzotae: Liquid, 80%,IR (KBr, cm^{-1}): 3058-2990 (Aromatic CH str) 2954-2888 (Aliphatic CH str), 1730 (-CO str) 1598-1460 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 2H), 7.41 (d, *J* = 6.7, 1.0 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.02 – 6.96 (m, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.94 (s, 3H).

4-(benzyloxy)benzoic acid: White solid, 70%, (mp: 188-190°C), IR (KBr, cm^{-1}), 3058-3000 (Aromatic CH str), 2954-2888 (Aliphatic CH str), 1700 (-CO str) 1597-1465 (Aromatic C-C str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.87 (m, 2H), 7.41 (dq, *J* = 6.7, 1.0 Hz, 2H), 7.38 – 7.36 (m, 2H), 7.36 – 7.27 (m, 1H), 7.03 – 6.97 (m, 2H), 5.01 (t, *J* = 0.9 Hz, 2H).

A-1: (4-(benzyloxy)phenyl)(4-(2-chlorophenyl)piperazin-1-yl)methanone: White solid, 52%, (mp: 144-146 °C) IR (KBr, cm^{-1}), 3057-2990 (Aromatic CH str), 2944-2901 (Aliphatic CH str), 1631 (-CO str), 1590-1464 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.63 – 3.57 (m, 4H), 3.20 – 3.13 (m, 4H), ESI MS: m/z = 408.1 $(M + 2\ H)^+$, 407.1 $(M + H)^+$.

A-2: [4-(benzyloxy)phenyl](4-4-chlorophennyllpiperazin-1-yl)methanone: White solid, 50%, (mp: 166-168 °C); IR (KBr, cm^{-1}), 3067-2989 (Aromatic CH str) 2954-2906 (Aliphatic CH str), 1631 (-CO str), 1596-1455 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.63 – 3.56 (m, 4H), 3.20 – 3.12 (m, 4H).

A-3: [4-(benzyloxy)phenyl](4-2-flurophennyllpiperazin-1-yl)methanone: Off white solid, 49%, (mp: 176-178 °C;, IR (KBr, cm^{-1}), 3055-3010 (Aromatic CH str), 2899-2868 (Aliphatic CH str), 1633 (-CO str), 1596-1459 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.08 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.63 – 3.57 (m, 4H), 3.21 – 3.14 (m, 4H).

A-4: [4-(benzyloxy)phenyl](4-4-flurophennyllpiperazin-1-yl)methanone: White solid, 50%, (mp: 186-188 °C); IR (KBr, cm^{-1}), 3035-2995 (Aromatic CH str), 2878, 2862 (Aliphatic CH str),

1631 (-CO str), 1599-1469 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.35 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.64 – 3.57 (m, 4H), 3.22 – 3.15 (m, 4H).

A-5: [4-(benzyloxy)phenyl](4-4-nitrophennyllpiperazin-1-yl)methanone: Yellow solid, 52%, (mp: 188-190 °C); IR (KBr, cm^{-1}), 3032-3005 (Aromatic CH str), 2869-2864 (Aliphatic CH str), 1612 (-CO str), 1589-1460 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.79 (m, 2H), 7.41 (dq, *J* = 7.5, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.53 (ddd, *J* = 7.9, 2.2, 1.1 Hz, 1H), 6.37 (t, *J* = 2.0 Hz, 1H), 6.27 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.78 (s, 3H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.31 – 3.17 (m, 4H).

A-6: [4-(benzyloxy)phenyl](4-2-methoxyphennyllpiperazin-1-yl)methanone: Off white solid, 56%, (mp: 170-172 °C); IR (KBr, cm^{-1}), 3030-2995 (Aromatic CH str), 2930-2865 (Aliphatic CH str), 1630 (-CO str), 1598-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.40 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.35 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.69 – 3.56 (m, 4H), 3.20 – 3.13 (m, 4H).

A-7: **[4-(benzyloxy)phenyl](4-3-methoxyphennyllpiperazin-1-yl)methanone:** White solid, 46%, (mp: 186-188 °C); IR (KBr, cm^{-1}), 3067-3000 (Aromatic CH str), 2934-2901 (Aliphatic CH str), 1625-1630 (-CO str), 1598-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.47 – 7.39 (m, 3H), 7.39 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 7.07 – 6.99 (m, 2H), 6.99 – 6.95 (m, 2H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.28 (dt, *J* = 11.9, 5.4 Hz, 2H), 3.19 (dt, *J* = 11.9, 5.4 Hz, 2H).

A-8: **[4-(benzyloxy)phenyl](4-4-methoxyphennyllpiperazin-1-yl)methanone:** Off white solid, 56%, (mp: 178-180 °C); IR (KBr, cm^{-1}), 3070-3010 (Aromatic CH str) 2910-2868 (Aliphatic CH str), 1627 (-CO str), 1595-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.79 (m, 1H), 7.44 – 7.27 (m, 3H), 7.07 – 7.01 (m, 1H), 7.01 – 6.95 (m, 1H), 6.89 – 6.83 (m, 1H), 5.01 (t, *J* = 0.9 Hz, 1H), 3.78 (s, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H); ESI MS: m/z = 403.1 $(M + H)^+$.

A-9: [4-(benzyloxy)phenyl](4-2,3-dichlorophennyllpiperazin-1-yl)methanone: Off white solid, 45%, (mp: 168-170 °C); IR (KBr, cm^{-1}), 3010 (Aromatic CH str), 2910-2866(Aliphatic CH str), 1628 (-CO str), 1595-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.80 (m, 3H), 7.44 – 7.38 (m, 3H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 4H), 7.23 – 7.14 (m, 3H), 7.01 – 6.95 (m, 3H), 6.89 (dd, *J* = 7.1, 2.0 Hz, 2H), 5.01 (t, *J* = 0.9 Hz, 3H), 3.60 (t, *J* = 5.3 Hz, 6H), 3.27 (dt, *J* = 11.9, 5.3 Hz, 3H), 3.18 (dt, *J* = 11.7, 5.3 Hz, 3H).

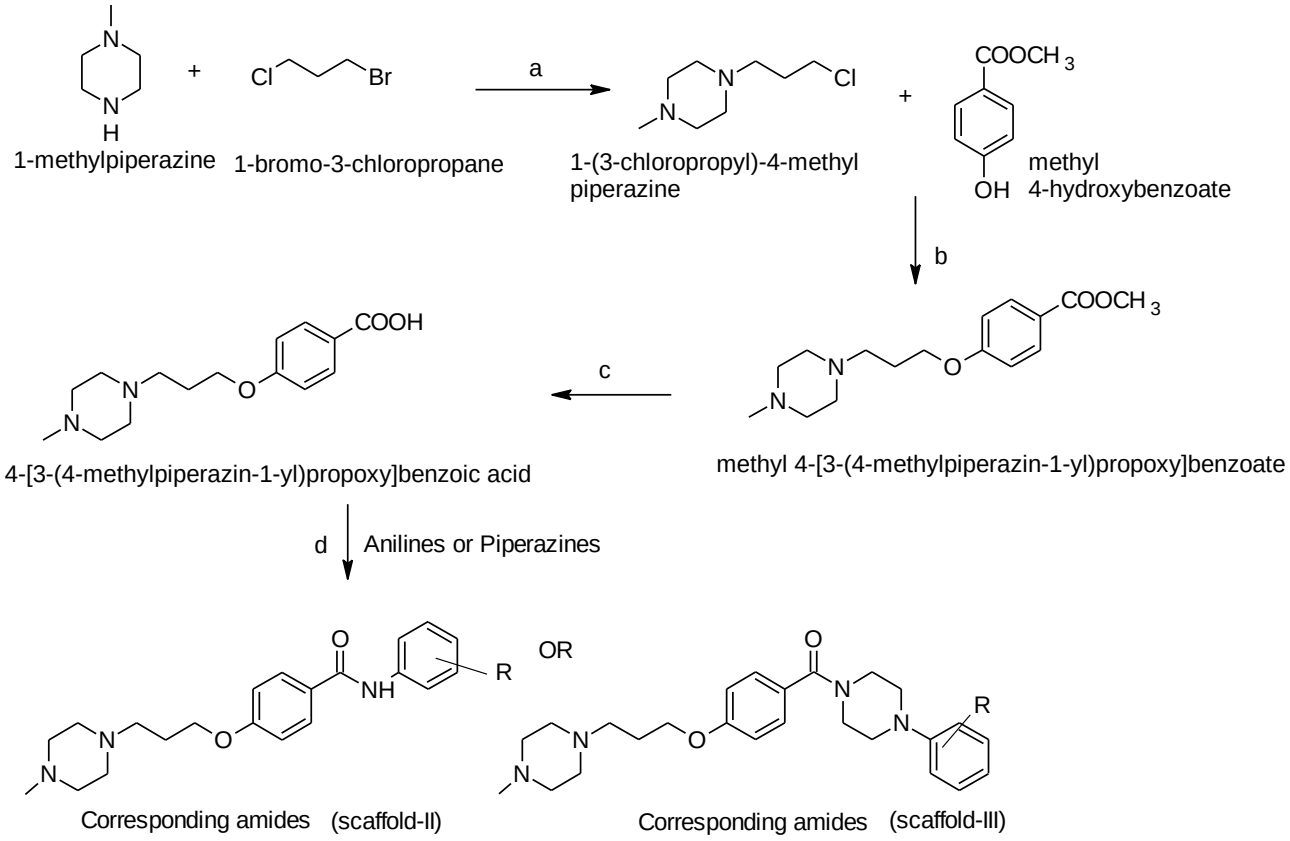
A-10: **[4-(benzyloxy)phenyl](4-2-methylphennyllpiperazin-1-yl)methanone:** Off white solid, 53%, (mp: 182-184 °C); IR (KBr, cm^{-1}), 3028-3000 (Aromatic CH str), 2910-2866 (Aliphatic CH str), 1633 (-CO str), 1592-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.63 – 3.57 (m, 4H), 3.20 – 3.13 (m, 4H), 2.29 (d, *J* = 0.7 Hz, 3H).

A-11: **[4-(benzyloxy)phenyl](4-3-methylphennyllpiperazin-1-yl)methanone:** Off white solid, 45%, (mp: 188-190 °C); IR (KBr, cm^{-1}), 3054-2990 (Aromatic CH str) 2889-2852 (Aliphatic CH str), 1631 (-CO str) 1590-1465 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.79 (m, 1H), 7.44 – 7.27 (m, 3H), 7.19 – 7.13 (m, 1H), 7.01 – 6.95 (m, 1H), 6.88 – 6.82 (m, 1H), 5.01 (t, *J* = 0.9 Hz, 1H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.33 (d, *J* = 0.9 Hz, 2H).

A-12: [(4-(benzyloxy)phenyl)(4-(p-tolyl)piperazin-1-yl)methanone;: Off white solid, 43%, (mp: 172-174 °C), IR (KBr, cm^{-1}), 3044 (Aromatic CH str) 2879-2855 (Aliphatic CH str), 1681 (-CO str), 1591-1468 (Aromatic CC str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 2H), 7.41 (dq, *J* = 7.4, 1.0 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.36 – 7.27 (m, 2H), 7.17 (ddt, *J* = 7.7, 1.4, 0.8 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.95 (m, 3H), 6.75 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.01 (t, *J* = 0.9 Hz, 2H), 3.63 – 3.57 (m, 4H), 3.20 – 3.13 (m, 4H), 2.29 (d, *J* = 0.7 Hz, 3H), ESI MS: m/z = 387.2 $(M + 1\ H)^+$.

4.2 4-(3-(4-methylpiperazin-1-yl)propoxy)-*N*-phenylbenzamide (scaffold-II) and (4-(3-methoxyphenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl)methanone derivatives (scaffold-III)

Synthesis: Sixteen compounds were synthesized using following scheme and pharmacophoric distances are reported in table 4.2



Scheme-2: Reagents and conditions: (a) K_2CO_3, $(CH_3)_2CO$, RT, 6h; (b) K_2CO_3, CH_3CN, Reflux, 6h; (c) NaOH, H_2O, CH_3OH, reflux, 3h; (d) HOBt, EDC.HCl, THF, TEA, substituted piperazines/anilines, 0°C, 12h.

Table 4.2: Pharmacophoric distances of synthesized compounds of scaffold-II and III

Compound code	R	Distances in angstrom (Å)			
		BM-HA	HA-AM	BM-AM	BM- IIAM
Aniline substituent's (scaffold-II)					
B-1	H	4.87	2.72	7.51	13.94
B-2	4-CH3	4.88	2.73	7.52	13.95
B-3	3-CH3	4.86	2.76	7.55	13.90
B-4	2,4 di-CH3	4.89	2.72	7.51	13.95
B-5	3,4 di-CH3	4.88	2.79	7.49	13.89
B-6	2,5 di-CH3	4.83	2.71	7.52	13.85
B-7	4-OCH3	4.90	2.72	7.55	13.81
B-8	4-Cl	4.88	2.71	7.54	13.89
B-9	4-Br	4.89	2.72	7.55	13.90
B-10	4-F	4.88	2.73	7.51	13.88
Piperazine substituent's (scaffold-III)					
B-11	3-OCH3	4.89	2.76	7.55	12.69
B-12	4-OCH3	4.90	2.76	7.56	12.68
B-13	2-Cl	4.89	2.75	7.52	12.68
B-14	4-Cl	4.88	2.76	7.51	12.70
B-15	2,3-diCl	4.87	2.77	7.53	12.72
B-16	4-CH3	4.89	2.77	7.55	12.72

Step-1: Synthesis of 1-(3-chloropropyl)-4-methylpiperazine

1 mole of *N*-Methyl piperazine was dissolved in acetone, to it 3 moles of potassium carbonate was added with constant stirring. After 30 min, 1.5 mole of 1-bromo-3-chloropropane was added in drop wise manner and stirred for 12 h at RT. Later, solvent was evaporated from the reaction mixture and transferred to separating funnel having water and ethyl acetate. Organic

layer was collected and evaporated to get crude residue of 1-(3-chloropropyl)-4-methylpiperazine as oily liquid.

Step-2: Synthesis of methyl 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoate

1 mole of 1-(3-chloropropyl)-4-methylpiperazine was dissolved in acetonitrile and 3 moles of potassium carbonate was added to it. 4-hydroxymethyl benzoate (1.5 mole) was added to the mixture and then refluxed for 7 h. Solvent was evaporated and water, ethyl acetate workup was done. Ethyl acetate layer was collected and washed with 0.1 N NaOH to remove unreacted 4-hydroxymethyl benzoate. Finally, organic layer was evaporated to get methyl 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoate as oily yellow liquid.

Step-3: Synthesis of 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoic acid: Methyl 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoate was dissolved in methanol and equal amount of 0.5 N NaOH was added to it and was refluxed for 3 h. Methanol was removed by vacuum distillation and reaction mixture was neutralized with excess 1 N HCl on an ice bath. Crystalline precipitate of 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoic acid was obtained and washed with ice cold water to remove excess HCl.

Step-4: Synthesis of final corresponding amide

To 1 equivalent of synthesized carboxylic acids dissolved in DCM, 1 equivalent of hydroxy-O-benztriazole (HOBt) and 1 mole *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbidiimide.HCl (EDC.HCl) were added. The mixture was stirred for 15-20 min at ice cold condition. To this solution, triethylamine (TEA) and 0.9 equivalents of anilines/piperazines was added. After completion of reaction, solvent was evaporated; workup was done by separating in water and ethyl acetate. Organic layer was collected and washed with dil. HCl and sodium biocarbonate ($NaHCO_3$). Finally, organic layer was collected and evaporated to get solid/liquid product.

Spectral data of synthesized compounds:

1-(3-chloropropyl)-4-methylpiperazine: Liquid, 80%, IR (KBr, cm^{-1}): 2954-2858 (Aliphatic-C-H str), 1355 (C-N str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.54 (t, *J* = 3.9 Hz, 2H), 2.61 – 2.50 (m, 8H), 2.90 – 2.570 (m, 2H), 2.32 (s, 3H), 1.98 (tt, *J* = 6.4, 4.0 Hz, 2H).

Methyl-4-[3-(4-methylpiperazin-1-yl)propoxy]benzoate: Liquid, 75%, IR (KBr, cm^{-1}): 3217-3004 (Aromatic CH str), 2954-2858 (Aliphatic CH str), 1750-1735 (-CO str), 1373 (-CN str); ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 2H), 7.05 – 6.99 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.94 (s, 3H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.58 – 2.50 (m, 8H), 2.32 (s, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

Methyl-4-[3-(4-methylpiperazin-1-yl)propoxy]benzoic acid: White solid, 70%, (mp: 180-184 °C), IR (KBr, cm^{-1}), 3210-3010 (Aromatic C-H str) 2954-2858 (Aliphatic-CH str), 1703 (-CO), 1373 (-CN str) 1280-1300 (CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 2H), 7.05 – 6.99 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.58 – 2.50 (m, 8H), 2.32 (s, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

B-1: 4-(3-(4-methylpiperazin-1-yl)propoxy)-*N*-phenylbenzamide: White solid, 55%, (mp: 134-136 °C); IR (KBr, cm^{-1}), 3344 (-NH str) 3010-2980 (Aromatic CH str), 2881-2852 (Aliphatic CH str), 1633 (-CO amide str) ; ^{1}H NMR (400 MHz, Chloroform-*d*), 8.04 – 7.98 (m, 2H), 7.73 – 7.67 (m, 2H), 7.36 – 7.29 (m, 2H), 7.09 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.54 (d, *J* = 1.2 Hz, 8H), 2.32 (s, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

B-2: 4-(3-(4-methylpiperazin-1-yl)propoxy)-*N*-(p-tolyl)benzamide: White solid, 58%, (138-140 °C); IR (KBr, cm^{-1}), 3350 (-NH str), 3005-2933 (Aromatic CH str), 2875-2792 (Aliphatic CH str), 1651 (CO str); ^{1}H NMR (400 MHz, Chloroform-*d*), 8.04 – 7.90 (m, 2H), 7.44 – 7.37 (m, 2H), 7.18 – 7.12 (m, 2H), 7.00 – 6.90 (m, 2H), 3.96 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.51 (m, 8H), 2.31 (d, *J* = 6.0 Hz, 6H), 1.86 (p, *J* = 6.2 Hz, 2H); ESI MS: m/z = 368.2 $(M + H)^+$

B-3: 4-(3-(4-methylpiperazin-1-yl)propoxy)-N-(m-tolyl)benzamide: Off white solid, 52%, (mp: 132-134 °C); IR (KBr, cm^{-1}), 3350 (-NH str) 3000-2931 (Aromatic CH str), 2875-2767 (Aliphatic CH str), 1643 (CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*), 8.03 – 7.91 (m, 2H), 7.50 (t, *J* = 1.9 Hz, 1H), 7.44 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.90 (m, 3H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.50 (m, 8H), 2.30 (s, 3H), 2.27 (d, *J* = 0.7 Hz, 3H), 1.81 (p, *J* = 6.2 Hz, 2H).

B-4: *N*-(2,4-dimethylphenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: White solid, 55%, (mp: 144-146 °C), IR (KBr, cm^{-1}), 3300 (-NH str), 3000-2931 (Aromatic CH str), 2875-2767 (Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*), 8.01 – 7.92 (m, 2H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.03 – 6.94 (m, 4H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.51 (m, 8H), 2.32 (s, 3H), 2.24 – 2.17 (m, 6H), 1.81 (p, *J* = 6.2 Hz, 2H).

B-5: *N*-(3,4-dimethylphenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: White solid, 58%, (mp: 138-140 °C); IR (KBr, cm^{-1}), 3300 (-NH str), 3010-2931 (Aromatic CH str), 2875-2767 (aliphatic CH str), 1645 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.55 – 7.45 (m, 2H), 7.06 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.50 (m, 8H), 2.32 (s, 3H), 2.21 – 2.17 (m, 6H), 1.86 (p, *J* = 6.2 Hz, 2H).

B-6: *N*-(2,5-dimethylphenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: Off white solid, 52%, (mp: 130-132 °C); IR (KBr, cm^{-1}), 3300 (-NH str), 3020-2931 (Aromatic CH str), 2875-2767 (Aliphatic CH str), 1644 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.98 (m, 2H), 7.51 (d, *J* = 2.1 Hz, 2H), 7.00 – 6.94 (m, 2H), 6.90 – 6.85 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.50 (m, 8H), 2.31 (s, 3H), 2.24 (s, 6H), 1.80 (p, *J* = 6.2 Hz, 2H); ESI MS: m/z = 382.2 $(M + H)^+$.

B-7: *N*-(4-methoxyphenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: White solid, 59%, (mp: 140-142 °C); IR (KBr, cm^{-1}), 3304 (-NH str), 3000-2931 (Aromatic CH str), 2866-2781 (Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.96 (m, 2H), 7.74 – 7.69 (m, 2H), 7.42 – 7.35 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.54 (d, *J* = 1.1 Hz, 8H), 2.32 (s, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

B-8: *N*-(4-chlorophenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamid: Brown solid, 57%, (mp: 146-148 °C); IR (KBr, cm^{-1}), 3300 (-NH str) 3012-2937 (Aromatic CH str), 2875-2791 (Aliphatic CH str), 1633 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ, 8.04 – 7.98 (m, 2H), 7.75 – 7.69 (m, 2H), 7.42 – 7.36 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.50 (d, *J* = 1.1 Hz, 8H), 2.32 (s, 3H), 1.89 (p, *J* = 6.2 Hz, 2H).

B-9: *N*-(4-bromophenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: Brown solid, 57%, (mp: 156-158 °C); IR (KBr, cm^{-1}), 3317 (-NH str), 3016-2937 (Aromatic CH str), 2855-2769 (Aliphatic CH str), 1645 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.69 – 7.63 (m, 2H), 7.53 – 7.47 (m, 2H), 7.00 – 6.92 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.53 (d, *J* = 1.1 Hz, 8H), 2.32 (s, 3H), 1.79 (p, *J* = 6.2 Hz, 2H).

B-10: *N*-(4-fluorophenyl)-4-(3-(4-methylpiperazin-1-yl)propoxy)benzamide: Off white solid, 52%, (mp: 142-144 °C); IR (KBr, cm^{-1}), 3300 (-NH str) 3000-2975 (Aromatic CH str), 2873-2791

(Aliphatic CH str), 1656 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ, 8.04 – 7.93 (m, 2H), 7.62 – 7.54 (m, 2H), 7.17 – 7.09 (m, 2H), 7.01 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.64 (t, *J* = 6.4 Hz, 2H), 2.54 (d, *J* = 1.1 Hz, 8H), 2.32 (s, 3H), 1.81 (p, *J* = 6.2 Hz, 2H).

B-11: (4-(3-methoxyphenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl) methanone: Brown solid, 45%, (mp: 166-168 °C); IR (KBr, cm^{-1}), 3050-2956 (Aromatic CH str), 2858-2762 (Aliphatic CH str), 1633 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.45 (ddd, *J* = 7.9, 2.0, 1.3 Hz, 1H), 6.27 (ddd, *J* = 7.9, 1.9, 1.2 Hz, 1H), 6.20 (t, *J* = 1.9 Hz, 1H), 3.98 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 3.61 (t, *J* = 5.3 Hz, 4H), 3.36 – 3.17 (m, 4H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.50 (m, 8H), 2.30 (s, 3H), 1.82 (p, *J* = 6.2 Hz, 2H).

B-12: (4-(4-methoxyphenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl) methanone: White solid, 45%, (mp: 160-162 °C); IR (KBr, cm^{-1}) 3012-2958 (Aromatic CH str), 2868-2762 (Aliphatic CH str), 1633 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.77 (m, 1H), 7.07 – 7.01 (m, 1H), 7.00 – 6.94 (m, 1H), 6.89 – 6.83 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.61 (t, *J* = 6.3 Hz, 1H), 2.54 (d, *J* = 1.1 Hz, 4H), 2.31 (s, 2H), 1.82 (p, *J* = 6.2 Hz, 1H). ESI MS: m/z = 453.2 $(M + 1 H)^+$.

B-13: (4-(2-chlorophenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl) methanone: Off white solid, 49%, (mp: 168-170 °C); IR (KBr, cm^{-1}), 3010-2954 (Aromatic CH str), 2900-2810 (Aliphatic CH str), 1631 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.27 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.04 (td, *J* = 7.6, 1.5 Hz, 1H), 7.00 – 6.93 (m, 3H), 6.77 (td, *J* = 7.6, 1.6 Hz, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.27 (dt, *J* = 11.9, 5.3 Hz, 2H), 3.18 (dt, *J* = 11.9, 5.3 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.57 – 2.50 (m, 8H), 2.36 (s, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

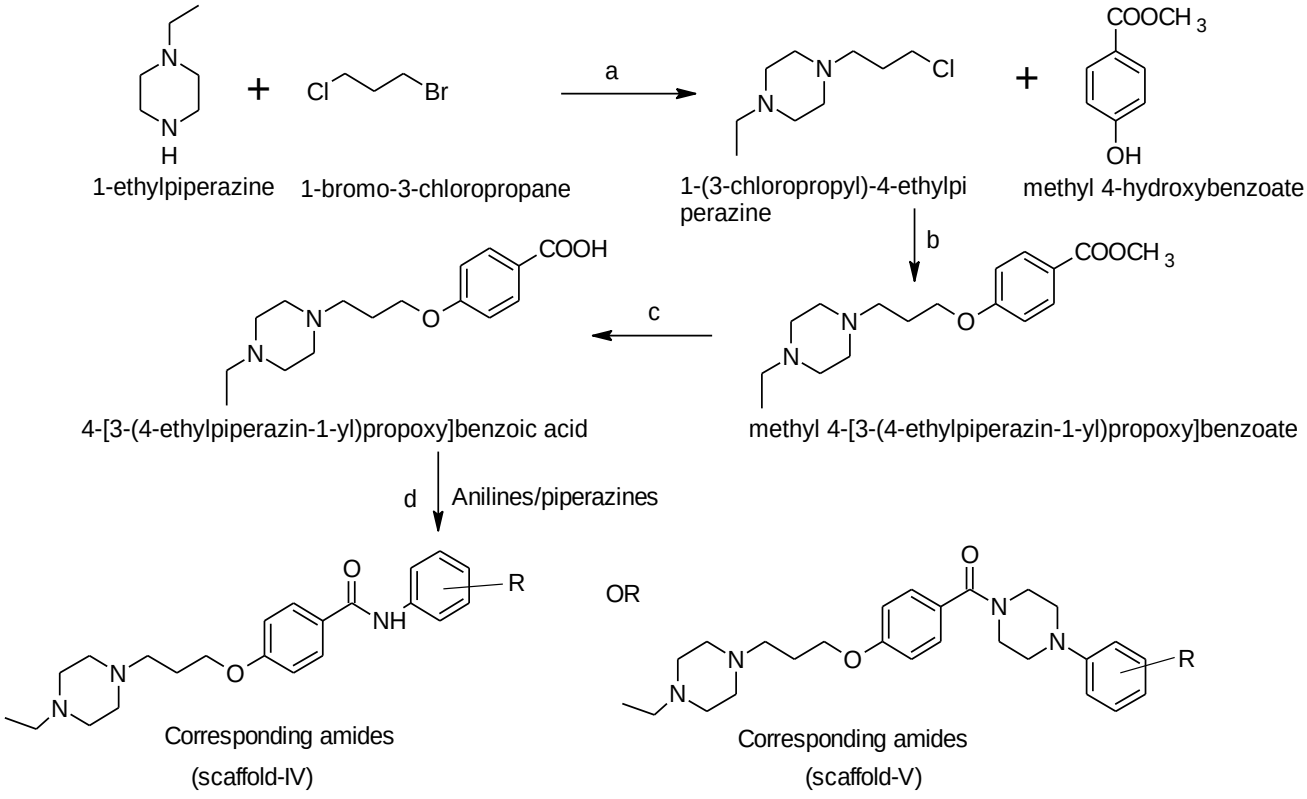
B-14: (4-(4-chlorophenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl) methanone: Off white solid, 46%, (mp: 174-176 °C); IR (KBr, cm^{-1}) 3000-2954 (Aromatic CH str), 2900-2810 (Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.78 (m, 1H), 7.26 – 7.20 (m, 1H), 7.00 – 6.94 (m, 1H), 6.77 – 6.73 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.27 – 3.15 (m, 2H), 2.61 (t, *J* = 6.4 Hz, 1H), 2.54 (d, *J* = 1.1 Hz, 4H), 2.32 (s, 2H), 1.83 (p, *J* = 6.2 Hz, 1H), ESI MS: m/z = 458.2 $(M + 2 H)^+$, 457.2 $(M + H)^+$.

B-15: (4-(2,3-dichlorophenyl)piperazin-1-yl)(4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl) methanone: Off white solid, 41%, (mp: 156-158 °C); IR (KBr, cm^{-1}), 3061-2904 (Aromatic CH str), 2870-2787 (Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.23 – 7.14 (m, 2H), 7.00 – 6.92 (m, 2H), 6.89 (dd, *J* = 7.1, 2.0 Hz, 1H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.61 (t, *J* = 5.3 Hz, 4H), 3.27 (dt, *J* = 11.9, 5.3 Hz, 2H), 3.18 (dt, *J* = 11.7, 5.3 Hz, 2H), 2.60 (t, *J* = 6.4 Hz, 2H), 2.54 – 2.50 (m, 8H), 2.32 (s, 3H), 1.81 (p, *J* = 6.2 Hz, 2H).

B-16: (4-(3-(4-methylpiperazin-1-yl)propoxy)phenyl)(4-(p-tolyl)piperazin-1-yl) methanone: White solid, 42%, (mp: 196-198 °C); IR (KBr, cm^{-1}) 3000-2950 (Aromatic CH str), 2880-2778 (Aliphatic CH str), 1630 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 1H), 7.19 – 7.12 (m, 1H), 7.00 – 6.94 (m, 1H), 6.82 – 6.76 (m, 1H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.27 – 3.14 (m, 2H), 2.61 (t, *J* = 6.4 Hz, 1H), 2.57 – 2.50 (m, 4H), 2.32 (d, *J* = 6.0 Hz, 3H), 1.83 (p, *J* = 6.2 Hz, 1H).

4.3 4-(3-(4-ethylpiperazin-1-yl)propoxy)-N-phenylbenzamide (scaffold-IV) and (4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl)(4-(2-methoxyphenyl)piperazin-1-yl)methanone derivatives (scaffold-V)

Synthesis: Sixteen compounds were synthesized using following scheme and pharmacophoric distances are reported in table 4.3.



Scheme-3: Reagents and conditions: (a) K_2CO_3, $(CH_3)_2CO$, RT, 6h; (b) K_2CO_3, CH_3CN, Reflux, 6h; (c) NaOH, H_2O, CH_3OH, reflux, 3h; (d) HOBt, EDC.HCl, THF, TEA, substituted anilines/piperazines, 0^0C, 12h.

Table 4.3: Pharmacophoric distances of synthesized compounds of scaffold IV and V.

Compound code	R	Distances in angstrom (Å)			
		BM-HA	HA-AM	BM-AM	BM- IIAM
Aniline substituent's (scaffold-IV)					
C-1	H	4.88	2.71	7.52	13.94
C-2	4-CH3	4.87	2.73	7.51	13.94
C-3	3-CH3	4.88	2.75	7.54	13.92
C-4	2,4 di-CH3	4.87	2.71	7.52	13.95
C-5	3,4 di-CH3	4.89	2.78	7.48	13.90
C-6	2,5 di-CH3	4.86	2.72	7.51	13.91
C-7	4-OCH3	4.91	2.73	7.54	13.85
C-8	4-Cl	4.87	2.72	7.54	13.88
C-9	4-Br	4.88	2.72	7.54	13.92
C-10	4-F	4.88	2.73	7.53	13.89
Piperazine substituent's (scaffold-V)					
C-11	2-OCH3	4.89	2.76	7.55	12.69
C-12	4-OCH3	4.90	2.76	7.56	12.68
C-13	2-Cl	4.89	2.75	7.52	12.68
C-14	4-Cl	4.88	2.76	7.51	12.70
C-15	2,3-diCl	4.87	2.77	7.53	12.72
C-16	4-CH3	4.89	2.77	7.55	12.72

Step-1: Synthesis of 1-(3-chloropropyl)-4-methylpiperazine

1 mole of 1-ethyl piperazine was dissolved in acetone and to it 3 moles of potassium carbonate was added with constant stirring. After 30 min, 1.5 mole of 1-bromo-3-chloropropane was added in drop wise manner and stirred for 12 h at RT. Later, solvent was evaporated from the

reaction mixture and transferred to separating funnel having water and ethyl acetate. Organic layer was collected and evaporated to get 1-(3-chloropropyl)-4-ethylpiperazine as oily liquid.

Step-2: Synthesis of methyl 4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoate

1 mole of 1-(3-chloropropyl)-4-ethylpiperazine was dissolved in acetonitrile and to it 3.0 moles of potassium carbonate was added. 1.5 moles of 4-hydroxymethyl benzoate was added to the mixture and then refluxed for 7 h. Solvent was evaporated and water, ethyl acetate workup was done. Later ethyl acetate layer was collected and washed with 0.1N NaOH to remove unreacted 4-hydroxymethyl benzoate. Finally, organic layer was evaporated to get methyl 4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoate as oily yellow liquid.

Step-3: Synthesis of 4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoic acid: Methyl 4-[3-(4-methylpiperazin-1-yl)propoxy]benzoate was dissolved in methanol and equal amount of 0.5 N NaOH solution was added and was refluxed for 3 h. Methanol was removed by vacuum distillation and reaction mixture was neutralized with excess 1 N HCl on an ice bath. Crystalline precipitate of 4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoic acid was obtained and was washed with ice cold water to remove excess HCl.

Step-4: Synthesis of final corresponding amide

To 1 equivalent of synthesized carboxylic acid was added, 1 equivalent of hydroxy-O-benztriazole (HOBt) and 1 mole *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbidiimide.HCl (EDC.HCl) and stirred for 15-20 min at ice cold condition. To this solution, triethylamine (TEA) and 0.9 equivalents of anilines/piperazines were added. Solvent was evaporated; workup was done by separating in water and ethyl acetate. Organic layer was collected and washed with dil. HCl and sodium biocarbonate ($NaHCO_3$). Finally, organic layer was collected and evaporated to get solid/liquid product.

Spectral data of synthesized compounds

1-(3-chloropropyl)-4-ethylpiperazine: Oily liquid, 85%, IR (KBr, cm^{-1}), 2954-2858 (Aliphatic CH str), 1350-1365 (-CN str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.54 (t, *J* = 4.0 Hz, 2H), 3.16 – 3.06 (m, 2H), 3.10 – 2.99 (m, 2H), 2.63 – 2.54 (m, 8H), 1.94 (tt, *J* = 6.3, 4.0 Hz, 2H), 1.08 – 1.01 (m, 3H).

Ethyl 4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoate: Oily liquid, 85%, IR (KBr, cm^{-1}), 3017-2985 (Aromatic CH str), 2954-2858 (Aliphatic CH str), 1732 (-CO, ester str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 2H), 7.05 – 6.99 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.94 (s, 2H), 3.15 – 3.00 (m, 3H), 2.64 – 2.54 (m, 8H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

4-[3-(4-ethylpiperazin-1-yl)propoxy]benzoic acid: Off white solid, 70%, (mp: 186-188 °C); IR (KBr, cm^{-1}), 3217-3000 (Aromatic CH str), 2954-2858 (Aliphatic CH str), 1707 (-CO Acid str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.86 (m, 2H), 7.11 – 7.05 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 1H), 2.64 – 2.54 (m, 8H), 2.51 (t, *J* = 7.2 Hz, 1H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-1: 4-(3-(4-ethylpiperazin-1-yl)propoxy)-*N*-phenylbenzamide: Off white solid, 55%, (mp: 142-146 °C); IR (KBr, cm^{-1}), 3317 (-NH str), 3050-2945 (Aromatic CH str), 2875-2785 (Aliphatic CH str), 1645 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.73 – 7.67 (m, 2H), 7.36 – 7.29 (m, 2H), 7.09 (tt, *J* = 7.0, 1.2 Hz, 1H), 7.00 – 6.95 (m, 2H), 3.98 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.01 (m, 4H), 2.64 – 2.48 (m, 8H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-2: 4-(3-(4-ethylpiperazin-1-yl)propoxy)-*N*-(*p*-tolyl)benzamide: Off white solid, 59%, (mp: 162-164 °C); IR (KBr, cm^{-1}), 3354 (-NH str), 3021-2947 (Aromatic CH str), 2872-2767 (Aliphatic CH str), 1658 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.45 – 7.38 (m, 2H), 7.15 (dq, *J* = 7.9, 0.8 Hz, 2H), 7.00 – 6.94 (m, 2H), 3.98 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.00 (m, 4H), 2.65 – 2.48 (m, 8H), 2.33 (d, *J* = 0.8 Hz, 3H), 1.84 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H); ESI MS: m/z = 342.2 $(M + H)^+$.

C-3: 4-(3-(4-ethylpiperazin-1-yl)propoxy)-*N*-(*m*-tolyl)benzamide: Off white solid**,** 52%, (mp: 152-154 °C); IR (KBr, cm^{-1}), 3354 (-NH str), 3000-2947 (Aromatic CH str), 2872-2767 (Aliphatic CH str), 1658 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ, 8.04 – 7.98 (m, 2H), 7.53 (t, *J* = 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.89 (m, 3H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.00 (m, 4H), 2.64 – 2.48 (m, 8H), 2.27 (d, *J* = 0.7 Hz, 3H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-4: *N*-(2,4-dimethylphenyl)-4-(3-(4-ethylpiperazin-1-yl)propoxy)benzamide: White solid, 55%, (mp: 158-160 °C); IR (KBr, cm^{-1}) 3317 (-NH str), 3050-2966 (Aromatic CH str), 2873-2769

(Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 8.04 – 7.98 (m, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.03 – 6.94 (m, 4H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.00 (m, 4H), 2.65 – 2.48 (m, 8H), 2.24 – 2.17 (m, 6H), 1.84 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-5: *N*-(3,4-dimethylphenyl)-4-(3-(4-ethylpiperazin-1-yl)propoxy)benzamide: Off white solid**,** 51%, (mp: 134-136 °C); IR (KBr, cm^{-1}), 3309 (-NH str), 3010-2945 (Aromatic CH str), 2872-2771 (Aliphatic CH str), 1643 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.92 (s, 1H), 7.55 – 7.45 (m, 2H), 7.06 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.60 – 2.54 (m, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.22 – 2.17 (m, 6H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-6: *N*-(2,5-dimethylphenyl)-4-(3-(4-ethylpiperazin-1-yl)propoxy)benzamide: Creamy white solid, 59%, (mp: 144-146 °C); IR (KBr, cm^{-1}), 3304 (-NH str), 3000-2945 (Aromatic CH str), 2802-2777 (Aliphatic CH str), 1637 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 8.04 – 7.98 (m, 2H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.10 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.93 – 6.86 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.00 (m, 4H), 2.65 – 2.48 (m, 8H), 2.34 (d, *J* = 1.0 Hz, 3H), 2.28 (d, *J* = 0.8 Hz, 3H), 1.85 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-7: 4-(3-(4-ethylpiperazin-1-yl)propoxy)-*N*-(4-methoxyphenyl)benzamide: Creamy white solid, 52%, (mp: 138-142 °C); IR (KBr, cm^{-1}), 3317 (-NH str), 3000-2943 (Aromatic CH str), 2875-2771 (Aliphatic CH str), 1637 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.04 – 7.98 (m, 2H), 7.61 – 7.54 (m, 2H), 7.00 – 6.94 (m, 2H), 6.94 – 6.88 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 2.64 – 2.54 (m, 6H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H); ESI MS: m/z = 398.2 $(M + H)^+$

C-8: *N*-(4-chlorophenyl)-4-(3-(4-ethylpiperazin-1-yl)propoxy)benzamide: White solid, 59%, (mp: 144-148 °C); IR (KBr, cm^{-1}), 3313 (-NH str), 3030-2945 (Aromatic CH str), 2875-2765 (Aliphatic CH str), 1645.28 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.04 – 7.98 (m, 2H), 7.75 – 7.69 (m, 2H), 7.42 – 7.36 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 5.3 Hz, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-9: *N*-(4-bromophenyl)-4-(3-(4-ethylpiperazin-1-yl)propoxy)benzamide: White solid, 49%, (mp: 154-156 °C); IR (KBr, cm^{-1}), 3332 (-NH str), 3000-2950 (aromatic CH str), 2873-2771

(Aliphatic CH str), 1651 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.04 – 7.98 (m, 2H), 7.69 – 7.63 (m, 2H), 7.53 – 7.47 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 2.62 (t, *J* = 6.4 Hz, 2H), 2.59 – 2.54 (m, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-10: 4-(3-(4-ethylpiperazin-1-yl)propoxy)-*N*-(4-fluorophenyl)benzamide: White solid, 55%, (mp: 146-148 °C); IR (KBr, cm^{-1}), 3325 (-NH str), 2999-2945 (Aromatic CH str), 2873-2773 (Aliphatic CH str), 1645 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.04 – 7.98 (m, 2H), 7.62 – 7.55 (m, 2H), 7.17 – 7.09 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.15 – 3.06 (m, 2H), 3.06 – 3.00 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 5.3 Hz, 4H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

C-11: (4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl)(4-(2-methoxyphenyl)piperazin-1-yl) methanone: White solid, 45%, (mp: 162-164 °C); IR (KBr, cm^{-1}) 2990-2945 (Aromatic CH str), 2873-2767 (Aliphatic CH str), 1631 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 1H), 7.07 – 7.01 (m, 1H), 7.00 – 6.94 (m, 1H), 6.89 – 6.83 (m, 1H), 3.98 (t, *J* = 6.1 Hz, 1H), 3.78 (s, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 3.15 – 3.06 (m, 1H), 3.06 – 3.00 (m, 1H), 2.64 – 2.54 (m, 3H), 2.51 (t, *J* = 7.2 Hz, 1H), 1.84 (p, *J* = 6.2 Hz, 1H), 1.07 – 1.02 (m, 2H).

C-12: (4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl)(4-(4-methoxyphenyl)piperazin-1-yl) methanone: Off white solid, 41%, (mp: 178-180 °C); IR (KBr, cm^{-1}), 2988-2945 (Aromatic CH str), 2875-2767 (Aliphatic CH str), 1638 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 1H), 7.07 – 7.01 (m, 1H), 7.00 – 6.94 (m, 1H), 6.89 – 6.83 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (s, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 3.15 – 3.06 (m, 1H), 3.06 – 3.00 (m, 1H), 2.64 – 2.54 (m, 3H), 2.51 (t, *J* = 7.2 Hz, 1H), 1.83 (p, *J* = 6.2 Hz, 1H), 1.08 – 1.01 (m, 2H); ESI MS: m/z = 467.2 $(M + H)^+$

C-13: (4-(2-chlorophenyl)piperazin-1-yl)(4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl) methanone: Off white solid, 49%, (mp: 182-184 °C); IR (KBr, cm^{-1}), 3000-2956 (Aromatic CH str), 2875-2775 (Aliphatic CH str), 1633 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 2H), 7.27 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.04 (td, *J* = 7.6, 1.5 Hz, 1H), 7.00 – 6.93 (m, 3H), 6.77 (td, *J* = 7.6, 1.6 Hz, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.27 (dt, *J* = 11.9, 5.4

Hz, 2H), 3.18 (dt, *J* = 11.9, 5.3 Hz, 2H), 3.13 – 3.00 (m, 4H), 2.64 – 2.54 (m, 6H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H), 1.08 – 1.01 (m, 3H).

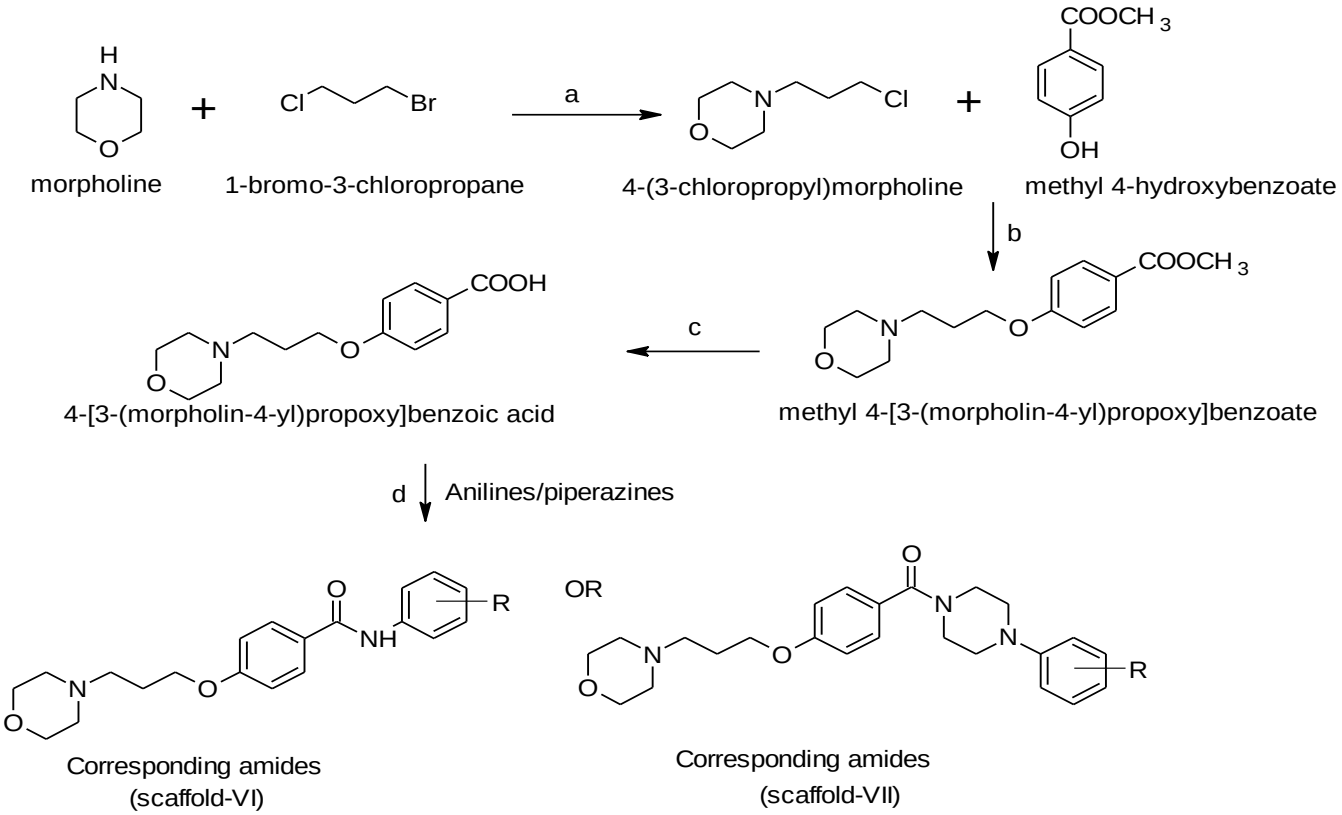
C-14: (4-(4-chlorophenyl)piperazin-1-yl)(4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl) methanone: Brown solid, 48%, (mp: 170-172 °C); IR (KBr, cm^{-1}), 2965-2945 (Aromatic CH str), 2875-2767 (Aliphatic CH str), 1631 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 1H), 7.26 – 7.20 (m, 1H), 7.00 – 6.95 (m, 1H), 6.79 – 6.73 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 3.15 – 3.06 (m, 1H), 3.06 – 3.00 (m, 1H), 2.64 – 2.54 (m, 3H), 2.51 (t, *J* = 7.2 Hz, 1H), 1.83 (p, *J* = 6.2 Hz, 1H), 1.08 – 1.01 (m, 2H); ESI MS: m/z = 472.2 $(M + 2 H)^+$,471.2 $(M + 1 H)^+$.

C-15: (4-(2,3-dichlorophenyl)piperazin-1-yl)(4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl) methanone: White solid, 40%, (mp: 174-176°C); IR (KBr, cm^{-1}), 2985-2945 (Aromatic CH str), 2865-2757 (Aliphatic CH str), 1621 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 6H), 7.23 (d, *J* = 2.1 Hz, 3H), 7.03 (dd, *J* = 8.4, 2.0 Hz, 3H), 7.00 – 6.94 (m, 6H), 6.72 (d, *J* = 8.4 Hz, 3H), 3.98 (t, *J* = 6.1 Hz, 6H), 3.60 (t, *J* = 5.3 Hz, 12H), 3.27 (dt, *J* = 11.9, 5.4 Hz, 6H), 3.18 (dt, *J* = 11.9, 5.3 Hz, 6H), 3.13 – 3.00 (m, 12H), 2.60 (dd, *J* = 12.4, 6.1 Hz, 9H), 2.57 – 2.51 (m, 13H), 2.50 (s, 1H), 1.82 (p, *J* = 6.2 Hz, 6H), 1.08 – 1.01 (m, 9H).

C-16: (4-(3-(4-ethylpiperazin-1-yl)propoxy)phenyl)(4-(p-tolyl)piperazin-1-yl)methanone: Off white solid, 50%, (mp: 168-170 °C); IR (KBr, cm^{-1}), 3020-2945 (Aromatic CH str), 2873-2792(Aliphatic CH str), 1633 (-CO amide str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.78 (m, 1H), 7.19 – 7.13 (m, 1H), 7.00 – 6.94 (m, 1H), 6.84 – 6.78 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.27 – 3.15 (m, 2H), 3.14 – 3.00 (m, 2H), 2.62 – 2.54 (m, 3H), 2.51 (t, *J* = 7.2 Hz, 1H), 2.33 (d, *J* = 0.8 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 1H), 1.08 – 1.01 (m, 2H).

4.4 4-[3-(morpholin-4-yl)propoxy]-*N*-phenylbenzamide derivative (scaffold-VI) and (4-(2-methoxyphenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone derivatives (scaffold-VII)

Synthesis: Twenty compounds were synthesized using following scheme and pharmacophoric distances are reported in table 4.4



Scheme 4: Reagents and conditions: (a) K_2CO_3, $(CH_3)_2CO$, RT, 6h; (b) K_2CO_3, CH_3CN, Reflux, 6h; (c) NaOH, H_2O, CH_3OH, reflux, 3h; (d) HOBt, EDC.HCl, THF, TEA, substituted piperazines/anilines, 0^0C, 12h.

Table 4.4 : Pharmacophoric distances of synthesized compounds of scaffold VI and VII

Compound code	R	Distances in angstrom (Å)			
		BM-HA	HA-AM	BM-AM	BM- IIAM
Aniline substituent's (scaffold-VI)					
D-1	H	4.86	2.73	7.47	13.90
D-2	4-CH3	4.89	2.72	7.46	13.96
D-3	3-CH3	4.88	2.72	7.47	13.95
D-4	2,4 di-CH3	4.90	2.74	7.48	13.94
D-5	3,4 di-CH3	4.89	2.72	7.51	13.85
D-6	2,5 di-CH3	4.87	2.73	7.52	13.86
D-7	4-OCH3	4.86	2.72	7.51	13.90
D-8	4-Cl	4.85	2.71	7.56	13.91
D-9	4-Br	4.89	2.71	7.54	13.96
D-10	4-F	4.80	2.72	7.52	13.91
D-11	2-Cl	4.80	2.72	7.50	13.99
Piperazine substituent's (scaffold-VII)					
D-12	2-OCH3	4.90	2.72	7.52	12.63
D-13	3-OCH3	4.91	2.71	7.50	12.68
D-14	4-OCH3	4.93	2.72	7.49	12.65
D-15	2-Cl	4.90	2.73	7.48	12.68
D-16	4-Cl	4.91	2.72	7.48	12.69
D-17	2,4-diCl	4.90	2.72	7.49	12.67
C-18	2-F	4.89	2.71	7.48	12.68
D-19	4-CH3	4.88	2.72	7.48	12.69
D-20	4-NO2	4.90	2.72	7.48	12.70

Step-1: Synthesis of 4-(3-chloropropylmorpholine)

Morpholine 1 mole was dissolved in acetone and to it 3 moles of potassium carbonate was added with constant stirring. After 30 min, 1.5 mole of 1-bromo-3-chloropropane was added in drop wise manner and stirred for 12 h at RT. Later, solvent was evaporated from the reaction mixture and transferred to separating funnel having water and ethyl acetate. Organic layer was collected and evaporated to get 4-(3-chloropropyl)morpholine as oily liquid.

Step-2: Synthesis of methyl 4-[3-(morpholin-4-yl)propoxy]benzoate

1 mole of 4-(3-chloropropyl)morpholine was dissolved in acetonitrile and to it 3 moles of potassium carbonate was added. To it, 1.5 moles of 4-hydroxymethyl benzoate was added and the mixture was refluxed for 7 h. Solvent was evaporated and mixture was transferred to water, ethyl acetate containing separating funnel. Ethyl acetate layer was collected and washed with 0.1 N NaOH to remove unreacted 4-hydroxymethyl benzoate. Finally, organic layer was evaporated to get methyl 4-[3-(morpholin-4-yl)propoxy]benzoate as oily yellow liquid.

Step-3: Synthesis of 4-[3-(morpholin-4-yl)propoxy]benzoic acid

1 mole of methyl 4-[3-(morpholin-4-yl)propoxy]benzoate was dissolved in methanol and equal amount of 0.5 N NaOH solution was added to the mixture and was refluxed for 3 h. Methanol was removed by vacuum distillation and reaction mixture was neutralized with excess 1 N HCl on an ice bath. Crystalline precipitate of 4-[3-(morpholin-4-yl)propoxy]benzoic acid was obtained and was washed with ice cold water to remove excess HCl.

Step-4: Synthesis of final amide product

1 equivalent of synthesized carboxylic acids was dissolved in dichloromethane and to it was added, 1 equivalent of hydroxy-O-benztriazole (HOBt) and 1 mole *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbidiimide.HCl (EDC.HCl) and stirred for 15-20 min at ice cold condition. To this solution, triethylamine (TEA) and 0.9 equivalent of anilines/piperazines were added in drop wise manner. After 3-10 h solvent was evaporated, workup was done; organic layer was collected and washed with dil. HCl and sodium biocarbonate ($NaHCO_3$). Finally, organic layer was collected and evaporated to get solid/liquid product.

Spectral data of synthesized compounds

4-(3-chloropropyl)morpholine: Yellow liquid, 85%, IR (KBr, cm^{-1}), 2954-2858 (Aliphatic CH str), 1373 (-CN str), 1255-1120 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ1.92, (2H), 2.41 (4H); 2.45, (2H, NCH_2), 3.6 (2H, $ClCH_2$), 3.8 (4H, OCH_2).

4-[3-(morpholin-4-yl)propoxy]benzoate: Oily liquid 70%, IR (KBr, cm^{-1}), 3217 (Aromatic CH str), 2954-2858 (Aliphatic CH str), 1750-1735 (-CO str), 1373 (-CN str), 1255-1120 (-C-O, ether str); ^{1}H NMR (400 MHz, Chloroform) δ 7.71 (d, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 4.00 – 3.92 (m, 5H), 3.78 (t, *J* = 4.7 Hz, 4H), 2.72 (t, *J* = 4.7 Hz, 2H), 2.47 (dt, *J* = 15.4, 6.2 Hz, 4H), 1.94 – 1.87 (m, 2H).

4-[3-(morpholin-4-yl)propoxy]benzoic acid: White solid 82% IR (KBr, cm^{-1}), (mp: 182-184 °C); 3217-3050 (Aromatic C-H str), 2954-2858 (Aliphatic CH str), 3000-2700, (OH stretch acid), 1760-1720 (-CO str), 1373 (-C-N str), 1255-1120 (-CO ether str); 1H NMR (400 MHz, Chloroform) δ 8.06 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.5 Hz, 1H), 3.96 (t, J = 7.7 Hz, 1H), 3.78 (t, J = 4.7 Hz, 2H), 2.72 (t, J = 4.7 Hz, 1H), 2.50 (t, J = 4.7 Hz, 1H), 2.44 (t, J = 7.7 Hz, 1H), 1.90 (p, J = 7.7 Hz, 1H)

D-1: 4-(3-morpholinopropoxy)-*N*-phenylbenzamide: Off white solid, 60%, (mp: 132-134°C), IR (KBr, cm^{-1}) 3317 (-NH str), 3010-2953 (Aromatic CH str), 2881-2852 (Aliphatic CH str), 1645 -(CO str) 1373 (-CN str), 1255-1120 (-C-O, ether str); ^{1}H NMR (400 MHz, Chloroform) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 12.1, 9.6 Hz, 5H), 7.13 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 3.97 (t, *J* = 7.7 Hz, 2H), 3.78 (t, *J* = 4.7 Hz, 4H), 2.72 (t, *J* = 4.8 Hz, 2H), 2.48 (dt, *J* = 15.4, 6.2 Hz, 4H), 1.94 – 1.87 (m, 2H). ESI MS: m/z = 341.1 $(M + H)^+$.

D-2: 4-(3-morpholinopropoxy)-*N*-(*p*-tolyl)benzamide: off white solid, 55%, (mp: 120-122°C), IR (KBr, cm-1), 3318 (-NH str), 3015-2953 (Aromatic CH str), 2881-2852 (Aliphatic CH str), 1648 (-CO str), 1373 (-CN str), 1255 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.42 (s, 1H), 7.38 (t, *J* = 1.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 16.9, 7.4 Hz, 3H), 4.01 (t, *J* = 4.8 Hz, 2H), 3.78 (t, *J* = 4.8 Hz, 4H), 2.72 (t, *J* = 4.8 Hz, 2H), 2.57 – 2.48 (m, 4H), 2.37 (s, 3H), 1.90 (tt, *J* = 7.7, 4.8 Hz, 2H).ESI MS: m/z = 355.1 $(M + H)^+$

D-3: 4-(3-morpholinopropoxy)-*N*-(*m*-tolyl)benzamide: White solid, 61%, (mp-111-113°C) IR (KBr, cm^{-1}) 3318 (-NH stretch) 2953 (-CH Aromatic str), 2881-2852 (-CH Alkyl str), 1645 (CO amide str), 1373 (-C-N str), 1255 (-C-O, ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s,

1H), 8.04 – 7.98 (m, 2H), 7.53 (t, *J* = 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.89 (m, 3H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.49 (tq, *J* = 12.6, 6.4 Hz, 4H), 2.27 (d, *J* = 0.7 Hz, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-4: *N*-(2,4-dimethylphenyl)-4-(3-morpholinopropoxy)benzamide: Light yellow solid, 65%, (mp:136-140 °C); IR (KBr, cm^{-1}), 3323 (-NH str), 3045-2951 (Aromatic CH str), 2881-2771 (Aliphatic CH str), 1651 (-CO str), 1373 (-CN str), 1255-1125 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.03 – 6.94 (m, 4H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 2.24 – 2.17 (m, 6H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-5: *N*-(3,4-dimethylphenyl)-4-(3-morpholinopropoxy)benzamide: Creamy white solid, 55% (mp:126-128 °C), IR (KBr, cm^{-1}), 3382 (-NH str) 3020-2949 (aromatic CH str), 2881-2771 (Aliphatic CH str), 1641 (-CO str), 1373 (-CN str), 1250-1110 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ, 8.04 – 7.98 (m, 2H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.10 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.92 – 6.86 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.49 (tq, *J* = 12.6, 6.4 Hz, 4H), 2.34 (d, *J* = 1.1 Hz, 3H), 2.28 (d, *J* = 0.8 Hz, 3H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-6 *N*-(2,5-dimethylphenyl)-4-(3-morpholinopropoxy)benzamide: White solid, 57%, (mp:134-136 °C); IR (KBr, cm^{-1}), 3386 (-NH str), 3016-2952 (Aromatic CH str), 2881-2771 (Aliphatic CH str), 1641 (-CO str), 1373 (-CN str), 1245 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.51 (d, *J* = 2.2 Hz, 2H), 7.00 – 6.94 (m, 2H), 6.90 – 6.85 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 2.23 (s, 6H), 1.83 (p, *J* = 6.2 Hz, 2H); ESI MS: m/z = 369.2 $(M+H)^{+}$.

D-7: *N*-(4-methoxyphenyl)-4-(3-morpholinopropoxy)benzamide: Off white solid, 55%, (mp: 154-156 °C); IR (KBr, cm^{-1}), 3348 (-NH str), 3056-2953 (Aromatic CH str), 2856-2769 (Aliphatic Ch str), 1656 (-CO str), 1373 (-CN str), 1254-1119 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.61 – 7.54 (m, 2H), 7.00 – 6.94 (m, 2H), 6.94 – 6.89 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.81 – 3.74 (m, 7H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-8: *N*-(4-chlorophenyl)-4-(3-morpholinopropoxy)benzamide: Creamy white solid, 69%, (mp: 144-146 °C); IR (KBr, cm^{-1}), 3344 (-NH str), 3015-2951 (Aromatic CH str), 2856-2769 (Aliphatic CH str), 1654 (-CO str), 1373 (-CN str), 1250 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.75 – 7.69 (m, 2H), 7.42 – 7.36 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.84 (p, *J* = 6.2 Hz, 1H).

D-9: *N*-(4-bromophenyl)-4-(3-morpholinopropoxy)benzamide: Brown solid, 59%, (mp: 136-138 °C); IR (KBr, cm^{-1}), 3346 (-NH str), 3000-2945 (Aromatic CH str), 2855-2769 (Aliphatic CH str), 1654 (-CO str), 1373 (-CN str), 1255 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.69 – 7.63 (m, 2H), 7.53 – 7.47 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.83 (p, *J* = 6.2 Hz, 1H).

D-10: *N*-(4-fluorophenyl)-4-(3-morpholinopropoxy)benzamide: Creamy solid, 64%, (mp: 154-156 °C); IR (KBr, cm^{-1}), 3305 (-NH str), 3011-2949 (Aromatic CH str), 2893-2860 (Aliphatic Ch str), 1651 (-CO str), 1373 (-CN str), 1251 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.62 – 7.55 (m, 2H), 7.17 – 7.09 (m, 2H), 7.00 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-11: *N*-(2-chlorophenyl)-4-(3-morpholinopropoxy)benzamide: White solid, 60%, (mp: 122-124 °C); IR (KBr, cm^{-1}), 3344 (-NH str), 2951 (Ar. CH str), 2769 (-CH Str), 1654 (-CO str), 1373 (-CN str), 1255 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.76 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.39 (td, *J* = 7.7, 1.5 Hz, 1H), 7.03 (td, *J* = 7.7, 1.5 Hz, 1H), 6.99 – 6.94 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-12: (4-(2-methoxyphenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: Brown solid, 36%, (mp: 156-158 °C); IR (KBr, cm^{-1}), 3010 (Ar CH str), 2858 (CH str), 1631 (-CO str), 1375 (-CN str), 1255 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 1H), 7.00 – 6.94 (m, 1H), 6.94 – 6.87 (m, 1H), 6.87 – 6.80 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.85 (s, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.26 (dt, *J* = 11.9, 5.3 Hz, 1H), 3.17 (dt, *J* = 11.9, 5.2 Hz, 1H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.83 (p, *J* = 6.2 Hz, 1H).

D-13: (4-(3-methoxyphenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: White solid, 40%, (mp: 164-168 °C); (KBr, cm^{-1}), 3012 (Ar CH str), 2870 (CH str), 1631.78 (-CO str), 1375 (-CN str), 1258 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.79 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.43 (ddd, *J* = 7.7, 2.2, 1.1 Hz, 1H), 6.32 – 6.24 (m, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.81 – 3.74 (m, 7H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.31 – 3.17 (m, 4H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.49 (tq, *J* = 12.6, 6.4 Hz, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-14: (4-(4-methoxyphenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: White solid, 35%, (178-180 °C); IR (KBr, cm^{-1}) 2954 (Ar CH str), 2762 (CH str), 1631 (-CO str), 1375 (-CN str), 1250 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.79 (m, 1H), 7.07 – 7.01 (m, 1H), 7.00 – 6.94 (m, 1H), 6.89 – 6.83 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.81 – 3.74 (m, 4H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.83 (p, *J* = 6.2 Hz, 1H); ESI MS: m/z = 440.2 $(M + H)^+$.

D-15: (4-(2-chlorophenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: Sticky off white solid, 45%, (mp: 148-152 °C); IR (KBr, cm^{-1}), 3010 (Ar CH str), 2810 (Aliphatic CH str), 1631(-CO str), 1375 (-CN str), 1132 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 2H), 7.30 – 7.24 (m, 1H), 7.08 – 7.01 (m, 2H), 7.00 – 6.94 (m, 2H), 6.78 (ddd, *J* = 7.9, 5.1, 3.7 Hz, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.27 (dt, *J* = 11.9, 5.4 Hz, 2H), 3.18 (dt, *J* = 11.9, 5.3 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-16: **(4-(4-chlorophenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone:** Light yellow solid, 45%, (mp: 180-182 °C); IR (KBr, cm^{-1}), 2954 (Ar CH str), 2900-2810 (-CH str), 1643 (-CO str), 1375 (-CN str), 1269-1130 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.79 (m, 1H), 7.26 – 7.20 (m, 1H), 7.00 – 6.94 (m, 1H), 6.79 – 6.72 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.83 (p, *J* = 6.2 Hz, 1H).

D-17: (4-(2,4-chlorophenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: Brown solid, 39%, (mp: 170-172 °C); IR (KBr, cm^{-1}) 3020-2951 (Aromatic CH str), 2854-2771 (Aliphatic CH str), 1632 (-CO str), 1380 (-CN str), 1269-1140 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H), 7.23 – 7.14 (m, 2H), 7.00 – 6.94 (m, 2H), 6.89 (dd, *J* = 7.1,

2.0 Hz, 1H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 4H), 3.60 (t, *J* = 5.3 Hz, 4H), 3.27 (dt, *J* = 11.9, 5.3 Hz, 2H), 3.18 (dt, *J* = 11.7, 5.3 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.56 – 2.43 (m, 4H), 1.83 (p, *J* = 6.2 Hz, 2H).

D-18: (4-(2-flurophenyl)piperazin-1-yl)(4-(3-morpholinopropoxy)phenyl)methanone: Brown solid, 39%, (mp: 190-192 °C); IR (KBr, cm^{-1}), 2945 (Aromatic Ch str), 2858-2777 (Aliphatic CH str), 1631 (-CO str), 1310 (-CN str), 1269-1140 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.80 (m, 1H), 7.00 – 6.88 (m, 2H), 6.77 – 6.66 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.26 (dt, *J* = 11.9, 5.3 Hz, 1H), 3.17 (dt, *J* = 11.9, 5.3 Hz, 1H), 2.63 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 1.83 (p, *J* = 6.2 Hz, 1H).

D-19: (4-(3-morpholinopropoxy)phenyl)(4-(p-tolyl)piperazin-1-yl)methanone: White solid, 42%, (mp: 184-188 °C); IR (KBr, cm^{-1}), 3100-2947 (Aromatic CH str), 2880-2775 (Aliphatic CH str), 1620 (-CO str), 1314 (-CN str), 1249-1121 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.79 (m, 1H), 7.19 – 7.13 (m, 1H), 7.00 – 6.94 (m, 1H), 6.87 – 6.80 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.64 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.33 (d, *J* = 0.8 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 1H); ESI MS: m/z = 424.2 $(M + 1\ H)^{+}$.

D-20: (4-(3-morpholinopropoxy)phenyl)(4-(4-nitrophenyl)piperazin-1-yl)methanone: Yellow solid, 54%, (mp:164-168 °C); IR (KBr, cm^{-1}), 3080-2947 (Aromatic CH str), 2880-2775 (Aliphatic CH str), 1620 (-CO str), 1314 (-CN str), 1249-1150 (-CO ether str); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.79 (m, 1H), 7.19 – 7.13 (m, 1H), 7.00 – 6.94 (m, 1H), 6.87 – 6.80 (m, 1H), 3.99 (t, *J* = 6.1 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.60 (t, *J* = 5.3 Hz, 2H), 3.28 – 3.15 (m, 2H), 2.64 (t, *J* = 6.4 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.33 (d, *J* = 0.8 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 1H).