4.1 EXPERIMENTAL DESIGN

Chemicals Used

Benzyol piperazine, 1-(diphenyl methyl) piperazine, 1-pyridyl piperazine, 8- amino quinoline, 5-amino indan, tryptamine, N-ethyl methyl amine, 1-methyl piperazine, 1-ethyl piperazine, 1-bromo-3-chloro propane, 2,6-dimethyl piperidine, 2-methyl piperidine, homopiperazine & 4-methyl piperidine, were obtained from Acros organics. Silica gel G, Silica gel (60-120), potassium carbonate (K₂CO₃), Sodium sulphate, Dichloromethane (DCM), Ethyl acetate, methanol were obtained from qualigens. Chloroacetyl chloride, chloro propanoyl chloride, 4-chloro butyryl chloride & 1, 4-Dioxane were obtained from SD-Fine Chem Ltd Mumbai. Several Secondary amines, like dimethyl amine, diethyl amine, ethyl methyl amine, morpholine & dicyclohexyl amine etc were obtained from sigma Aldrich.

Apparatus & Glass ware used

Reflux condenser, round bottom flask, beaker, separating funnel, iodine flask, glass rod, magnetic stirrer, pipettes, heating mantle, rotary vacuum evaporator and TLC plates, magnetic stirrer with hot plate, melting point apparatus, hot air oven, column, volumetric flask, magnetic beds, UV chamber and weighing balance etc.

Analytical Work

The melting points were determined in open glass capillary using melting point apparatus (Veego, Bombay, India) and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) on silica gel G plates using, various solvent system, iodine vapours and UV chamber as visualizing agent. Infrared (IR) spectra were recorded using a Perkin Elmer FTIR model. Nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker DRX-400 and 300 and chemical shifts (δ, ppm) relative to TMS as an internal standard. Spin multiplets are given as s (singlet), d (doublet), t (triplet), m (multiple) q (quartet). Mass spectra were recorded on the DART-MS was recorded on a JEOL-Accu TOF.
JMS-T100 LC mass spectrometer. Column chromatography was performed using Silica gel (60–120 mesh) and Merck made TLC plates.

4.2 CHEMISTRY

4.2.1 REACTION SCHEME (1):

Fig: Synthesis of piperazine derivatives. Reagent Conditions :- (I) –ClCH₂CH₂Br, K₂CO₃,
DMF, RT (II) -ClCH₂CH₃CH₂Br, K₂CO₃, DMF, RT  (IV) - CICH₂COCl, DCM, 0-5°C, TEA (V) -Cl(CH₂)₃COCl, dioxane, 0-5°C, RT ,6-12 h (VI) -Cl(CH₂)₃COCl, dioxane, 0-5°C, RT ,6-12 h (2) - DCM, SOCl₂, Piperazine, 40°C, 3 h, CH₃CN

4.2.2 REACTION SCHEME (2):

Fig: Reagent Conditions :
(I) CICH₂COCl, TEA, DCM  (2) benzhydryl piperazine, K₂CO₃, DMF

General formula:
Table 2: Physical and analytical data

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<td>75%</td>
<td>0.63</td>
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</tbody>
</table>

4.2.2.1 Synthetic procedures and characterization:

4.2.2.1.1 Synthesis of benzhydryl piperazine (1 & Z):

Benzhydrol (53.36g, 0.29 mol) [1] was dissolved in dichloromethane (100 mL). Thionyl chloride (50 mL, 0.69 mol) was added to the reaction mixture and reaction mixture was stirred at 40 °C for 3 h. The solvent was evaporated under vacuum and the residue was
dissolved in acetonitrile (20 mL), yield was 90%. Benzhydryl chloride (58.58g, 0.29mol,) was taken in a RBF and piperazine (1.44g, 0.29 mol) was added and the mixture was refluxed for 12 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (250 mL) and washed with water (100 mL) followed by 1N HCl (100 mL). The acid phase was washed with ethyl acetate (3 ×60 mL). The ethyl acetate layer was discarded and the remaining water layer was neutralized with 3N NaOH aqueous solutions (40 mL) to pH> 10. The aqueous solution was extracted with dichloromethane (3 × 80 mL). The combined dichloromethane was washed successively with brine, dried over Na$_2$SO$_4$ and evaporated under vacuum to provide the title compound obtained as solid. (Yield was 80%), mp 93°C. Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5).

**1H NMR (300 Hz in CDCl$_3$):** $\delta ,7.13$-$7.42$ (m, 10H, Ar-H ), $4.20$ (s, 1H, -CH of benzhydryl moiety), $2.85$ (t, 3H, -CH$_2$ of pip, $J=4.5$ ), $2.34$ (t, 4H, piperazine). (Fig.30)

**4.2.2.1.2 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (5y):- [2, 3]**

A solution of benzhydryl piperazine (2.52g, 10 mmol,) in dioxane (15 mL) was taken and heat for 10 minutes, then after cooled to 0-5°C in an ice bath. Then Chloro propanoyl chloride (13mmol, 1.25 mL) was added with stirring. The reaction mixture was allowed to stirred at Room temperature for 4-6 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride Solution, and finally water wash was given to a organic layer. The organic layer was dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (80%), mp 135° C. Solvent system for TLC was used Methanol: Ethyl acetate (3: 7).

**IR (ATR) 3026 (C-H$_{ar}$ (Ar), 2974 (C-H$_{aliph}$), 1705 (C=0), 1643 (C=C$_{ar}$ (Ar), 1087 (C-N<) , 785 (-Cl), 671 (C-H$_{def}$). (Fig.53)**

**1H NMR (300 Hz in CDCl$_3$):** $\delta ,7.17$-$7.44$ (m, 10H, Ar-H ), $5.26$ (s, 1H, -of CH of benzhydryl moiety) , $3.75$ (t, 2H, -CH$_2$ at $\beta$ position of CH$_2$ ), $3.67$ (t, 4H, -CH$_2$ of pip), $2.77$ (t, 2H, -CH$_2$ at $\alpha$ position) $2.22$ (t, 4H, -CH$_2$ of piperazine). (Fig.28)
4.2.2.1.3 Synthesis of 1-(4-benzhydryl piperazin-1-yl)-2-chloro ethanone (3):

A solution of benzhydryl piperazine (1.96 g, 15.8 mmol,) in dry dichloromethane was taken and cooled to 0-5°C in an ice bath. TEA (3.30mL, 23.8mmol) was added to the cooled reaction mixture and stirred for 10 min, and then chloro acetyl chloride (1.38 mL, 17.4 mmol) was added. The reaction mixture was allowed to stirred at room temperature for 4-6 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. Firstly the organic layer was washed with 10 % ammonium chloride Solution then after with distilled water three times approximately and dried with anhydrous sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (85%), mp-121°C. Solvent system for TLC was used Methanol: DCM (3: 7). \[4, 5\].

4.2.2.1.4 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-4-chlorobutan-1-one (4):

For the synthesis of compound (4) procedure was same as for compound (5). Only Chloro propanoyl chloride was replaced by Chloro butanoyl chloride. The yield of pure compound was (70%), mp 149°C. Solvent system for TLC was used Methanol: Ethyl acetate (8: 2).

4.2.2.1.5 Synthesis of 1-benzhydryl-4-(2-chloroethyl / propyl) piperazine (6 & k):

To a solution of benzhydryl piperazine (3g, 3.96 mmol,) in acetone (50 mL) and 45 mL of 25% aqueous sodium hydroxide solution was added and stirred for 10 minutes. The spacer or linker 1-bromo-3-chloro propane,(1.23 mL, 3.96mmol) was added to the reaction mixture and further stirred for a certain time (20 h approximately) at 25°C.Water was added to the mixture and 25 mL of diethyl ether dried over sodium sulphate, filtered , concentrated & purified by column (acetone/ heptane) give as yellow syrup. Solvent system for TLC used was methanol: ethyl acetate (8:2). For the synthesis of intermediate (6) procedures was same as for intermediate compound (k). Only 1-bromo-3-chloro ethane was replaced by 1-bromo-2-chloro propane. Solvent system for TLC was used Methanol: Ethyl acetate (8: 2). \[6, 8\]

MS (ESI+) m/z =328, (M+) = 329, (M+2) = 331 (Fig.31)

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4.2.2.1.6 Synthesis of \( N-(2-(1H\text{-indol}-3\text{-yl})\text{-ethyl})-2-(4\text{-benzhydrylpiperazin}-1\text{-yl})\text{acetamide (7a):} \)

A suspension of \( N-(2-(1H\text{-indol}-3\text{-yl})\text{-ethyl})\text{-2-chloroacetamide (0.236 g, 0.001mol), benzhydryl piperazine (0.252g, 0.001mol) and } K_2\text{CO}_3 \text{(0.414 g, 0.003mol) in DMF (10 mL) was stirred at 60°C for 3 h. The reaction is quenched with water (100 ml) and extracted with ethyl acetate (3×50mL). The combined organic layer was washed with brine, dried & removed in vacuo. The residue was purified by column chromatography. mp 230°C. Solvent system for TLC was used Pet ether: Ethyl acetate (5: 5). [6]}

\[ 1^H \text{NMR (400 MHz, CDCl}_3 \] : \( \delta \), 8.18 (s, 1H, -CONH ), 6.84-7.29 (m, 10H, Ar-H ), 7.11-7.49 (m, 4H , indole), 5.17 (s, 1H,-CH of benzhydryl moiety), 3.51 (s, 2H , -CH\text{2 at } \alpha \text{ position of C=O }, 3.49 (t, 2H , J= 6.4 Hz , -CH\text{2 at } \alpha \text{ position of } -\text{NH} ), 2.82 (t, 2H, -CH\text{2 at } \beta \text{ position of } -\text{NH} ), 2.37 (s , 8H , piperazine) (Fig.16).

Found: C, 76.93; H, 7.19; N, 12.33 . \( C_{29}H_{32}N_4O \), Requires: C, 76.96; H, 7.13; N, 12.38.

4.2.2.1.7 Synthesis of \( N-(2-(1H\text{-indol}-3\text{-yl})\text{-ethyl})-3-(4\text{-benzhydrylpiperazin}-1\text{-yl})\text{propan-1-amine (7c):} \)

Compound (7c) was prepared according to the procedure reported for (7i), starting from 1-benzhydryl-4-(3-chloropropyl)piperazine,(0.328g, 0.001 mol), tryptamine (0.48g, 0.003 mol), \( K_2\text{CO}_3 \text{ (0.414g, 0.003mol) in dichloromethane (10 mL) .The yield of pure compound was (57\%) , mp 215°C. Solvent system for TLC was used n-hexane: Ethyl acetate (8: 2). [7]}

\[ 1^H \text{NMR } (400 \text{ MHz, CDCl}_3 ) : \delta , 8.51 (s, 1H, -NH of indole) , 6.92-7.49 (m, 14H, Ar-H ), 5.19 (s, 1H, -CH of benzhydryl moiety), 2.90(t, 2H, J= 3.2 Hz -CH\text{2 at } \alpha \text{ position of } -\text{NH}), 2.82 (t ,2H , J= 6.8 Hz -CH\text{2 at } \beta \text{ of } -\text{NH}), 2.62 (t , 2H, J= 6.4 Hz, -CH\text{2 at } \gamma \text{ of pip}), 2.25 (s , 8H , piperazine), 1.60 (m, 2H, -CH\text{2 at } \beta \text{ position of pip}) .\text{Found: C, 77.57; H, 8.06; N, 12.35 .} \ C_{30}H_{36}N_4\text{ }, Requires: C, 79.61; H, 8.02; N, 12.38. (Fig.18)\]

4.2.2.1.8 Synthesis of 2-(4-benzhydrylpiperazin-1-yl)-\( N-(\text{quinolin}-8\text{-yl})\text{acetamide (7d):} \)

Same as reported for compound (7a). In this 2-chloro-\( N-(\text{quinolin}-8\text{-yl}) \text{ acetamide (0.220g,
0.001 mol) was taken as a starting material. mp 198°C. Solvent system for TLC was used n-hexane: Ethyl acetate (8: 2) \[6\]

$^1$H NMR (300 MHz, CDCl$_3$) : δ 11.43 (s, 1H, NH of quinoline), 7.24-8.79 (m, 16H, Ar-H), 5.19 (s, 1H, -CH of benzhydryl moiety), 3.31 (s, 2H, -CH$_2$ at α position of pip), 2.36 (s, 8H, piperazine), Found: C, 77.00; H, 6.53; N, 12.80. C$_{28}$H$_{28}$N$_4$, Requires: C, 77.04; H, 6.46; N, 12.83 (Fig.19)

4.2.2.1.9 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-2-(2,3-dihydro-1H-inden-5-ylamino) ethanone (7f) :- Compound 7f was prepared according to the procedure reported for 7g, starting from 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone,(0.328g, 0.001mol) 5-aminoIndan (0.399g, 0.003 mol) and Sod. carbonate (0.318g, 0.001 mol) in dry ethanol (10 mL). The yield of pure compound was (35%), mp 254°C. Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5) \[8\]

Found: C, 79.05; H, 7.38; N, 9.84. C$_{28}$H$_{31}$N$_3$, Requires: C, 79.02; H, 7.34; N, 9.87

4.2.2.1.10 Synthesis of N-(2-(4-benzhydrylpiperazin-1-yl) ethyl)-2, 3-dihydro-1H-inden-5-amine (7g):-

A mixture of 1-benzhydryl-4-(2-chloroethyl)piperazine (0.314g, 0.001mol), 5-aminoIndan (0.399g, 0.003 mol) and Sod. carbonate (0.318g, 0.001 mol) in dry ethanol (10mL) was refluxed under stirring for 7 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. mp 202 °C. Solvent system for TLC was used n-hexane: Ethyl acetate (6: 4) \[8\]

Found: C, 81.68; H, 8.04; N, 10.24. C$_{28}$H$_{33}$N$_3$, Requires: C, 81.71; H, 8.08; N, 10.21.

4.2.2.1.11 Synthesis of 2-(2-(1H-indol-3-yl)ethylamino)-1-(4-benzhydrylpiperazin-1-yl) ethanone (7h):-

Compound (7h) was prepared according to the procedure reported for (7i), starting from 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone,(0.328g, 0.001mol), K$_2$CO$_3$ (0.414g, 0.003 mol)
in dichloromethane (10 mL). The yield of pure compound was (36%), mp 187 °C. Solvent system for TLC was used n-hexane: Ethyl acetate (8: 2). [7].

$^1$H NMR :-(300 MHz, CDCl$_3$) : δ ,10.84 (s, 1H, -NH of indole ) δ ,6.96-7.49 (m, 14H, Ar-H), 5.10 (s,1H, -CH of benzhydryl moiety), 3.58 (t, 4H, pip). 3.32 (t, 2H, $J=12.9$Hz , -CH$_2$ at α position –NH) , 3.22 (t, 2H, $J=5.8$ Hz, -CH$_2$ at β position of –NH ), 3.19(s, 2H, -CH$_2$ between the C=O (CH$_2$) -NH ), 3.15 (t, 4H, $J=5.8$ Hz, piperazine). (Fig. 21) Found: C, 76.93; H, 7.12; N, 12.36. C$_{29}$H$_{32}$N$_4$, Requirs: C, 76.96; H, 7.13; N, 12.38.
4.2.2.2 RESULTS AND DISCUSSION

Chemistry

The key starting material (1&Z) were synthesized according to published procedure (Meng T et al., 2010). The synthesis of compound (7c, 7f, 7g, 7h, and 7i) has been carried out as presented in scheme-1 and compound (7a, 7d) as presented in Scheme-2. The intermediate compounds (3, 4 & 5) were synthesized by the reaction of benzhydryl piperazine with the various acyl chlorides. The intermediate compound (6) was synthesized by the reaction of benzhydryl piperazine and 1-bromo-2-chloro ethane, and intermediate compound (k) was synthesized by the reaction of 1-bromo-3-chloro propane and benzhydryl piperazine.

The title compounds 2-(2-(1H-indol-3-yl) ethylamino)-1-(4-benzhydrylpiperazin-1-yl)ethanone (7h) was synthesized by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone (3) and tryptamine. The compound 1-(4-benzhydrylpiperazin-1-yl)-2-(2,3-dihydro-1H-inden-5-ylamino)ethanone (7f) was synthesized by refluxing of 1-(4-benzhydrylpiperazin-1-yl)-2-chloroethanone (3) with the 5-AminoIndan. The compound 3-(2-(1H-indol-3-yl)ethyl amino)-1-(4-benzhydrylpiparizin-1-yl) propan-1-one (7i) was synthesized by the reaction of tryptamine and 1-(4-benzhydrylpiparizin-1-yl)-3-chloropropan-1-one (5), was synthesized by the reaction of tryptamine and 1-(4-benzhydrylpiparizin-1-yl)-4-chlorobutan-1-one (4).

The compound N-(2-(4-benzhydrylpiparizin-1-yl)ethyl)-2,3-dihydro-1H-inden-5-amine (7g) was synthesized by refluxing of 1-benzhydryl-4-(2-chloroethyl)piparazine and 5-amine Indan. The compound N-(2-(1H-indol-3-yl)ethyl)-3-(4-benzhydrylpiparizin-1-yl)propan-1-amine (7c) was synthesized by the refluxing of 1-benzhydryl-4-(3-chloropropyl)piparazine and tryptamine.

The compound N-(2-(1H-indol-3-yl) ethyl)-2-(4-benzhydrylpiparizin-1-yl)acetamide (7a) was synthesized by the reaction of N-(2-(1H-indol-3-yl) ethyl)-2-chloroacetamide and benzhydryl piperazine. The compound 2-(4-benzhydrylpiparizin-1-yl)-N-(quinolin-8-
yl)acetamide (7d) was synthesized by refluxing of 2-chloro-N-(quinolin-8-yl)acetamide and benzhydryl piperazine.

Progress of the reaction was checked by TLC and their structures were confirmed by means of IR, $^1$H-NMR, mass spectrometry and elemental analysis. The spectral data are in total agreement with the proposed structures. $^1$H-NMR spectra of all prepared compounds are in agreement with the suggested structure; $^1$H-NMR spectra of compounds showed signals corresponding to aromatic, aliphatic, acetamide, and NH protons.
4.2.3 REACTION SCHEME (3):-
General formula:

![General formula image]

Table 3: Physical and analytical data of compounds

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<th>MOLECULAR WEIGHT</th>
<th>YIELD</th>
<th>Rf VALUE*</th>
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<tr>
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4.2.3.1 Synthesis procedures & Characterization

4.2.3.1.1 Synthesis of benzhydryl piperazine (1):

The procedure is same for the compound (1) as given above in the reaction scheme 1. Spectral data is also given above. [1]

4.2.3.1.2 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (5y):

A solution of benzhydryl piperazine (2.52g, 10 mmol,) in dioxane (15 mL) was taken and heat for 10 minutes, then after cooled to 0-5°C in an ice bath. Then Chloro propanoyl chloride (1.25 mL,13mmol) was added with stirring. The reaction mixture was allowed to stirred at room temperature for 4-6 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10 % ammonium chloride Solution, and finally water wash was given to a organic layer. The organic layer was dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (80%). Solvent system for TLC was used Methanol: Ethyl acetate (3: 7).

IR (ATR): 3026 (C-H str (Ar), 2974 (C-H str (aliph), 1705 (C=O), 1643 (C=C str (Ar), 1520 (C-C str (Ar), 1087 (C-N<), 785 (-Cl), 671 (C-H def)).[2, 3] (Fig.52)

1H NMR (300 Hz in CDCl3): δ ,7.17-7.44 (m, 10H, Ar-H ), 5.26 (s, 1H, -of CH of benzhydryl moiety), 3.75 (t, 2H, -CH2 at β position of CH2 ), 3.67 (t, 4H, -CH2 of pip), 2.77 (t, 2H, -CH2 at α position) 2.22 (t, 4H, -CH2 of piperazine). (Fig.28)

4.2.3.1.3 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperazin-1-yl)propan-1-one (1a):

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001mol), 1-methyl piperazine (0.11 mL, 0.001 mol) and dry K2CO3 (0.414g, 0.003 mol) in alcohol (10 mL) was stirred for 1 h at 25°C. After this the mixture was refluxed & stirred at 60°C for 24 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times.
approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (50%). Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5).

$^1$H NMR :-(400 MHz, CDCl$_3$) : δ ,7.24-7.34 (m, 10H, Ar-H ), 4.22 (s, 1H, -CH of benzhydryl moiety), 3.67 (t, 2H, -CH$_2$ at β of C=O ), 3.44 (t, 4H, piperazine ), 2.50 (t, 4H, piperazine), 2.49 (t, 2H, -CH$_2$ at α of C=O ), 1.89 (s, 8H, piperazine at β of C=O), 1.23 (s,3H, N-CH$_3$). [8, 9] (Fig.1)

MS (ESI+): m/z =406 (M$^+$), 407 (M$^+$$+1$), 408 (Fig.32)

$^{13}$C NMR (CDCl$_3$):- δ 45.5, 52.9 (2), 53.8 (2), 54.8, 46.0 (2), 30.6, 51.4(2), 169, 76.5, 127 (2), 128.4(4), 141.9(2), 129.2(4). (Fig.2)

IR (KBr, cm$^{-1}$): 3053 (C-H str (Ar), 2952 (C-H str (aliph) 2917 (Asym Str. Of –CH$_3$), 2860 (C-H str in CH$_3$), 1693 (C=O), 1545 (C=C str (Ar), 1516 (C-C str(Ar), 1470(C-H bend in –CH$_3$), 1460 (Asym def.), 1366 (Sym def.), 1028 (C-N), 753 (C-H def), (Fig.48)

Found: C, 73.83; H, 8.46; N, 13.78. C$_{25}$H$_{34}$N$_4$O. Requires: C, 73.85; H, 8.43; N, 13.78.

4.2.3.1.4 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(4-ethylpiperazin-1-yl)propan-1-one (1b):-

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001 mol), 1-ethyl piperazine (0.14 mL, 0.001 mol) and dry K$_2$CO$_3$ (0.414g, 0.003 mol) in alcohol (10 mL) was stirred for 1 h at 25 °C. After this the mixture was refluxed & stirred at 60°C for 24 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (54%). Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5).[8, 9] $^1$H NMR :-(400 MHz, CDCl$_3$) : δ ,7.49-6.84 ( m,10H, Ar-H), 2.83 (t, 4H, piperazine), 2.28 (t, 4H, piperazine), 4.01 (t, 2H, -CH$_2$ at β of C=O), 4.50 (s, 1H, of benzhydryl moiety), 1.95 (s, 8H, piperazine at β of C=O), 3.49 (q, 2H, N-CH$_2$), 1.15
(t, 3H, N-C-CH₃ of piperazine). Found: C, 74.20; H, 8.61; N, 13.34. C₂₆H₃₆N₄O. Requires: C, 74.25; H, 8.63; N, 13.32. (Fig.3)

4.2.3.1.5 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(4-(piperidin-2-yl) piperazin-1-yl) propan-1-one (1c)

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001 mol), 1-(2-pyridyl piperazine (0.15mL, 0.001mol) and dry K₂CO₃ (0.414g, 0.003 mol) in dichloromethane (10 mL) was stirred for1 hours at 25 ⁰C. After stirring the mixture was refluxed for 6-12 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (60%). Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5). [8, 9] IR (KBr, cm⁻¹): 3565 (NH str), 3061 (C-H str (Ar), 2982 (C-H₆ (aliph), 1692 (C=O), 1516 (C-C str (Ar), 1483 (C=C str (Ar), 1461(C-H bend (alip), 885 (NH wag), 760 (C-H def).  (Fig.49)

Found: C, 73.24; H, 8.67; N, 14.75. C₂₉H₄₁N₅O. Requires: C, 73.23; H, 8.69; N, 14.72.

4.2.3.1.6 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(2-methylpiperidin-1-yl)propan-1-one (1d):-

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001mol), 2-methyl piperidine (0.36 mL, 0.003 mol) and dry K₂CO₃ (0.414g, 0.003 mol) in dichloromethane (10 mL) was stirred for1 h at 25 ⁰C. After stirring the mixture was refluxed for 6-12 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound (65%). ¹H NMR :-(300 MHz, CDCl₃ ) : δ 7.24-7.36 (m, 10H, Ar-H), 2.51 (t, 4H, piperazine), 2.28 (t, 2H, -CH₂ at α of C=O), 2.64 (t, 2H, -CH₂ at β of C=O), 1.12 (d, 3H, -CH₃ of piperidine), 1.55-2.51 (m, 9H, piperidine), 4.21 (s, 1H, -CH of benzhydryl moiety). [8, 9] (Fig.4)
**IR (KBr, cm⁻¹):** 3062 (C-H str (Ar)), 2970 (C-H str (aliph)), 2933 (Asym Str. of –CH₃), 2894 (C-H str in CH₃), 1689 (C=O), 1545 (C=C str (Ar)), 1516 (C-C str (Ar)), 1482 (Asym def.), 1426 (C-H bend in –CH₃), 1371 (Sym def.), 1065 (C-N<), 688 (C-H def). Found: C, 77.02; H, 8.71; N, 10.33. C₂₆H₃₅N₃O Requires: C, 77.00; H, 8.70; N, 10.36. (Fig.50)

**4.2.3.1.7 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(2,6-dimethylpiperidin-1-yl)propan-1-one (1e):**

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342 g, 0.001 mol), 2, 6-dimethyl piperidine (0.40 mL, 0.003 mol) and dry K₂CO₃ (0.414 g, 0.003 mol) in dichloromethane (10 mL) was stirred for 1 h at 25 °C. After stirring the mixture was refluxed for 6-12 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (70%). Solvent system for TLC was used n-hexane: Ethyl acetate (6: 4).

**MS (ESI+): m/z =419 (M⁺), 420 (M⁺+1), 421.** (Fig.33) **¹³C NMR (CDCl₃):** δ 20.5 (2), 24.1, 33.4(2), 53.8(2), 45.5, 45.7 (2), 51.5(2), 169.9, 76.05, 128.4 (4), 126.7(2), 127.5(4), 142.53(2), 30.63. (Fig.5)

Found: C, 77.30; H, 8.87; N, 10.02. C₂₇H₃₇N₃O Requires: C, 77.00; H, 8.89; N, 10.01. [8, 9]

**4.2.3.1.8 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperidin-1-yl)propan-1-one (1f):**

Procedure is same as above of compound (1e). Change is only in this synthesis is that we take 4- methyl piperidine (0.34 mL, 0.003 mol) at the place of 2-methyl piperidine. The yield of pure compound was (60%). Solvent system for TLC was used n-hexane: Ethyl acetate (6: 4).

**MS (ESI+) m/z =405(M⁺), 406 (M⁺+1), 407.** (Fig.34)

Found: C, 77.01; H, 8.69; N, 10.36. C₂₇H₃₇N₃O Requires: C, 77.00; H, 8.70; N, 10.36. [8, 9]
4.2.3.2 Mass Fragmentation:

The DART-MS was recorded on a JEOL-Acu TOF JMS-T100 LC mass spectrometer. Dry helium was used with 4LPM flow rate for ionization at 350°C.

**Compound 1-(4-benzhydrylpiperazin-yl)-3-(4-methylpiperazin-yl)propan-1-one (1a):**

![Chemical Structure](image-url)
Compound 1-(4-benzhydrylpiperazin-1-yl)-3-(2,6-dimethylpipеридin-1-yl)propan-1-one (1e):
Compound 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperidin-1-yl) propan-1-one (1f):
4.2.3.3 RESULTS AND DISCUSSION

Chemistry

The key starting material (1) was synthesized according to published procedure (Meng T et al., 2010). The synthesis of compound (1a,1b,1c) has been carried out as presented reaction of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one with the piperazine and the synthesis of compound (1d, 1e, and 1f) has been carried out by the reaction of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one with the piperidine. The intermediate compound (5y) was synthesized by the reaction of benzhydryl piperazine with the chloro propanoyl chloride.

The title compound 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperazin-1-yl) propan-1-one (1a) was synthesized by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one & 1-methyl piperazine in the presence of K₂CO₃ and alcohol. The compound 1-(4-benzhydryl piperazin -1-yl)-3-(4-ethylpiperazin-1-yl) propan-1-one (1b) was synthesised by refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one & 1-ethyl piperazine in the presence of dry K₂CO₃ and alcohol. but the compound 1-(4-benzhydrylpiperazin-1-yl)-3-(4-(piperidin-2-yl) piperazin-1-yl)propan-1-one (1c) was prepared by the same procedure as mention above for (1a) the difference is only in this the reaction takes place in the presence of dichloromethane. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(2-methylpiperidin-1-yl)propan-1-one (1d) was synthesised by refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one & 2-methyl piperidine in the presence of dry K₂CO₃ in dichloromethane. The procedure is same for 1-(4-benzhydrylpiperazin-1-yl)-3-(2, 6-dimethylpiperidin-1-yl) propan-1-one (1e) as of the compound (1d). Only the difference is that at the place of 2-methyl piperidine, we were taken 2, 6-dimethyl piperidine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(4-methylpiperidin-1-yl) propan-1-one (1f) was synthesised same as above compound (1e). The change is only in this synthesis was that we take 4-methyl piperidine at the place of 2-methyl piperidine. Progress of the reaction was checked by TLC and their structures were confirmed by means of IR, ¹H-NMR, mass spectrometry and
elemental analysis. The spectral data are in total agreement with the proposed structures. \(^1\)H-NMR spectra of all prepared compounds are in agreement with the suggested structure.

4.2.4 REACTION SCHEME (4):-

![Reaction Scheme Image]

Fig 6.9
4.2.5 REACTION SCHEME (5):

![Reaction Scheme 5]

Fig 7.0

4.2.6 REACTION SCHEME (6):

![Reaction Scheme 6]
Fig 7.1: Synthesis of piperazine derivatives. Reagent Conditions (I) –ClCH₂CH₂Br, K₂CO₃, DMF, RT  (II) ClCH₂CH₂Br, K₂CO₃, DMF, RT  (III) 8-amino quinoline, dry toluene, Na₂CO₃  (IV) Same As III (V) Tryptamine, Na₂CO₃, Dry Ethanol, RT  (VI) Cl(CH₂)₂COCl, DCM, 0-5°C, RT, 6-12 h  (VII) ClCH₂COCl, DCM, 0-5°C, TEA  (IX) benzoyl piperazine, Na₂CO₃, Dry Ethanol, RT  (X) Cl(CH₂)₃COCl, DCM, 0-5°C, RT, 6-12 h  (XI) 2-chloro propionyl chloride, DCM, 0-5°C, RT, 6-12 h  

General formula:

![General formula image]

Table 4: - Physical and analytical data of compounds

<table>
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<tr>
<th>S. No.</th>
<th>CODE NO.</th>
<th>R</th>
<th>X</th>
<th>MOLECULAR FORMULA</th>
<th>MOLECULAR WEIGHT</th>
<th>YIELD</th>
<th>Rf VALUE*</th>
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<td></td>
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<td>2.</td>
<td>(6b)</td>
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<td></td>
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<td>71%</td>
<td>0.75</td>
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<tr>
<td>3.</td>
<td>(6c)</td>
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<td></td>
<td>C₂₂H₂₄N₄O</td>
<td>360</td>
<td>40%</td>
<td>0.67</td>
</tr>
<tr>
<td>4.</td>
<td>(6d)</td>
<td><img src="image" alt="Compound 1" /></td>
<td><img src="image" alt="Compound 2" /></td>
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<td><img src="image" alt="Compound 2" /></td>
<td>C$<em>{24}$H$</em>{28}$N$_4$O$_2$</td>
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<td>0.55</td>
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<td>6.</td>
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<td><img src="image" alt="Compound 2" /></td>
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<td>56%</td>
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</tr>
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<td><img src="image" alt="Compound 2" /></td>
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<td>45%</td>
<td>0.78</td>
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<td><img src="image" alt="Compound 2" /></td>
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<td>404</td>
<td>60%</td>
<td>0.69</td>
</tr>
<tr>
<td>9.</td>
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<td><img src="image" alt="Compound 2" /></td>
<td>C$<em>{23}$H$</em>{28}$N$_4$O$_2$</td>
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<td>40%</td>
<td>0.72</td>
</tr>
<tr>
<td>10.</td>
<td>(6j)</td>
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<td><img src="image" alt="Compound 2" /></td>
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</tr>
<tr>
<td>11.</td>
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<td><img src="image" alt="Compound 2" /></td>
<td>C$<em>{25}$H$</em>{30}$N$_4$O$_2$</td>
<td>418</td>
<td>41%</td>
<td>0.68</td>
</tr>
</tbody>
</table>
4.2.6.1 Synthesis & Characterization:

4.2.6.1.1 Synthesis of 4-(2-chloroethyl piperazin-1-yl) (phenyl) methanone (1X):

A mixture of benzoyl piperazine (0.01 mol), 1-bromo-2-chloro ethane (0.01 mol) and dry K$_2$CO$_3$ (0.012 mol) in DMF (10 mL) was stirred for 24 h at 25 °C. The mixture was diluted with water and extracted with dichloro methane. The organic layer was dried with sodium sulphate and evaporated under reduced pressure. The residue was purified by chromatography on a silica gel column eluting with ethyl acetate to afford the title compound. Solvent system for TLC was used DCM: Methanol (7: 3).

**IR (KBr, Cm$^{-1}$):** 3007 (C-H str (Ar), 2914 (C-H str (aliph), 1620 (C=O), 1496 (C-H bend (Ar), 1439 (C=C str (Ar), 1369 (C-H bend (Alip), 1219 (-CO-N), 1131 (C-N), 750 (-Cl). (Fig.47)

The compound (2) was synthesized as same as compound (1). Only 1-bromo-3-chloro propane was taken at the place of 1-bromo-2-chloro ethane. [6, 8]

4.2.6.1.2 Synthesis of 4-(2-(2-(1H-indol-3-yl) ethyl amino) ethyl) piperazin-1-yl) (phenyl) methanone (6f):

A mixture of 4-(2-chloro ethyl) piperazin-1-yl (phenyl)methanone (0.001 mol), tryptamine (0.003 mol) and Sod.carbonate (0.001 mol) in dry ethanol was refluxed under stirring for 7 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. mp was 177° C. Solvent system for TLC was used Chloroform: Methanol (7: 3). [8]

**IR (KBr, cm$^{-1}$) 3270 (NH str), 3043 (C-H str (Ar), 2929 (C-H str (aliph), 1663 (C=0), 1229 (-CO-N), 1508 (C=C str (Ar), 1337 (C-C str (Ar), 1090 (-CN), 745 (C-H str)). (Fig.42)

4.2.6.1.3 Synthesis of N-(2-(1H-indol-3-yl) ethyl)-2-chloroacetamide (7):

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A mixture of tryptamine (1.60g, 10mmol) and TEA (2.68 mL, 30mmol) was stirred in dichloromethane (20 mL) at room temperature for 10 min. A sol’n of chloro acetyl chloride (0.91 mL, 11.5 mmol) in dichloromethane (10 mL) was added dropwise in the above solution at 0°C for 20 minutes. The resultant mixture was stirred at room temperature for 24 h approximately. The reaction mixture was extracted with dichloromethane. The combined organic layer was dried by sodium sulphate. The solvent was removed by reducing pressure. mp was 86 °C. Solvent system for TLC was used DCM: Methanol (9: 1). [7, 10]

**IR (KBr, cm⁻¹):** 3394 (NH str), 2952 (C-H str (aliph), 1641 (C=O), 740 (-Cl) (Fig.44)

The synthesis of compound 8, 9 and 10 was same. Only different acyl chlorides were taken.

**4.2.6.1.4 Synthesis of 3-chloro-N-(quinolin-8-yl)propanamide (5):**

Procedure is same as of above compound (7). We take 8-amino quinoline (1.44 g, 10 mmol) and chloro propanoyl chloride (11.5 mmol). mp 107 °C. Solvent system for TLC was used DCM: Methanol (8: 2). [7, 10]

**IR (KBr, cm⁻¹):** 3331 (NH str), 3128 (C-H str (Ar), 1685 (C=O), 750 (-Cl) (Fig.46)

**4.2.6.1.5 Synthesis of 2-chloro-N-(quinolin-8-yl)acetamide (6):**

Procedure is same as of above compound (5). We take chloro acetyl chloride (11.5 mmol) at the place of chloro propanoyl chloride. Solvent system for TLC was used DCM: Methanol (7: 3). [7, 10]

**IR (KBr, cm⁻¹):** 3440 (NH str), 2938 (C-H str (Aliph), 1661 (C=O), 770 (-Cl) (Fig.45)

**4.2.6.1.6 Synthesis of 1-(4-benzoyl piperazin-1-yl)-2-chloroethanone (4):**

A solution of Chloro acetyl chloride (0.01 mol) in dry THF was added to a solution of benzooyl piperazine (0.01 mol) in the same solvent. The mixture was stirred at room temperature for 5 h or until thin layer chromatography showed the reaction to be complete.
After filtration, the compound obtained was crystallized from ethanol. Solvent system for TLC was used DCM: Methanol (7: 3). [3]

4.2.6.1.7 Synthesis of N-(2-(1H-indol-3-yl)ethyl)-2-(4-benzoypiperazin-1-yl)acetamide (6j):-

A mixture of N-(2-(1H-indol-3-yl)ethyl)-2-chloroacetamide, (0.236 g, 0.001 mol) benzoyl piperazine (0.190 g, 0.001 mol) and Sod. carbonate (0.106 g, 0.001 mol) in dry ethanol was refluxed under stirring for 12 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. Thin layer chromatography showed the single spot in DCM: Methanol (6:4). The yield of the pure compound was 57%, mp 156° C. Solvent system for TLC was used DCM: Methanol (8: 2). [8]

$^1$H NMR : (400 MHz, CDCl$_3$): δ 7.0-7.5 (m, 10H, Ar-H) 2.59 (t, 4H, $J$=6.4 Hz, piperazine), 3.43 (t, 2H, $J$=6.8 Hz, -CH$_2$ at α position of –NH), 3.65 (t, 4H, pip), 2.85 (t, 2H, -CH$_2$ at β position of –NH), 3.28 (t, 2H, -CH$_2$ at α position of piperazine). (Fig.14)

4.2.6.1.8 Synthesis of 3-(4-benzoypiperazin-1-yl)-N-(quinolin-8-yl)propanamide (6a):-

Procedure is same as above of compound 6j. Only we have taken 3-chloro-N-(quinolin-8-yl) propanamide (0.23 g, 0.001 mol). The yield of the pure compound was 43%. Solvent system for TLC was used DCM: Methanol (7: 3). [8]

4.2.6.1.9 Synthesis of 3-(4-benzoypiperazin-1-yl)-N-(quinolin-8-yl)propanamide (6b):-

Procedure is same as above of compound (6j). Only we take 2-chloro-N-(quinolin-8-yl) acetamide (0.22 g, 0.001 mol). The yield of the pure compound was 71%. Solvent system for TLC was used DCM: Methanol (6: 4). [8]

4.2.6.1.10 Synthesis of N-(2-(1H-indol-3-yl)ethyl)-4-(4-benzoypiperazin-1-yl)butanamide (6k):-

A mixture of N-(2-(1H-indol-3-yl)ethyl)-4-chlorobutanamide, (0.265 g, 0.001 mol) benzoyl piperazine (0.190 g, 0.001 mol) and Sod. carbonate (0.106 g, 0.001 mol) in dry ethanol was
refluxed under stirring for 16 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. Thin layer chromatography showed the single spot in DCM: Methanol (9:1). The yield of the pure compound was 41%. [8]

4.2.6.1.11 Synthesis of \(N-(\text{2-}(1\text{H-indol-3-yl})\text{ethyl})\text{-3-(4-benzoypiperazin-1-yl)}\text{propanamide (6L)}\):-

A mixture of \(N-(\text{2-}(1\text{H-indol-3-yl})\text{ethyl})\text{-3-chloropropanamide, (0.251g, 0.001 mol) benzoyl piperazine (0.190g, 0.001 mol) and sodium carbonate (0.106g, 0.001 mol) in dry ethanol was refluxed under stirring for 20 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. Thin layer chromatography showed the single spot in DCM: Methanol (9:1). The yield of the pure compound was 40%. [8]

\[\text{H NMR : (400 MHz, CDCl}_3\text{) : } \delta ,6.9-7.5 \text{ (m, 10H, Ar-H ), 7.9(s, 1H, -NH ), 2.40 (t, 4H , } J=7.6 \text{ Hz piperazine ), 3.19 (t, 2 H, -CH}_2\text{ at } \alpha \text{ position of } \text{-NH ), 3.53 (t, 4 H , pip ), 2.79 (t, 2H, } -\text{CH}_2\text{ at } \beta \text{ position of pip), 8.8(s, 1H, of } \text{-NH of indole), 3.58(t, 2H, } -\text{CH}_2\text{ at } \alpha \text{ position of piperazine). (Fig.15)}\]

4.2.6.1.12 Synthesis of \(N-(\text{2-}(1\text{H-indol-3-yl})\text{ethyl})\text{-2- (4-benzoypiperazin -1 - yl) propanamide (6e)}\):-

A mixture of \(N-(\text{2-}(1\text{H-indol-3-yl})\text{ethyl)}\text{-2-chloropropanamide, (0.250g,0.001 mol) benzoyl piperazine (0.190 g, 0.001mol) and Sod. carbonate (0.106 g, 0.001 mol) in dry ethanol was refluxed under stirring for 20 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. Thin layer chromatography showed the single spot in DCM: Methanol (9:1). The yield of the pure compound was 51%. Solvent system for TLC was used DCM: Methanol (8: 2).

\[\text{H NMR : (400 MHz, CDCl}_3\text{) : } \delta ,7.0-7.6 \text{ (m, 10H, Ar-H ), 7.64 (d, 1H, } J= 7.6\text{,ArH at ortho), 8.27 (s, 1H, -NH), 2.9 (t, 4H, } J =6.4 \text{ Hz, piperazine ) , 3.26. (t, 2H, } -\text{CH}_2\text{ at } \alpha \text{ position of } \text{-NH ), 4.33 (t, 4H, } J =7.2 \text{ Hz, pip), 3.6(q, 1H, } J =7.6 \text{ Hz -CH}_2\text{ at } \alpha \text{ position of}

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piperazine), 1.38 (t, 2H, J = 6.0 Hz, -CH₂ at β position of –NH ), 2.1 (d, 3H, J = 8.8 Hz, of –CH₃) (Fig.13)

### 4.2.6.1.13 Synthesis of Phenyl (4-(3-(quinolin-8-ylamino)propyl) piperazin-1yl) methanone (6d):- 

A mixture of (4-(3-chloropropyl) piperazin-1-yl)(phenyl) methanone (0.26 g, 0.001mol), 8-amino quinoline (0.43g, 0.003 mol) and Sod. carbonate (0.106 g, 0.001 mol) in dry toluene (10 mL) was refluxed under stirring for 7 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. The yield of pure compound was (63%). Solvent system for TLC was used DCM: Methanol (8: 2).[8, 11]

**¹H NMR**: (300 MHz, CDCl₃): δ, 8.06 (m, 5H, Ar-H), 6.93-7.40 (m, 6H, Ar-H), 3.37 (t, 4H, piperazine, J =7.2 Hz), 3.46. (t, 2H, J =6.6 Hz -CH₂ at α position of –NH ), 2.51 (t, 4H, J =6.6 Hz , pip ), 2.42 (t, 2H, J =7.5 Hz, -CH₂ at α position of piperazine), 1.34 (m, 2H, -CH₂ at β position of piperazine). (Fig.12)

### 4.2.6.1.14 Synthesis of Phenyl (4-(2-(quinolin-8-ylamino)ethyl) piperazin-1-yl)methanone (6c):- 

Procedure is same as above of compound 6d. Only we have taken (4-(2-chloroethyl) piperazin-1-yl) (phenyl)methanone ((0.001. 0.25 gm), The yield of pure compound was (40% ). Solvent system for TLC was used DCM: Methanol (8: 2).

**IR (KBr, cm⁻¹)** 3010 (C-H str (Ar), 2926 (C-H str (aliph), 1623 (C=O), 1521 (C=C str(Ar), 1377 (C-C str(Ar), 1273 (-CO-N ), 1010 (C-N ), 752 (C-H def ). [8, 11] (Fig.41)

### 4.2.6.1.15 Synthesis of (4-(3-(2-(1H-indol-3-yl)ethyl amino) propyl )piperazin-1-yl) (phenyl) methanone (6g):-

A mixture of 4-(3-chloropropyl)piperazin-1-yl)(phenyl)methanone (0.26g, 0.001mol) tryptamine (0.43g, 0.003 mol) and Sod.carbonate (0.106 g, 0.001 mol) in dry toluene (10 mL)
was refluxed under stirring for 7 h. The mixture was filtered and the organic phase was evaporated under reduced pressure. Solvent system for TLC was used DCM: Methanol (7: 3).

[8, 11]. Procedure is same as above of compound (6h) and (6i) also.

### 4.2.6.2 RESULTS AND DISCUSSION

#### Chemistry

The starting material (1X&2) was synthesized by the reaction of benzoyl piperazine with the 1-bromo-2-chloro ethane & 1-bromo-3-chloro propane respectively in the presence of dry K$_2$CO$_3$ and dimethyl formamide. The synthesis of compound (6c, 6d, 6f, 6g, 6h & 6i) has been carried out as presented in scheme-4 and compound (6a, 6b) as presented in Scheme-5. The synthesis of compound (6e, 6k, 6L, 6j) has been carried out as presented in scheme-6. The intermediate compounds (3, 4, 5, 6, 7, 8, 9 & 10) were synthesized by the reaction of benzoyl piperazine with the various acyl chlorides.

The title compound 3-(4-benzoylpiperazin-1-yl)-N-(quinolin-8-yl)propanamide (6a) was synthesized by the refluxing of N-(2-(1H-indol-3-yl) ethyl)-2-chloroacetamide and benzoyl piperazine in the presence of Sod.carbonate and dry ethanol. The compound 3-(4-benzoyl piperazin-1-yl)-N-(quinolin-8-yl)propanamide (6b) was synthesized as same as the compound (6a). The compound phenyl (4-(2-(quinolin-8-ylamino)ethyl) piperazin-1-yl)methanone (6c) was synthesized by the refluxing of (4-(2-chloroethyl) piperazin-1-yl) (phenyl)methanone and 8-amino quinoline in the presence of Sod.carbonate in dry toluene. The compound N-(2-(1H-indol-3-yl) ethyl)-2-(4-benzoylpiperazin-1-yl)propanamide (6e) was synthesized as same as the compound (6a). The compound (4-(3-(2-(1H-indol-3-yl) ethyl amino)propyl)piperazin-1-yl) (phenyl)methanone (6g) was prepared by the refluxing of (4-(3-chloropropyl) piperazin-1-yl) (phenyl)methanone & tryptamine in the presence of Sod.carbonate in dry toluene. N-(2-(1H-indol-3-yl)ethyl)-4-(4-benzoylpiperazin-1-yl)butanamide (6k) and N-(2-(1H-indol-3-yl)ethyl)-3-(4-benzoylpiperazin-1-yl)propanamide (6L) was synthesized same as (6a & 6b). Progress of the reaction was checked by TLC and their structures were confirmed by means of IR, $^1$H-NMR, mass spectrometry and elemental analysis. The spectral data are in total

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agreement with the proposed structures. \(^1\)H-NMR spectra of all prepared compounds are in agreement with the suggested structure.

4.2.7 REACTION SCHEME (7)
General formula:

![Chemical structure](image)

Table 5: Physical and analytical data of compounds

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<th>S. No.</th>
<th>CODE NO.</th>
<th>R</th>
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<th>MOLECULAR WEIGHT</th>
<th>YIELD</th>
<th>Rf VALUE*</th>
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<tr>
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<td>0.58</td>
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<tr>
<td>6.</td>
<td>(3f)</td>
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<td>393</td>
<td>60%</td>
<td>0.57</td>
</tr>
</tbody>
</table>
4.2.7.1 SYNTHESIS & CHARACTERIZATION

4.2.7.1.1 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (5y):

A solution of benzhydryl piperazine (2.52g, 10 mmol) in dioxane (15 mL) was taken and heat for 10 minutes, then after cooled to 0-5°C in an ice bath. Then Chloro propanoyl chloride (1.25 mL, 13mmol) was added with stirring. The reaction mixture was allowed to stirred at Room temperature for 4-6 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride Solution, and finally water wash was given to an organic layer. The organic layer was dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (80%). IR (ATR) 3026 (C-H str (Ar), 2974 (C-H str (aliph), 1705 (C=O), 1643 (C=C str (Ar), 1520 (C-C str (Ar), 1087 (C-N<), 785 (Cl), 671 (C-H def)). [3, 13, 14] (Fig.53)

4.2.7.1.2 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(diethylamino) propan-1-one (3a):

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001 mol), diethyl amine (0.29 mL, 0.003 mol) and dry K2CO3 (0.414g, 0.003 mol) in benzene (10 mL) was stirred for 12 h at 25°C. The solvent was removed under reduced pressure. The residue was taken in water and extracted with dichloromethane. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (75%). Solvent system for TLC was used n-hexane: Ethyl acetate (7: 3) [3]

1H NMR : (300 MHz, CDCl3) : δ 7.13-7.40 (m, 10H, Ar-H), 5.28(s, 1H, of benzhydryl moiety) 3.78-3.82 (t, 2H, J= 6 Hz –COCH2(CH3), 3.57-3.61 (t, 2H, J=6 Hz, pip), 3.40-3.44 (t, 2H, J=6 Hz pip), 2.71-2.77(q, 4H, of –N-(CH2)-CH3), 2.46-2.51 (t, 6H, J= 7.5 Hz in which 4H of pip, 2H of –COCH2), 1.11-1.16 (t, 6H, J= 7.5 Hz of –N-CH2-(CH3)).(Fig.6)

IR (KBr, cm⁻¹): 3021 (C-H str (Ar), 2977 (C-H str (aliph), 2822 (Asym Str. of –CH3), 1631 (C=0), 1545 (C=C str (Ar), 1343 (C=C str (Ar), 1482 (Asym def.), 1422(C-H bend in –CH3), 1215

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4.2.7.1.3 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethyl amino) propan-1-one (3b):

The procedure is same as of compound (3a). At the place of diethyl amine we take dimethyl amine (0.15 mL, 0.003 mol). The yield of pure compound was (70%). Solvent system for TLC was used Ethyl acetate (7: 3). [3]

\[ \text{Found: } C, 75.13; \text{ H, 8.35; N, 11.95. } \]
\[ \text{C}_{22}\text{H}_{29}\text{N}_{3}O, \text{ Required: } C, 75.18; \text{ H, 8.32; N, 11.96} \]

4.2.7.1.4 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino)propan-1-one (3c):

The procedure is same as of compound (3a). At the place of diethyl amine we take N-ethyl methyl amine. The yield of pure compound was (54%). Solvent system for TLC was used n-hexane: Ethyl acetate (7: 3) [3]

\[ \text{IR (KBr, cm}^{-1}) : 3065 (\text{C-H str (Ar)}, 2941 (\text{C-H str (aliph)}), 2914 (\text{Asym Str. of } \text{–CH}_3), 2809 (\text{C-H str in CH}_3), 1684 (\text{C=C str (Ar)}), 1600 (\text{C=C str (Ar)}), 1465 (\text{Asym def.}), 1421 (\text{CN str }), 1394 (\text{C-H bend in } \text{–CH}_3), 1371 (\text{CH bend (alip)}), 684 (\text{C-H def}).\] (Fig.51)

\[ \text{Found: } C, 75.13; \text{ H, 8.35; N, 11.95. } \]
\[ \text{C}_{22}\text{H}_{29}\text{N}_{3}O, \text{ Required: } C, 75.18; \text{ H, 8.32; N, 11.96} \]
The procedure is same as of compound (3a). At the place of diethyl amine we take N-methyl cyclohexyl amine. The yield of pure compound was (58%). Solvent system for TLC was used n-hexane: Ethyl acetate (7: 3).

\[ ^1H \text{ NMR :-(300 MHz, CDCl}_3 :\ \delta \ 7.16-7.41 \ (m,10H, \text{Ar-H}), \ 5.27 \ (s, 1H, of benzhydryl moiety) 3.58-3.62 \ (t, 2H, J= 6 Hz -CO-CH}_2-(CH}_2), \ 3.46-3.49 \ (t, 4H, J=4.5 Hz, pip), \ 2.83 \ (t, 2H, J=7.5Hz, CO-CH}_2), \ 2.57 \ (m, 1H, of cyclohexane), \ 1.47-1.79 \ (m, 10H of cyclohexane).\ ](Fig.9)

4.2.7.1.6 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl)propan-1-one (3e):-

A mixture of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (0.342g, 0.001mol), piperidine (0.001 mol) and dry K\textsubscript{2}CO\textsubscript{3} (0.414g, 0.003 mol) in benzene (10 mL) was stirred for 1 h at 25 °C. After stirring the mixture was refluxed for 12 hrs. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (80%). Rf=0.85. Solvent system for TLC was used n-hexane: Ethyl acetate (3: 7) \[14]\)

\[ ^1H \text{ NMR :-(300 MHz, CDCl}_3 :\ \delta \ 7.16-7.41 \ (m,10H, \text{Ar-H}), \ 5.27(s, 1H, of benzhydryl moiety) 3.58-3.62 \ (t, 2H, J= 4.65 Hz pip), \ 3.45-3.48 \ (t, 2H, J=4.8 Hz , pip), \ 2.66 \ (t, 4H, J=9 Hz, pip), \ 2.49-2.51 \ (t, 2H, J= 15 Hz of –COCH}_2), \ 2.37 \ (t, 2H, J= 9 Hz –COCH}_2(CH}_2), \ 2.35 \ (m, 4H, piperidine), \ 1.55 \ (m, 6H, piperidine).\ ](Fig.10)

4.2.7.1.7 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f):-

The procedure is same as of compound (3e). At the place of piperidine we take morpholine. The yield of pure compound was (65%). Rf= 0.65. Solvent system for TLC was used n-hexane: Ethyl acetate (5: 5).
**EXPERIMENTAL PROTOCOL**

**CHAPTER 4**

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\[ ^{1}H \text{NMR (300 MHz, CDCl}_3 \]: \[ \delta ,7.13-7.41 \text{ (m,10H , Ar-H), 5.172 (s, 1H, of benzhydryl moiety) 3.77-3.82 \text{ (t, 2H, } J= 7.05 \text{ Hz } \text{–COCH}_2(\text{CH}_2), 3.67-3.70 \text{ (t, 4H, } J= 4.5 \text{ Hz, morpholine), 3.59-3.62 \text{ (t, 2H, } J=4.65 \text{ Hz pip), 3.44-3.47 \text{ (t, 2H, } J=4.65 \text{ Hz pip), 2.47-2.51 \text{ (t, 6H, } J= 6 \text{ Hz in which 4H of pip, 2H of } \text{–COCH}_2),} 2.41-2.45 \text{ (t, 4H, } J= 6.9 \text{ Hz of morpholine).} \](Fig.11)

### 4.2.7.2 RESULTS AND DISCUSSION

**Chemistry**

The key starting material (5y) was synthesized according to same procedure as mention for the reaction scheme 1. The synthesis of compound (3a, 3b, 3c, 3d, 3e & 3f) has been carried out as presented in scheme. These compounds were synthesized by the reaction of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one with the various disubstituted amines, piperidine and morpholine.

The title compound 1-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one (3a) was synthesized by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one and diethyl amine in the presence of dry K$_2$CO$_3$ and dichloromethane. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethylamino)propan-1-one (3b) was synthesized as same as of compound (3a). At the place of diethyl amine we take dimethyl amine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl)amino)propan-1-one (3c) was synthesized as same as of compound (3a). At the place of diethyl amine we take N-ethyl methyl amine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl)propan-1-one (3e) was also synthesized as same as of compound (3a). At the place of diethyl amine we take piperidine.

The compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) was synthesized as same as of compound (3a). At the place of diethyl amine we take morpholine.

Structure of the prepared compounds was confirmed with the help of spectral analysis. In the prepared series, 1-(4-benzhydrylpiperazin-1-yl)-3-(cyclohexyl (methyl) amino)propan-1-one (3d) and 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino)propan-1-one (3e) showed average activity. Compound 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl)propan-1-one (3e) was not found. Out of six compounds one compound 1-(4-benzhydrylpiperazin-1-yl)-3-
(dimethyl amino) propan-1-one (3b) exhibited very poor activity and compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) showed excellent activity. All compounds exhibited neurotoxicity at a maximum dose level of 300 mg/kg. None of the compounds showed neurotoxicity at a dose of 30 mg/kg.

4.2.7.3 Introduction of computational:-

In order to further elucidate the requirement of the essential pharmacophoric features in the 3D space we selected the pharmacophore modeling tool for this study. The hypotheses generation methods both in HipHop and HypoGen modules of the Catalyst software for the rational drug design has been reported and successfully applied in drug discovery and research. Previously we had applied the pharmacophore strategy in the discovery of novel scaffolds in diabetes, cancer, and tuberculosis and alzhiemers disease. The catalyst program can be used to mimic the ligand receptor interactions by defining the chemical features of the predefined dataset qualitatively (HipHop) or quantitatively by explaining the correlation between the activity and binding features (HypoGen). The hypotheses generated may be used to analyze the biological activity concerned to the predefined target. In addition to this the hypotheses generated can be used as pharmacophore query for the virtual screening of the available database of commercially available compounds. The pharmacophore based virtual screening protocol could identify novel ligands which may exhibit potent activities to the concerned target enzyme. The literature reveals the large no. of successful applications of the pharmacophore based virtual screening protocol in the modern drug discovery paradigm. The HipHop algorithm finds the common feature pharmacophore model among the set of the highly active ligands and thus referred as qualitative model without the use of the activity data representing the 3D arrangement of the essential features important for the specific activity. In addition we also have carried out the docking studies in order to get the better insights at the molecular level for these compounds mechanistic pathway.
Fig : Essential pharmacophore of anticonvulsant drugs. A= Hydrophobic unit, B= Hydrogen bonding domain, C= Hydrophobic-hydrophillic site, F= lipophillic group
4.2.7.3.1 Result and Discussion of Computational

4.2.7.3.1.1 Common Feature Pharmacophore Development [15, 16, 17]

Structures of training set compounds

Table showed the activities of the training set compounds. Due to the small activity range difference we used the HipHop protocol for the pharmacophore generation. We assume that the most active ligand from the training set was considered to bind in the similar fashion at the receptor active site we evaluated the common feature required for binding by using the HipHop module of catalyst software. The seven training set molecules were submitted for the pharmacophore generation based on common chemical features.

![Structures of training set compounds](image)

**Fig. (i)** Structures of the 18 training set of molecules the pharmacophore development.
4.2.7.3.1.2 Pharmacophore modelling [18, 19]

3D pharmacophore generation

In the training set the highest weight was assigned to the most active ligand PC-23 from selected series this was done by assigning value 2 (which ensures that all of the chemical features in the compound will be considered in building hypothesis space) and 0 (which ensures that all the features were mapped). For the all other compounds the value of 1 (ensures that at least one mapping for each of generated hypotheses will be found), 1 (all but one feature must map) in principle and maximum omitting feature column respectively (for a detailed description Catalyst4.10)

All other parameters were kept at default. The ten hypotheses generated had the scores ranging from 360.378-354.65. The entire ten hypotheses contain seven features viz. hydrogen bond acceptor lipid feature (H, 2), ring aromatic features (R, 3), hydrogen bond donor features (D, 2) common for all hypotheses. Out of ten hypotheses Hypo-1 was selected as it map all the features of the most active compound from the training set molecule. The two H functions maps the on one oxygen from phenoxybenzene part of the most active compound PC-23 from the series (Figure iiB), while the other H function was mapped by the C=S group from the N-(4-bromophenyl)-2-methylene hydrazinecarbothioamide. The three benzene ring from the most active compound PC-23 was mapped for the R function of this pharmacophore model. The remaining two D functions were compiled by the two N-H functions from the N-(4-bromophenyl)-2-methylene hydrazine carbothioamide part at one end of this molecule. The best conformation search method was used in hypothesis generation and the conformations were calculated within the 20 kcal/mol energy threshold.
Table 6: The characteristics of the generated pharmacophore model.

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<th>Hypo.</th>
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<th>Partial Hit</th>
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**4.2.7.3.1.3 Pharmacophore Validation [15, 18, 19]**

The developed pharmacophore model was validated by using the external test set of 6 compounds which are known anticonvulsant drugs. The mapping was carried out using the ligand pharmacophore mapping protocol using the best conformation generation with flexible fitting mode. The table 7 showed the results of the ligand pharmacophore mapping while figure (iiiA) and (iiiB) showed the mapping of the Progabide and Ramesemide on the best pharmacophore model Hypo-1. This validated pharmacophore model was used as a query for the designing of the compounds. Total 20 compounds were designed on the basis of these features and out of 20 top 5 compounds were selected for the synthesis and biological evaluation to further validate this model. The alignment of the most active compound on Hypo-1 along with the mapping of compounds designed on the basis of this pharmacophore were presented in the figure (iiiC and D). The designed compound maps 5 out of the required seven features. The analysis showed these compounds have potential anticonvulsant agents.

**Table 7**: The pharmacophore mapping of the isolated compounds on the best hypothesis (Hypo-1).

<table>
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<th>Comp.</th>
<th>Fit Value</th>
<th>Comp.</th>
<th>Fit Value</th>
</tr>
</thead>
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<tr>
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Fig (iii). A and B mapping of the clinically used compounds Progabide and Ramacemide on Hypo-1. C and D mapping of the top ranked designed compounds on the Hypo-1.

4.2.7.4 Materials and Methods

4.2.7.4.1 Common feature pharmacophore model [15, 18, 19]

The molecules reported earlier for anticonvulsant activity were curetted from literature. The biological activity data did not show required 3 log unit variation necessary for development
of quantitative pharmacophore model using hypogen module of catalyst software. We built common feature pharmacophore ‘Hip-Hop’ model using sixteen structurally diverse compounds encompassing variable activity (training set, Figure. (i))

4.2.7.4.2 Common feature pharmacophore generation [18, 19]

The set of eighteen diverse compounds with maximum activity at the dose of 250mm was used as a training set. Pharmacophore generation was performed on a Windows-based operating system having an Intel Pentium dual core 2.8 GHz processor using the Hip-hop algorithm of CATALYST implemented in the Discovery Studio 2.0 software package (DS 2.0). All compounds used in the study were built using ISIS Draw 2.5 and imported to DS 2.0 Windows. These compounds were optimized using the CHARMm force field (2-4). The conformation generation of these compounds was carried out in the diverse conformation generation protocol of the DS with the parameters of 255 conformations with the energy cut off range of 20 kcal/mol above the global minimum. In the DS, the principal value of 2 and maximum omit feature were assigned to 0 for the most active compound from the training set whereas 1 and 0 were assigned to all other compounds to assign them as moderately active compounds. Minimum inter-feature distance was set to a default value of 2.97 Å in order to consider the functional groups that are present in the training set compounds. This has been done to include the closely related functional groups present in the training set compounds (C=O and –OH) in carboxylic acid which are present in most of the training set compounds involved in the 3T3-L1 inhibition. Feature mapping protocol was used to identify the common features present in the training set compounds. As predicted, HBAL (min. 1 - max. 5), RA (min. 1- max. 5), and HBD (min. 1 - max. 5) were selected during the pharmacophore generation.

4.2.7.4.3 Validation of pharmacophore model
In this validation process the complete strategy was followed to ensure that the acceptability of the pharmacophore model for further studies. For this purpose Hypo-1 was used to predict the training set and some standard compounds from literature. The ligand pharmacophore mapping protocol of DS 2.0 was used to map all the hit compounds with best flexible search option.

4.2.8 REACTION SCHEME (8):-
General formula:-

OH

H

N

N

N

O

Cl

Dioxane,

ClCH₂CH₂COCl

K₂CO₃

+ Piperazine/ Piperidine

+ Tryptamine

(w)

(2)

(5g)

Cl

OH

N

N

N

O

H

N

N

O

Cl
Table 8: Physical and analytical data of compounds

<table>
<thead>
<tr>
<th>S. No.</th>
<th>CODE NO.</th>
<th>R</th>
<th>MOLECULAR FORMULA</th>
<th>MOLECULAR WEIGHT</th>
<th>YIELD</th>
<th>Rf VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(5a)</td>
<td><img src="image1" alt="R" /></td>
<td>C_{26}H_{36}N_{4}O</td>
<td>420</td>
<td>58%</td>
<td>0.71</td>
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<tr>
<td>2.</td>
<td>(5b)</td>
<td><img src="image2" alt="R" /></td>
<td>C_{27}H_{38}N_{4}O</td>
<td>434</td>
<td>66%</td>
<td>0.73</td>
</tr>
<tr>
<td>3.</td>
<td>(5c)</td>
<td><img src="image3" alt="R" /></td>
<td>C_{30}H_{43}N_{5}O</td>
<td>489</td>
<td>69%</td>
<td>0.70</td>
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<tr>
<td>4.</td>
<td>(5d)</td>
<td><img src="image4" alt="R" /></td>
<td>C_{27}H_{37}N_{5}O</td>
<td>419</td>
<td>65%</td>
<td>0.77</td>
</tr>
<tr>
<td>5.</td>
<td>(5e)</td>
<td><img src="image5" alt="R" /></td>
<td>C_{28}H_{39}N_{5}O</td>
<td>433</td>
<td>70%</td>
<td>0.71</td>
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</tbody>
</table>
4.2.8.1 Synthesis & Characterization:-

4.2.8.1.1 Synthesis of benzhydryl homopiperazine (W):-

Benzhydrol (53.36 g, 0.29mol) was dissolve in dichloromethane (100 mL). Thionyl chloride (50 mL, 0.69mol) was added to the reaction mixture and reaction mixture was stirred at 40°C for 3 h. The solvent was evaporated under vacuum and the residue was dissolved in acetonitrile (20 mL), yield was 90%. Benzhydryl chloride (58.58g, 0.29mol) was taken in a RBF and homopiperazine (24.6g, 0.29mol) was added and the mixture was refluxed for 12 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (250 mL) and washed with water (100 mL) followed by 1N HCl (100 mL). The acid phase was washed with ethyl acetate (3 × 60 mL). The ethyl acetate layer was discarded and the remaining water layer was neutralized with 3N NaOH aqueous solutions (40 mL) to pH>10. The aqueous solution was extracted with dichloromethane (3 × 80 mL). The combined dichloromethane was washed successively with brine, dried over Na₂SO₄ and evaporated under vacuum to provide the title compound obtained as yellow oil. (Yield was 85%). Solvent system for TLC was used Pet ether: Ethyl acetate (4: 1). [1]

\(^1H\) NMR :-(400 MHz, CDCl₃ ) : \( \delta \) 7.18-7.45 (m, 10H, Ar-H), 3.50 (t, 2H, of -CH₂), 3.46 (t, 2H, of -CH₂), 3.32 (t, 2H, -CH₂ of homopiperazine ), 2.63 (t, 2H, -CH₂), 1.97 (s, 1H, -NH), 1.54. (t, 2H, -CH₂ in ring). (fig.29)

4.2.8.1.2 Synthesis of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(4-methylpiperazin-1-yl) propan-1-one (5a):-

<table>
<thead>
<tr>
<th>6.</th>
<th>(5f)</th>
<th>![Chemical Structure]</th>
<th>C₂₇H₃₇N₃O</th>
<th>419</th>
<th>60%</th>
<th>0.64</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>(5g)</td>
<td>![Chemical Structure]</td>
<td>C₃₁H₃₆N₄O</td>
<td>479</td>
<td>45%</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Kuldeep Singh, Ph.D. Thesis, Integral University, Lucknow*
A mixture of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-chloropropan-1-one (0.356g, 0.001 mol), 1-methyl piperazine (0.11 mL, 0.001 mol) and dry K$_2$CO$_3$ (0.414g, 0.003 mol) in alcohol (10 mL) was stirred for 1 h at 25 °C. After this the mixture was refluxed & stirred at 60 °C for 24 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound was (58%). Solvent system for TLC was used Pet ether: Ethyl acetate (5: 5). [8]

MS (ESI+) m/z =420 (M$^+$) 421, (M$^+$+1) = 422 (fig.35)

Found: C, 74.27; H, 8.60; N, 13.35. C$_{26}$H$_{36}$N$_4$O, Required: C, 74.25; H, 8.63; N, 13.32

4.2.8.1.3 Synthesis of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(4-ethylpiperazin-1-yl) propan-1-one (5b) :-

The procedure is same as of compound (5a). At the place of 1-methyl piperazine we take 1-ethyl piperazine (0.14 mL, 0.001 mol). The yield of pure compound was (66%). Solvent system for TLC was used Pet ether: Ethyl acetate (5: 5) [8]

Elemental: Found: C, 74.60; H, 8.86; N, 12.88. C$_{27}$H$_{38}$N$_4$O, Requires: C, 74.61; H, 8.81; N, 12.89

4.2.8.1.4 Synthesis of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(4-(pyridin-2-yl)piperazin-1-yl) propan-1-one (5c):-

The procedure is same as of compound (5a). At the place of 1-methyl piperazine we take 1-(2-pyridyl piperazine (0.46 mL, 0.003 mol). The yield of pure compound was (69%).single spot was shown in n-hexane: EtoAc (8:2). [8]

4.2.8.1.5 Synthesis of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(2-methylpiperidin-1-yl) propan-1-one (5d):-

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The procedure is same as of compound (5a). At the place of 1-methyl piperazine we take 2-methyl piperidine (0.36 mL, 0.003 mol). The yield of pure compound was (65%). Single spot was shown in Petroleum ether: EtoAc (5:5). [8]

4.2.8.1.6 Synthesis of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(2, 6-dimethylpiperidin-1-yl) propan-1-one (5e):

The procedure is same as of compound (5a). At the place of 1-methyl piperazine we take 2, 6-dimethyl piperidine (0.40 mL, 0.003 mol). The yield of pure compound was (69%). Solvent system for TLC was used Pet ether: Ethyl acetate (5: 5). [8]

MS (ESI+) m/z =433 (M⁺) 434, (M⁺+1) = 435 (Fig.36)

4.2.8.1.7 Synthesis of 3-(2-(1H-indol-3-yl) ethyl amino)-1-(4-benzhydryl-1,4-diazepan-1-yl)propan-1-one (5g):

A mixture of 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-chloropropan-1-one (0.356g, 0.001mol), tryptamine (0.48g, 0.003 mol) and dry K₂CO₃ (0.414g, 0.003 mol) in dichloromethane (10 mL) was stirred for 1 h at 25 °C. After stirring the mixture was refluxed for 6-12 h. The solvent was removed under reduced pressure. The residue was taken in water and extracted with ethyl acetate. The organic layer was washed with distilled water three times approximately and dried with anhydrous Sodium sulphate. Solvent was removed under reduced pressure. The yield of pure compound (45%). Solvent system for TLC was used Pet ether: Ethyl acetate (5: 5). [7]

MS (ESI+) m/z =479, (M⁺) = 480, (M⁺+1) = 481 (Fig.37)
Mass fragmentation:-

Compound 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(4-methylpipеразин-1-yl) propan-1-one (5a):-

```
Chemical Formula: C_{13}H_{11}^+  
Exact Mass: 167.09
```

```
Chemical Formula: C_{13}H_{21}N_2^+  
Exact Mass: 265.17
```

```
Chemical Formula: C_5H_{11}N_2^+  
Exact Mass: 99.09
```

```
M+1=421
```

```
Chemical Formula: C_{13}H_{29}N_4O^+  
Exact Mass: 253.20
```

```
Chemical Formula: C_{13}H_{29}N_2O^+  
Exact Mass: 321.20
```
Compound 1-(4-benzhydryl-1, 4-diazepan-1-yl)-3-(2, 6-dimethylpiperidin-1-yl) propan-1-one (5e):-

Chemical Formula: C_{13}H_{11}+  
Exact Mass: 167.09

Chemical Formula: C_{10}H_{15}NO+  
Exact Mass: 168.14

Chemical Formula: C_{7}H_{14}N+  
Exact Mass: 112.11

Chemical Formula: C_{9}H_{19}N_{2}+  
Exact Mass: 265.17

M+1=434

Chemical Formula: C_{13}H_{25}N_{2}O+  
Exact Mass: 321.20

Chemical Formula: C_{15}H_{28}N_{3}O+  
Exact Mass: 266.22

Chemical Formula: C_{6}H_{10}N_{2}++  
Exact Mass: 98.08
Compound 3-(2-(1H-indol-3-yl) ethylamino)-1-(4-benzhydryl-1, 4-diazepan-1-yl) propan-1-one (5g):
4.2.8.2 RESULTS AND DISCUSSION

Chemistry

The key starting material (W) was synthesized by the reaction of benzhydrol and thionyl chloride in the presence of dichloromethane. Synthesis of benzhydrol chloride occurs. It refluxes with the homopiperazine in the presence of acetonitrile solvent. The compound 1-(4-benzhydryl-1, 4-diazepan-yl)-3-chloropropan-1-one (2) was synthesized by the stirring of benzhydryl piperazine and chloropropanoyl chloride firstly at 0 °C and finally at room temperature.

The title compound 1-(4-benzhydryl-1, 4-diazepan-yl)-3-(4-methylpiperazin-1-yl) propan-1-one (5a) was synthesized by the refluxing of 1-(4-benzhydryl-1, 4-diazepan-yl)-3-chloropropan-1-one and 1-methyl piperazine in the presence of K₂CO₃ and alcohol. The compound 1-(4-benzhydryl-1, 4-diazepan-yl)-3-(4-ethylpiperazin-1-yl) propan-1-one (5b) was synthesized by refluxing of 1-(4-benzhydryl-1, 4-diazepan-yl)-3-chloropropan-1-one & 1-ethyl piperazine in the presence of dry K₂CO₃ and alcohol. The compound 1-(4-benzhydryl-1,4-diazepan-yl)-3-(4-(pyridin-2-yl)piperazin-1-yl)propan-1-one (5c) was prepared by the same procedure as mention above for (5a) the difference is only in this the reaction takes place in the presence of dichloromethane. The compound 1-(4-benzhydryl-1, 4-diazepan-yl)-3-(2-methylpiperidin-1-yl) propan-1-one (5d) was synthesized by refluxing 1-(4-benzhydryl-1, 4-diazepan-yl)-3-chloropropan-1-one 2-methyl piperidine in the presence of dry K₂CO₃ in dichloromethane. The compound 1-(4-benzhydryl-1, 4-diazepan-yl)-3-(2, 6-dimethylpiperidin-1-yl) propan-1-one (5e) was synthesized by the same procedure as of compound (5d). Only the difference is that at the place of 2-methyl piperidine we take 2,6-dimethyl piperidine. The compound 3-(2-(1H-indol-3-yl) ethyl amino)-1-(4-benzhydryl-1, 4-diazepan-yl) propan-1-one (5g) was synthesized by the stirring and refluxing of 1-(4-benzhydryl-1, 4-diazepan-yl)-3-chloropropan-1-one and tryptamine in the presence of dry K₂CO₃ and dichloromethane. Progress of the reaction was checked by TLC and their structures were confirmed by means of IR, ¹H-NMR, mass spectrometry and elemental analysis. The spectral data are in total agreement with the proposed structures.
4.2.9 REACTION SCHEME (9):

\[ \text{OH} + \text{SOCl}_2 \rightarrow \\text{(Z)} \]

+ Br.CH₂.CH₂.CH₂Cl

Acetone

\[ \text{Cl} \]

(k)

\[ \text{K}_2\text{CO}_3 \]

+ R= Piperazine / Piperidine

8a=  
8b=  
8c=  
8d=  
8e=  
8f=  
8g=  
8h=  

Acetone
General formula:-

![General formula image]

Table 9:- Physical and analytical data of compounds

<table>
<thead>
<tr>
<th>S. No.</th>
<th>CODE NO.</th>
<th>R</th>
<th>MOLECULAR FORMULA</th>
<th>MOLECULAR WEIGHT</th>
<th>YIELD</th>
<th>Rf VALUE*</th>
</tr>
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<tbody>
<tr>
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<td>(8a)</td>
<td></td>
<td>C₂₆H₃₈N₄</td>
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<td>75%</td>
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<td>2.</td>
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<td>59%</td>
<td>0.71</td>
</tr>
<tr>
<td>3.</td>
<td>(8c)</td>
<td></td>
<td>C₂₅H₃₅N₃</td>
<td>377</td>
<td>67%</td>
<td>0.64</td>
</tr>
<tr>
<td>4.</td>
<td>(8e)</td>
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<td>C₂₄H₃₅N₃</td>
<td>365</td>
<td>70%</td>
<td>0.60</td>
</tr>
<tr>
<td>5.</td>
<td>(8f)</td>
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<td>C₂₄H₃₅N₃O₂</td>
<td>397</td>
<td>62%</td>
<td>0.64</td>
</tr>
<tr>
<td>6.</td>
<td>(8g)</td>
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<td>C₂₂H₃₁N₃</td>
<td>337</td>
<td>66%</td>
<td>0.59</td>
</tr>
<tr>
<td>8.</td>
<td>(8h)</td>
<td></td>
<td>C₂₀H₃₇N₅</td>
<td>455</td>
<td>71%</td>
<td>0.73</td>
</tr>
</tbody>
</table>
4.2.9.1 Synthesis & Characterization:

4.2.9.1.1 Synthesis of 1-benzhydryl-4-(3-chloropropyl)piperazine (k): [23, 24]

To a solution of benzhydryl piperazine (3g, 3.96 mmol,) in acetone (50 mL) and 45 mL of 25% aqueous sodium hydroxide solution was added and stirred for 10 minutes. The spacer or linker 1-bromo-3-chloro propane,(1.23 mL, 3.96mmol) was added to the reaction mixture and further stirred for a certain time (20 h approximately) at 25°C. Water was added to the mixture and 25 mL of diethyl ether dried over sodium sulphate, filtered, concentrated & purified by column (acetone/ heptane) give as yellow syrup. Solvent system for TLC used was methanol: ethyl acetate (8:2).

MS (ESI+) m/z =328, (M⁺) = 329, (M⁺+2) = 331 (Fig.31)

4.2.9.1.2 Synthesis of 1-benzhydryl-4-(3-(4-ethylpiperazin-1-yl)propyl)piperazine (8a): [23]

A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (3.28g, 0.01mol) and 1-ethyl piperazine (1.26 mL, 0.01 mol) was stirred in the presence of powdered potassium carbonate and potassium iodide in N,N-dimethylformamide for about 6 h at 50°C. The reaction was monitored by TLC (chloroform: methanol = 4.5:0.5). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralized water was added to the residue, extracted with ethyl acetate, and dried over anhydrous Na₂SO₄. mp was 212°C. Solvent system for TLC was used Chloroform : Methanol (4.5 : 0.5).

¹H NMR :-(300 MHz, CDCl₃ ) : δ ,7.12-7.98 (m, 10H, Ar-H), 4.19 (s,1H, -CH of benzhydryl moiety), 2.41 (t, 4H ,-N-CH₂), 2.38 (q, 2H,-N-(CH₂)-CH₃) , 2.34 (s, 16H, piperazine), 1.64 (m, 2H,-N-(CH₂-(CH₂)-CH₂-), 1.18 (t, 3H ,J=6, -N-CH₂-(CH₃). (Fig.22)

MS (ESI+) m/z =406, (M⁺) = 407 (Fig.38)

4.2.9.1.3 Synthesis of 4-(3-(4-benzhydrylpiperazin-1-yl)propyl)morpholine (8b): [24]
A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (3.28g, 0.01 mol) and morpholine (0.86 mL, 0.01 mol) was stirred in the presence of powdered potassium carbonate and potassium iodide in N,N-dimethylformamide for about 6 h at 50°C. The reaction was monitored by TLC (chloroform: methanol = 4.5:0.5). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralised water was added to the residue, extracted with ethyl acetate, and dried over anhydrous Na$_2$SO$_4$. mp was 220°C. Solvent system for TLC was used Chloroform : Methanol (4 : 1).

$^1$H NMR :-(300 MHz, CDCl$_3$ ) : δ ,7.13-7.98 (m, 10H, Ar-H ), 5.28 (s, 1H, -CH of benzhydryl moiety), 3.66(t, 4H, J=4.5, morpholine), 2.46 (t,4H, N-(CH$_2$)-CH$_2$-(CH$_2$), 2.36 (t, 4H, morpholine) , 2.33(s, 8H , piperazine), 1.69 (m, 2H ,N-(CH$_2$)-(CH$_2$)-CH$_2$). (Fig.23)

4.2.9.1.5 Synthesis of 3-(4-benzhydryl)piperazin-1-yl)-N,N-diethylpropan-1-amine (8e):-[24, 25]

A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (3.28 g, 0.01 mol) and diethyl amine (3.09 mL, 0.03 mol) was stirred in the presence of powdered potassium carbonate in acetone for about 3 h at room temperature. The reaction was monitored by TLC (chloroform: methanol = 4.5:0.5). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralised water was added to the residue, extracted with dichloromethane, and dried over anhydrous Na$_2$SO$_4$. mp was 196°C. Solvent system for TLC was used Methanol : EtoAc (8 : 2).

$^1$H NMR :-(300 MHz, CDCl$_3$ ) : δ ,7.14-7.99 (m, 10H , Ar-H ), 5.28 (s, 1H, -CH of benzhydryl moiety), 2.47 (t, 4H, -N-(CH$_2$)-CH$_2$-(CH$_2$) ,2.44 (t, 4H, piperidine ), 2.35 (s,16H, piperazine), 1.57 (m, 2H, -N-(CH$_2$)-(CH$_2$)-CH$_2$). (Fig.24)
reduced pressure. Demineralized water was added to the residue, extracted with dichloromethane, and dried over anhydrous Na$_2$SO$_4$.

$^1$H NMR -(300 MHz, CDCl$_3$) : δ 7.15-7.41 (m, 10H, Ar-H), 5.28 (s, 1H, -CH of benzhydryl moiety), 3.51 (q, 2H, -N-(CH$_2$)-CH$_3$), 2.45 (t, 4H, -N-(CH$_2$)-CH$_2$-(CH$_2$), 2.35 (s, 8H, piperazine), 1.90 (m, 2H, -N-(CH$_2$-(CH$_2$)-CH$_2$-), 1.18 (t, 3H, N-CH$_3$). (Fig.26)

4.2.9.1.6 Synthesis of 2, 2'-((3-(4-benzhydrylpiperazin-1-yl)propylazanediyl)diethanol (8f):-[24, 25]

A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (0.65 g, 0.01 mol) and diethanolamine (0.19 mL, 0.01 mol) was refluxed in the presence of powdered potassium carbonate and potassium iodide in acetonitrile for about 24 h. The reaction was monitored by TLC (chloroform: methanol = 4.5:0.5). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralized water was added to the residue, extracted with dichloromethane, and dried over anhydrous Na$_2$SO$_4$. mp was 263°C. 

$^1$H NMR -(300 MHz, CDCl$_3$) : δ 7.14-7.42 (m, 10H, Ar-H), 5.29 (s, 1H, -CH of benzhydryl moiety), 3.56 (t, 2H, -N-(CH$_2$-(CH$_2$)-OH), 2.55 (t, 2H, -N-(CH$_2$)-CH$_2$-OH), 2.45 (t, 4H, -N-(CH$_2$)-CH$_2$-(CH$_2$), 2.33 (s, 8H, piperazine), 1.60 (t, 2H, -N-CH$_2$-(CH$_2$)-CH$_2$-). (Fig.27)

4.2.9.1.7  Synthesis of 3-(4-benzhydrylpiperazin-1-yl)-N,N-dimethylpropan-1-amine (8g):-[24, 25]

A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (3.28 g, 0.01 mol) and dimethyl amine (2.01 mL, 0.03 mol) was stirred in the presence of powdered potassium carbonate in acetone for about 10 h at room temperature. The reaction was monitored by TLC (chloroform: methanol = 4.5:0.5). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralized water was added to the residue, extracted with dichloromethane, and dried over anhydrous Na$_2$SO$_4$. mp was 175°C.

MS (ESI+) m/z =337, (M$^+$) = 338 (Fig.39)
4.2.9.1.8 Synthesis of 1-benzhydryl-4-(3-(4-(pyridin-2-yl)piperazin-1-yl)propyl)piperazine (8h): [24, 25]

A mixture of 1-benzhydryl-4-(3-chloropropyl)piperazine (3.28 g, 0.01 mol) and 1-(2-pyridyl)piperazine (1.53 mL, 0.01 mol) was stirred in the presence of powdered potassium carbonate and potassium iodide in N,N-dimethylformamide for about 17 h at 60°C-70°C. The reaction was monitored by TLC (chloroform: methanol = 4:5:1). After completion of the reaction, the solvent was evaporated under reduced pressure. Demineralized water was added to the residue, extracted with dichloromethane, and dried over anhydrous Na₂SO₄. mp was 243°C.

MS (ESI+) m/z = 455, (M⁺) = 456 (Fig.40)

4.2.9.2 RESULTS AND DISCUSSION

Chemistry

The key starting material (Z) was synthesized according to published procedure (Meng T et al., 2010). Compound (k) was synthesized by the reaction of benzhydryl piperazine with 1-bromo-3-chloropropane in the presence of acetone and strong base. The synthesis of compound (8a, 8b, 8c) were synthesized by the reaction of 1-benzhydryl-4-(3-chloropropyl)piperazine with the 1-ethyl piperazine, morpholine and piperidine respectively in the presence of powdered potassium carbonate and potassium iodide in N,N-dimethylformamide for about 6 h at 50°C. The compound 3-(4-benzhydryl piperazin-1-yl)-N,N-diethylpropan-1-amine (8e) was synthesized in the presence of powdered potassium carbonate in acetone for about 3 h at room temperature.

The title compound 2, 2’-(3-(4-benzhydrylpiperazin-1-yl)propylazanediyl)diethanol (8f) was synthesized by the refluxing of 1-benzhydryl-4-(3-chloropropyl)piperazine & diethanolamine in the presence of powdered potassium carbonate and potassium iodide in acetonitrile for about 24 h. Compound 3-(4-benzhydrylpiperazin-1-yl)-N,N-dimethylpropan-1-amine (8g) was prepared as same as compound (8e). Compound 1-benzhydryl-4-(3-(4-(pyridin-2-yl)piperazin-1-yl)propyl)piperazine (8h) was prepared by stirring in the presence of powdered...
potassium carbonate and potassium iodide in N,N-dimethylformamide for about 17 h at 60°C-70°C. Progress of the reaction was checked by TLC and their structures were confirmed by means of IR, ¹H-NMR, mass spectrometry and elemental analysis. The spectral data are in total agreement with the proposed structures. ¹H-NMR spectra of all prepared compounds are in agreement with the suggested structure.

References:


