6. Experimental

The experimental work performed to achieve the goals of the proposed work carried out has been described in the following section.

6.1. *In silico* work

6.2. Chemical work

6.3. Biological work

6.1. *In silico* studies

6.1.1. Molecular Docking

To evaluate the binding affinity and the orientation of ligands on active site of receptor, i*n*-silico method such as molecular docking can be helpful. All the synthesized compounds were docked in the active site of *h*AChE, *h*BuChE and *h*MAO-B enzyme using Maestro 13.5 (Schrodinger LLC). Co-crystallized protein structures, *h*AChE **(PDB: 4EY7),** *h*BuChE **(PDB: 5K5E)** and *h*MAO-B **(PDB: 2V5Z)** were retrieved and imported from protein data bank (RCSB.org)[1] and prepared protein using "protein preparation wizard" of Schrodinger suite 2023. All the ligands were drawn with the help of ChemDraw 16.0 and imported for the ligand preparation. The ligand preparation was performed using ligPrep of Schrodinger suit 2023. OPLS force field was used to minimize the energy of imported ligands. Before performing molecular docking validation of binding site was done by redocking co-crystalized ligand on the active site of protein where grid was generated. Ligand docking was performed for prepared ligands using Standard Precision (SP) method and subsequently Extra Precision was performed for top ligands came from SP method. Docking scores (Kcal/mole) and binding modes were analyzed for docked ligands. The validation of docking protocol was done by comparing the interactions of donepezil and safinamide in the binding site of AChE and MAO-B enzyme, respectively.

6.1.2. Physicochemical and pharmacokinetic properties prediction

Physicochemical and pharmacokinetic properties was predicted using the QikProp program. All the drawn ligand structures using ChemDraw 16.0 were imported into the maestro suite and prepared by energy minimization using OPLS force field at the physiological pH using LigPrep module of Schrödinger. Qik-Prop predicted various physicochemical and pharmacokinetic descriptors for all the prepared ligands. Software predicted 51 properties among of them major descriptors were focused in this study which were Lipinski's rule of five (Rule of 5); NRB, number of rotatable bonds; PSA, polar surface area; SASA, total solvent accessible surface area; CNS, predicted central nervous system activity; QPPMDCK, predicted apparent MDCK cell permeability; QPPCaco, Caco-2 cell

permeability in nm/s; QPlogBB, brain/blood partition coefficient; QPlogKhsa, binding to human serum albumin; QPlogS, predicted aqueous solubility; and percent human-oral absorption, human oral absorption.

6.2. Chemical work

All the chemical and reagents used for synthesis were of analytical reagent grade and sourced from chemical providers like S. D. Fine Chemicals, Spectrochem, Qualigens, Loba Chemie, Sigma-Aldrich, and Avra Chemicals. The chemical reagents and solvents used in the synthesis of the intended compounds were purified using established laboratory techniques before utilization[2]. The progress of the reactions was monitored using thin layer chromatography (TLC) on aluminum-supported silica gel 60 G plates, with visualization achieved through ultraviolet light (254 nm) and ninhydrin reagent. Melting points of the synthesized compounds were measured using an oil bath melting point apparatus from Veego, employing the open glass capillary technique. Compounds were purified via column chromatography utilizing silica gel (100-200 mesh) or neutral alumina as stationary phases. The infrared spectra of the individual compounds were recorded with a Bruker FT-IR model ALPHA II (Germany) spectrophotometer, with wave numbers expressed in cm^{-1}. For ^{1}H-NMR and ^{13}C-NMR analysis, a Bruker Advance-II 400 MHz spectrometer was used in DMSO (d6) and CDCl3 solvents (with TMS as the internal standard). Proton multiplicities were designated as singlet (s), doublet (d), doublet of doublet (dd), doublet of triplet (dt), triplet (t), multiplet (m), and broad singlet (bs), with chemical shift values reported in δ ppm and coupling constants (J) in Hz. Mass spectra were obtained using a Waters single quad mass spectrometer with ESI as the ion source, while HRMS mass spectra were recorded on an Agilent 6540 UHD Accurate-mass spectrometer combined with a Q-TOF LC-MS mass analyzer.

For determining purity of the compounds, Agilent 1260 Infinity HPLC instrument was used to perform analysis with a quaternary pump which delivered the gradient mobile phase at a flow rate of 1.0 ml/min, Buffer: A :0.1% FA in H_2O; B: ACN+H_2O (90:10) (150MM). The gradient program followed was, T/B;0/10,3/10,10/100,19/100,19.5/10,24/10; with a 1260 ALS Agilent Infinity High Performance Autosampler, degasser and column compartment. The auto-sampler was equipped with a 100 well plate and was used to inject 20 µl samples onto the HPLC column. The column used was a HYPERSIL GOLD C18 (particle size 3 µm, diameter 2.1 mm, length 150 mm). The column was kept at 35°C with Agilent 1260 Infinity Thermostatted Column Compartment. 1260 Infinity II Variable Wavelength

Detector was used as detector for the sample analysis. Purity of the compounds was found to be higher than 95 %.

6.2.1. Synthesis of 1,2-bis(phenyl)ethanone (59)

In 50 ml RBF, 2-phenyl acetic acid (**53,** 1 gm, 6.01 mM) was reacted with thionyl chloride (1.74 ml, 24.07 mM) at reflux condition for 2-3 hrs in vacuum sealed and dry condition. Completion of the reaction was monitored by TLC. After completion of the reaction, fumes of HCl and gaseous by-products were removed by vacuum. In another 100 ml RBF, anhydrous aluminium chloride (1.20 gm, 9.02 mM) was taken in dry DCM at 0-4 ^{o}C and benzene (**56,** 0.65 ml, 6.01 mM) was added to it. To this reaction mixture 2-(phenyl) acetyl chloride in dry DCM was added slowly drop-wise in cold condition. The reaction mixture was then allowed to stir for 2 hrs. After completion of the reaction, the reaction mixture was poured into crushed ice containing conc. HCl. The mixture was then extracted with chloroform (30 ml X 3) and the combined organic layer was washed with $NaHCO_3$ solution (5%, aqueous). The organic layer was dried over anhydrous Na_2SO_4 and removed to obtain the desired product (**59,** 1.35 gm, 83%); m.p. 54 - 55 °C (Lit.[3,4] 54 - 55 ^{o}C).

Analysis:

TLC : R_f 0.89 *n*-Hexane: Ethyl acetate (8:2).

IR (cm^{-1}) : 3025, 2963, 1669, 1455, 1166, 1023.

6.2.2. Synthesis of 1,2-bis(4-methoxyphenyl)ethanone (60)

Compound **(60)** was prepared by using 2-(4-methoxyphenyl)acetic acid (**54**, 1 gm, 6.01 mM) and anisole (**57**, 0.65 ml, 6.01 mM) as per the procedure described for the synthesis of compound **(59)**. The titled compound **(60)** was obtained as white solid (**60**, 1.35 gm, 83%); m.p. 109-111 ^{o}C (Lit.[5] 110-112 ^{o}C).

Analysis:

TLC : R_f 0.82 *n*-Hexane: Ethyl acetate (8:2).

IR (cm^{-1}) : 3028, 2963, 1671, 1596, 1455, 1261, 1166, 1023, 825.

6.2.3. Synthesis of 1,2-bis(4-chlorophenyl)ethanone (61)

Compound **(61)** was prepared by treating 2-(4-chlorophenyl)acetic acid (**55**, 1 gm, 5.86 mM) with thionyl chloride (1.7 ml, 23.45 mM) and subsequent Friedel-Craft acylation reaction with chlorobenzene (**58**, 0.6 ml, 5.86 mM) following the procedure described for the synthesis of compound **(59)** to obtain a white solid (1.32 gm, 85%); m.p. 111-113 °C (Lit.[6,7]112-114 °C).

Analysis:

TLC : R_f 0.8 *n*-Hexane: Ethyl acetate (8:2).

IR (cm^{-1}) : 3092, 3039, 2897, 1689, 1585, 1489, 1205, 1090, 821.

6.2.4. Synthesis of *(E)*-3-(diphenylamino)-1,2-diphenylprop-2-e*n*-1-one (62)

In a 10 ml RBF, 1,2-bis(phenyl)ethanone (**59**, 1.00 gm, 3.9 mM) was reacted neat with DMF.DMA (1.39 gm, 11.7 mM) at 80 ºC for 16 hrs. After completion, the reaction mixture was cooled and *n*-hexane was added to get a yellow precipitate of product **(62)** which was further washed with pet. ether and used in the next step without purification (1.19 gm, 98%);m.p 129-131 °C (Lit [8,9]130-131 °C)

Analysis:

TLC : R_f 0.52 *n*-Hexane: Ethyl acetate (9:1).

IR (cm^{-1}) : 2847, 1651, 1589, 1262, 1160, 1020.

6.2.5. Synthesis of *(E)*-3-(dimethylamino)-1,2-bis(4-methoxyphenyl)prop-2-e*n*-1-one (63)

In a 10 ml RBF, 1,2-bis(4-methoxyphenyl)ethanone (**60,** 1.00 gm, 3.9 mM) was reacted neat with DMF.DMA (1.39 gm, 11.7 mM) at 80 ºC for 16 hrs. After completion, the reaction mixture was cooled and *n*-hexane was added to get a yellow precipitate of product **(63)** which was further washed with pet. ether and used in the next step without purification (1.15 gm, 96%) m.p. 117-119 ºC (116-118 °C) Lit[10].

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (9:1).

IR (cm^{-1}) : 2951, 1655, 1599, 1262, 1016, 877, 833, 750.

6.2.6. Synthesis of *(E)*-1,2-bis(4-chlorophenyl)-3-(dimethylamino)prop-2-e*n*-1-one (64)

Compound (**64**) was synthesized from 1,2-bis(4-chlorophenyl)ethanone (**55**, 1.0 gm, 3.77 mM) and DMF.DMA (1.25 gm, 11.31 mM) using the procedure described for the synthesis of compound **(62)** to obtain the desired product (**64**, 0.79 gm, 75%); m.p. 110-112 ºC (Lit[10] 110-112 ºC) .

Analysis:

TLC : R_f 0.52 *n*-Hexane: Ethyl acetate (9:1).

IR (cm^{-1}) : 3092, 2928, 1662, 1583, 1210, 1171, 1090, 879, 834, 764.

6.2.7. Synthesis of 3,4-diphenyl-1*H*-pyrazole (65)

(E)-3-(dimethylamino)-1,2-diphenylprop-2-e*n*-1-one (**62**, 1gm, 3.97 mmol) was dissolved in 20 ml methanol. Hydrazine hydrate (0.386 ml, 7.94mmol) was added and the reaction mixture was refluxed for 3-4 hrs. After the completion of reaction, excess methanol was removed under vacuum and reaction mixture was poured in ice-cold water. The solid precipitate obtained was then filtered, dried and stored (**65,** 0.85 gm, 95 %); m.p.126-128 ºC.

Analysis:

TLC : R_f 0.37 *n*-Hexane: Ethyl acetate (7:3).

IR (cm^{-1}) : 3140, 2838, 1602, 758.

Mass (m/z) : 220.9 $(M)^+$

^1H NMR($CDCl_3$, δ) :δ 7.65 (s, 1H), 7.47 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.35 – 7.32 (m, 3H), 7.31 (d, *J* = 4.4 Hz, 3H), 7.26 (d, *J* = 6.8 Hz, 2H).

6.2.8. Synthesis of 3,4-bis(4-methoxyphenyl)-1*H*-pyrazole (66)

(E)-3-(dimethylamino)-1,2-bis(4-methoxyphenyl)prop-2-e*n*-1-one (**63,** 1gm, 3.21 mmol) was dissolved in 20 ml methanol. Hydrazine hydrate (0.321 ml, 6.42 mmol) was added and the reaction mixture was refluxed for 3-4 hrs. After the completion of reaction, excess methanol was removed under vacuum and reaction mixture was poured in ice-cold water. The solid precipitate obtained **(66)** was then filtered, dried and stored (0.85 gm, 95%); m.p. 108-110 **º**C.

Analysis:

TLC : R_f 0.37 *n*-Hexane: Ethyl acetate (7:3)

IR (cm^{-1}) : 2832, 1759, 1612, 1435, 1285, 1243, 1072, 833.

Mass (m/z) : 281.2 $(M+H)^+$

^1H NMR($CDCl_3$, δ) : δ 7.61 (s, 1H), 7.42 – 7.34 (m, 2H), 7.25 – 7.21 (m, 2H), 6.90 – 6.82 (m, 4H), 3.81 (s, 6H).

6.2.9. Synthesis of 3,4-bis(4-chlorophenyl)-1*H*-pyrazole (67)

Compound **(67)** was synthesized from 1,2-bis(4-chlorophenyl)-3-(dimethylamino)prop-2-e*n*-1-one (**64,** 1gm, 3.12 mmol) and hydrazine hydrate (0.302 ml, 6.42 mmol) using the procedure described for the synthesis of compound **(65)** to obtain the desired product (**67,** 0.78 gm, 86%); m.p. 140-143 ºC.

Analysis:

TLC : R_f 0.51 *n*-Hexane: Ethyl acetate (7:3)

IR (cm^{-1}) : 3152, 2915, 1525, 1093, 828.

Mass (m/z) : 289 $(M+H)^+$, 291 $(M+2H)^+$

^1H NMR ($CDCl_3$) : δ 7.69 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.34 (dt, *J* = 7.4, 3.6 Hz, 4H), 7.24 (s, 2H).

6.2.10. Synthesis of phenyl 3,4-diphenyl-1*H*-pyrazole-1-carboxylate (68)

3,4-Diphenyl-1*H*-pyrazole (**65,** 0.5 gm, 2.27 mmol) was dissolved in 10 ml DCM. In ice-cold condition, triethylamine (0.631 ml, 4.54 mmol) and dropwise phenyl chloroformate (0.315 ml, 2.49 mmol) was added in 1 hr. The reaction mixture was stirred for 1-2 hrs. After

completion of the reaction, the reaction mixture was extracted with DCM and evaporated on rotary evaporator to obtain pale yellow solid (**68,** 0.3 gm, 92 %); m.p. 112-114 **º**C.

Analysis:

TLC : R_f 0.65 *n*-Hexane: Ethyl acetate (8:2)

IR (cm^{-1}) : 3129, 3060, 1757, 1492, 1401, 1223, 692.

Mass (m/z) : 341 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.50 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.39 (t, = 7.9 Hz, 2H), 7.26 (d, *J* = 13.9 Hz, 10H), 7.18 (s, 1H).

6.2.11. Synthesis of phenyl 3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxylate (69)

Compound **(69)** was synthesized from 3,4-bis(4-methoxyphenyl)-1*H*-pyrazole (**66,** 0.5 gm, 1.78 mmol), triethylamine (0.496 ml, 3.56 mmol) and phenyl chloroformate (0.247 ml, 1.96 mmol) using the procedure described for the synthesis of compound **(68)** to obtain the desired product (**69,** 0.3 gm, 92%); m.p. 94-96 **º**C.

Analysis:

TLC : R_f 0.65 *n*-Hexane: Ethyl acetate (8:2)

IR (cm^{-1}) : 2995, 1755, 1435, 1273, 1246, 1222, 1173, 741.

Mass (m/z) : 401.2 $(M+H)^+$

6.2.12. Synthesis of phenyl 3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxylate (70)

Compound **(70)** was synthesized from 3,4-bis(4-chlorophenyl)-1*H*-pyrazole (**67,** 0.5 gm, 1.73 mmol), triethylamine (0.481 ml, 3.46 mmol) and phenyl chloroformate (0.240 ml, 1.90 mmol) using the procedure described for the synthesis of compound **(68)** to obtain the desired product as pale yellow solid (**70,** 0.6 gm, 84%); m.p. 115-117 **º**C.

Analysis:

TLC : R_f 0.73 *n*-Hexane: Ethyl acetate (8:2)

IR (cm^{-1}) : 3120, 1752, 1487, 1438, 1221, 959, 740.

Mass (m/z) : 408.7 $(M)^+$, 410.7 $(M+2)^+$

6.2.13. Synthesis of *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (71)

3,4-Diphenyl-1*H*-pyrazole (**68**, 0.5 gm, 1.47 mmol) was dissolved in 10 ml DCM. In ice-cold condition, triethylamine (0.408 ml, 2.94 mmol) and ethylene diamine (0.293 ml, 4.40 mmol) were added. The reaction mixture was stirred for 1-2 hrs. After completion of the reaction, excess DCM was evaporated using rota evaporator and the obtained solid was purified by column chromatography using $CHCl_3$:MeOH (5%) as mobile phase to get desired product (**71,** 0.36 gm, 81%); m.p.100-102 **º**C.

Analysis:

TLC : R_f 0.25 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3376, 3309, 2934, 1698, 1506, 1274, 759, 694.

Mass (m/z) : 307 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.57 (t, *J* = 6.1 Hz, 1H), 7.47 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.31 (d, *J* = 1.6 Hz, 2H), 7.30 – 7.29 (m, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 2H), 7.25 (s, 1H), 7.22 (s, 1H), 4.79 (s, 2H), 3.50 – 3.47 (m, 2H), 2.94 (s, 2H).

6.2.14. Synthesis of *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (72)

Compound **(72)** was synthesized from phenyl3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxylate (**69,** 0.5 gm, 1.25 mmol), triethylamine (0.347 ml, 2.5 mmol) and ethylene diamine (0.225 gm, 3.75 mmol) using the procedure described for the synthesis of compound **(71)** to obtain the desired product (**72,** 0.36 gm, 81%); m.p. 88-90 **º**C.

Analysis:

TLC : R_f 0.25 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 2930, 2833, 1696, 1505, 1236, 1175, 1028, 829.

Mass (m/z) : 367.2 $(M+H)^+$

6.2.15. Synthesis of *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (73)

Compound **(73)** was synthesized from phenyl 3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxylate (**70,** 0.5 gm, 1.22 mmol), triethylamine (0.245 ml, 3.66 mmol) and ethylene diamine (0.339 ml, 2.44 mmol) using the procedure described for the synthesis of compound **(71)** to obtain the desired product (**73,** 0.4 gm, 87%); m.p. 123-125**º**C.

Analysis:

TLC : R_f 0.40 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3379, 3313, 3152, 3112, 2932, 1698, 1484, 1236, 1093.

Mass (m/z) : 374.8 $(M)^+$, 376.9 $(M+2)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.37 (s, 1H), 7.64 (t, *J* = 6.1 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.41 – 7.36 (m, 4H), 7.27 (s, 1H), 7.25 (d, *J* = 1.9 Hz, 1H), 3.62 – 3.57 (m, 2H), 3.06 (t, *J* = 5.9 Hz, 2H).

6.2.16. Synthesis of *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido) ethylcarbamoyl)piperidine-1-carboxylate (76)

1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (**75,** 0.62 gm, 2.72 mM) was dissolved in dry DCM (25 ml) at 0-4 ^{o}C under a stream of nitrogen gas. To this, 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (0.78 gm, 4.08 mM) and hydroxybenzotriazole (HOBt) (0.55 gm, 4.08 mM) were added and stirred the reaction mixture at 0-4 ^{o}C for 30 min. Anhydrous triethylamine (0.567 ml, 4.08 mM) was then added to the reaction mixture followed by *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 1.00 gm, 3.26 mM). The reaction mixture was allowed to stir for 4 hrs at rt. After completion of the reaction, excess of DCM was evaporated on rota evaporator and the reaction mixture was poured in ice cold water to get a solid. The solid was filtered, washed with water and dried to afford the desired product as a pale yellow solid (**76,** 1.5 gm, 90%); m.p. 102-104 **º**C.

Analysis:

TLC : R_f 0.54 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3328, 2930, 1715, 1689, 1644, 1525, 1425, 1216, 761.

Mass (m/z) : 517.9 $(M)^+$

^{1}H-NMR ($CDCl_3$, δ) **:** δ 8.28 (s, 1H), 7.61 (t, *J* = 6.1 Hz, 1H), 7.49 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.35 – 7.26 (m, 8H), 6.35 (d, *J* = 5.3 Hz, 1H), 4.11 (s, 2H), 3.61 (q, *J* = 5.9 Hz, 2H), 3.52 (q, *J* = 5.5 Hz, 2H), 2.73 (q, *J* = 14.5 Hz, 2H), 2.24 (tt, *J* = 11.5, 3.7 Hz, 1H), 1.84 – 1.76 (m, 2H), 1.61 (tt, *J* = 12.1, 6.2 Hz, 2H), 1.45 (s, 9H).

6.2.17. Synthesis of *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (77)

Compound **(77)** was synthesized from 1-(t.butoxycarbonyl)piperidine-4-carboxylic acid (**75,** 0.62 gm, 2.72 mM), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (0.78 gm, 4.09 mM), hydroxybenzotriazole (HOBt) (0.55 gm, 4.08 mM), triethylamine (0.567 ml, 4.09 mM) and *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 1.00 gm, 2.27 mM) using the procedure described for the synthesis of compound **(76)** to obtain the desired product as a pale yellow solid (**77,** 1.5 gm, 90%); m.p. 114-116 ^{o}C.

Analysis:

TLC : R_f 0.54 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3378, 3307, 1726, 1642, 1507, 1294, 1240, 1165, 832.

Mass (m/z) : 579.6 $(M+2H)^+$

^{1}H NMR ($CDCl_3$, δ) : 8.19 (s, 1H), 7.56 (t, *J* = 6.1 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.22 – 7.17 (m, 2H), 6.88 – 6.84 (m, 4H), 6.34 (t, *J* = 5.2 Hz, 1H), 4.15 – 4.05 (m, 2H), 3.81 (d, *J* = 1.2 Hz, 6H), 3.59 (td, *J* = 6.8, 4.5 Hz, 2H), 3.54 –

3.48 (m, 2H), 2.79 – 2.66 (m, 2H), 2.23 (tt, *J* = 11.6, 3.7 Hz, 1H), 1.86 – 1.75 (m, 2H), 1.67 – 1.56 (m, 2H), 1.44 (s, 9H).

6.2.18. Synthesis of *tert*-butyl-4-((2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1 carboxamido)ethyl)carbamoyl)piperidine-1-carboxylate (78)

Compound **(78)** was synthesized from 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (**75,** 0.61 gm, 2.65 mM), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (0.76 gm, 3.97 mM), hydroxybenzotriazole (HOBt) (0.54 gm, 3.97 mM), triethylamine (0.552 ml, 3.97 mM) and *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 1.00 gm, 3.18 mM) using the procedure described for the synthesis of compound **(76)** to obtain the desired product as a pale yellow solid (**78,** 1.4 gm, 89%); m.p. 190-193 ^{o}C.

Analysis:

TLC : R_f 0.61 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3377, 3277, 3118, 2957, 2928, 2847, 1730, 1693, 1642, 1515, 1415, 1220, 1158, 826.

Mass (m/z) : 586 $(M+H)^+$, 588.6 $(M+2H)^+$

^{1}H NMR ($CDCl_3$) : δ 8.27 (s, 1H), 7.58 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.29 (m, 4H), 7.22 – 7.16 (m, 2H), 6.20 (s, 1H), 4.11 (s, 2H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.54 (q, *J* = 5.6 Hz, 2H), 2.71 (d, *J* = 12.9 Hz, 2H), 2.23 (ddt, *J* = 11.5, 7.5, 3.8 Hz, 1H), 1.82 (s, 1H), 1.60 (qd, *J* = 12.2, 4.3 Hz, 3H), 1.44 (s, 9H).

6.2.19. Synthesis of *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)-1-benzylpiperidine-4-carboxamide (91)

In a 25 ml RBF, *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) was added in 10 ml DCM. Chilling was applied in ice bath and between 0-5 °C, 4 M HCl in dioxane (1ml) solution was added and reaction mixture was stirred for 1-2 hrs. The reaction was monitored with TLC. After completion of reaction, excess HCl dioxane was removed along with DCM under vacuum to obtain semi-solid *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide hydrochloride. In the RBF containing salt, 10 ml DCM and triethylamine (0.4 ml, 2.88mM) were added and the reaction mixture was stirred for 30 min. Benzyl bromide (**79,** 0.126 ml, 1.06 mM) was added and the reaction was further continued for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice-cold water and extracted with DCM. The obtained solid was further purified through

column chromatography using $CHCl_3$:CH_3OH (5%) mobile phase to obtain off-white solid (**91,** 0.38 gm, 75%) m. p. 172-174 **º**C (decomposed).

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3318, 1702, 1638, 1528, 698.

Mass (m/z) : 508.31 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ): δ 8.28 (s, 1H), 7.55 (d, *J* = 6.0 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.49 (t, *J* = 2.0 Hz, 1H), 7.35 – 7.26 (m, 12H), 7.25 – 7.21 (m, 1H), 6.15 (s, 1H), 3.61 (m, *J* = 6.8, 4.5 Hz, 2H), 3.56 – 3.50 (m, 2H), 3.48 (s, 2H), 2.90 (dt, *J* = 11.3, 3.5 Hz, 2H), 2.11 (ddt, *J* = 11.3, 8.2, 4.1 Hz, 1H), 1.98 (t, *J* = 11.2 Hz, 2H), 1.83 – 1.72 (m, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.90, 167.88, 152.13, 150.89, 132.54, 132.06, 131.87, 130.99, 129.60, 129.27, 128.90, 128.82, 128.77, 128.68, 128.57, 128.51, 128.33, 128.08, 127.56, 127.21, 124.05, 68.27, 63.13, 53.01, 40.26, 40.07, 38.83, 30.46, 29.79, 29.02, 28.75.

6.2.20. Synthesis of *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)-1-(4-chlorobenzyl)piperidine-4-carboxamide (92)

Compound **(92)** was synthesised from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 4-chlorobenzyl chloride (**80,** 0.166 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**92,** 0.36 gm, 70%) m. p. 179-182 **º**C.

Analysis:

TLC : R_f 0.46 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3312, 1697, 1637, 1527, 696.

Mass (m/z) : 542.29 $(M+H)^+$, 544.23$(M+2H)^+$.

^{1}H-NMR ($CDCl_3$, δ) **:** δ 8.28 (s, 1H), 7.58 (t, *J* = 6.1 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.32 (dq, *J* = 8.1, 2.3 Hz, 6H), 7.26 (dd, *J* = 10.4, 2.7 Hz, 6H), 6.23 (s, 1H), 3.61 (td, *J* = 6.8, 4.5 Hz, 2H), 3.53 (q, *J* = 5.6 Hz, 2H), 3.45 (s, 2H), 2.92 – 2.84 (m, 2H), 2.13 (m, 1H), 2.01 (m, 2H), 1.88 – 1.73 (m, 4H).

6.2.21. Synthesis of 1-(2-(trifluoromethyl)benzyl)-*N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (93)

Compound **(93)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 2-trifluoromethylbenzyl bromide (**81,** 0.170 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**93,** 0.39 gm, 71%), m. p. 156-158 ºC.

Analysis:

TLC : R_f 0.48 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3306, 1709, 1646, 1529, 1311, 1108, 765, 692.

Mass (m/z) : 576.34 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.82 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 1.9 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.36 – 7.25 (m, 10H), 6.25 (s, 1H), 3.70 – 3.58 (m, 4H), 3.58 – 3.50 (m, 2H), 2.89 (d, *J* = 11.1 Hz, 2H), 2.06 (d, *J* = 11.8 Hz, 3H), 1.80 (dd, *J* = 11.5, 3.4 Hz, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.85, 152.18, 150.94, 132.07, 131.96, 131.86, 130.39, 128.85, 128.78, 128.71, 128.58, 128.53, 128.08, 127.59, 126.85, 125.75, 125.69, 124.11, 58.25, 53.29, 40.27, 40.15, 29.81, 28.96.

6.2.22. Synthesis of *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)-1-(4-nitrobenzyl)piperidine-4-carboxamide (94)

Compound **(94)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM and 4-nitrobenzyl bromide (**84,** 0.228 gm, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**94,** 0.40 gm, 75%), m. p. 146-148 ºC (degraded).

Analysis:

TLC : R_f 0.47 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3312, 1696, 1650, 1516, 1338, 1216, 693.

HRMS (ESI+) m/z : Calculated, 553.2563 for $C_{31}H_{32}N_6O_4$ $[M+H]^+$; found, 553.2561.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.52 (q, *J* = 7.0 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.25 – 7.17 (m, 7H), 6.21 (s, 1H), 3.57 – 3.43 (m, 6H), 2.81 (d, *J* = 11.1 Hz, 2H), 2.08 (s, 3H), 1.74 (t, *J* = 12.4 Hz, 4H).

6.2.23. Synthesis of 1-(2,4-dichlorobenzyl)-*N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (95)

Compound **(95)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 2,4-dichlorobenzyl chloride (**85,** 0.148 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**95,** 0.40 gm, 72%), m. p. 166-169 **º**C.

Analysis:

TLC : R_f 0.48 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3305, 1699, 1637, 1526, 692.

HRMS (ESI+) m/z : Calculated, 576.1932 for $C_{31}H_{31}Cl_2N_5O_2$ $[M+H]^+$; found, 576.1901.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.49 (t, *J* = 6.1 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.27 (q, *J* = 2.2 Hz, 3H), 7.25 – 7.18 (m, 6H), 6.11 (s, 1H), 3.59 – 3.52 (m, 2H), 3.47 (d, *J* = 5.1 Hz, 4H), 2.86 – 2.76 (m, 2H), 2.10 – 1.95 (m, 3H), 1.76 – 1.67 (m, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.78, 152.19, 150.96, 134.77, 133.12, 132.05, 131.84, 131.48, 129.17, 128.86, 128.77, 128.72, 128.58, 128.53, 128.08, 127.61, 127.09, 124.12, 58.74, 53.17, 40.25, 40.17, 29.80, 28.90.

6.2.24. Synthesis of 1-(4-methybenzyl)-*N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (96)

Compound **(96)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 4-methylbenzyl chloride (**86,** 0.142 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**96,** 0.36 gm, 72%), m. p. 174-177 **º**C.

Analysis:

TLC : R_f 0.52 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3312, 2918, 1703, 1637, 1528, 1212, 693.

HRMS (ESI+) m/z : Calculated, 522.2868 for $C_{32}H_{35}N_5O_2$ $[M+H]^+$; found, 522.2837

^{1}H-NMR ($CDCl_3$, δ) : δ 8.27 (s, 1H), 7.55 (t, J = 6.1 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.34 – 7.29 (m, 6H), 7.28 (s, 1H), 7.25 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.7 Hz, 2H), 6.17 (s, 1H), 3.64 – 3.57 (m, 2H), 3.53 (t, J = 5.8 Hz, 2H), 2.90 (dt, J = 11.5, 3.5 Hz, 2H), 2.32 (s, 3H), 2.11 (s, 2H), 1.98 (d, J = 13.1 Hz, 3H), 1.74 (qd, J = 11.7, 3.6 Hz, 4H).

^{13}C-NMR ($CDCl_3$, δ) : δ 175.92, 152.15, 150.90, 136.80, 132.05, 131.87, 129.27, 129.01, 128.83, 128.78, 128.69, 128.58, 128.52, 128.29, 128.09, 127.56, 124.06, 62.89, 52.99, 40.23, 40.10, 29.81, 28.79, 21.22

HPLC purity : 97.89 %.

6.2.25. Synthesis of *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)-1-(3-chlorobenzyl)piperidine-4-carboxamide (97)

Compound **(97)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 3-chlorobenzyl chloride (**88,** 0.134 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**97,** 0.36 gm, 69 %), m. p. 170-172 ºC (decomposed).

Analysis:

TLC : R_f 0.52 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3318, 2915, 1694, 1655, 1526, 1213, 693.

HRMS (ESI+) m/z : Calculated, 542.2322 for $C_{31}H_{32}ClN_5O_2$ $[M+H]^+$; found, 542.2306.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.56 (s, 1H), 7.52 – 7.48 (m, 2H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.32 (dd, *J* = 5.3, 2.0 Hz, 5H), 7.28 (d, *J* = 2.9 Hz, 2H), 7.26 (s, 2H), 7.22 (d, *J* = 4.5 Hz, 2H), 6.17 (s, 1H), 3.65 – 3.57 (m, 2H), 3.54 (q, *J* = 5.6 Hz, 2H), 3.45 (s, 2H), 2.89 (bs, 2H), 2.12 (bs, 1H), 2.00 (bs, 2H), 1.82 (bs, 4H).

6.2.26. Synthesis of 1-(3,4-dichlorobenzyl)-*N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (98)

Compound **(98)** was synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and 3,4-dichlorobenzyl chloride (**89,** 0.148 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**98,** 0.41 gm, 74 %), m. p. 90-93 ºC.

Analysis:

TLC : R_f 0.54 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3305, 2939, 1706, 1639, 1525, 1215, 694.

Mass (m/z) : 576.28 $(M+H)^+$, 578.27 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.55 (t, *J* = 5.9 Hz, 1H), 7.52 – 7.48 (dd, 2H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.27 (m, 9H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.16 (s, 1H), 3.66 – 3.59 (m, 2H), 3.54 (q, *J* = 5.6 Hz, 2H), 3.41 (s, 2H), 2.85

(d, *J* = 11.1 Hz, 2H), 2.10 (d, *J* = 11.3 Hz, 1H), 1.99 (t, *J* = 11.1 Hz, 2H), 1.87 – 1.72 (m, 4H).

6.2.27. Synthesis of *N*-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethyl)-1-phenethyl piperidine-4-carboxamide (99)

Compound **(99)** synthesized from *tert*-butyl-4-(2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**76,** 0.5 gm, 0.96 mM) and phenylethyl bromide (**90,** 0.144 ml, 1.06 mM) using the procedure described for the synthesis of compound **(91)** to obtain the desired product as off-white solid (**99,** 0.38 gm, 75 %), m. p. 164-167 **º**C.

Analysis:

TLC : R_f 0.58 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3307, 2921, 1705, 1644, 1241, 694.

HRMS (ESI+) m/z : Calculated, 522.2868 for $C_{32}H_{35}N_5O_2$ $[M+H]^+$; found, 522.2867.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.29 (s, 1H), 7.62 (t, *J* = 6.0 Hz, 1H), 7.51 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.32 (dq, *J* = 5.3, 2.6 Hz, 7H), 7.29 – 7.26 (m, 3H), 7.19 (dd, *J* = 15.7, 7.3 Hz, 3H), 6.45 (s, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.14 – 3.09 (m, 2H), 2.86 (dd, *J* = 10.3, 5.9 Hz, 2H), 2.66 (dd, *J* = 10.4, 6.0 Hz, 2H), 2.30 (s, 3H), 2.01 (s, 2H), 1.89 (t, *J* = 11.6 Hz, 2H).

6.2.28. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)-1-benzylpiperidine-4-carboxamide (100)

In a 25 ml RBF, *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) was added in 10 ml DCM. Chilling was applied in ice bath and between 0-5 °C, 4 M HCl in dioxane (1ml) solution was added and reaction mixture was stirred for 1-2 hrs. The reaction was monitored with TLC. After completion of reaction, excess HCl dioxane was removed along with DCM under vacuum to obtain semi-solid *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide hydrochloride. In the RBF containing salt, 10 ml DCM and triethylamine (0.36 ml, 2.6 mM) were added and the reaction mixture was stirred for 30 min. Benzyl bromide (**79,** 0.112 ml, 0.95 mM) was added and the reaction was further continued for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice-cold water and extracted with DCM. The obtained solid was further purified through column chromatography using $CHCl_3$:CH_3OH (5%) mobile phase to obtain off-white solid (**100,** 0.36 gm, 75%), m. p. 162-165 **º**C.

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3321, 2941, 1728, 1633, 1514, 1241, 817, 699.

Mass (m/z) : 568.4 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 7.55 (t, *J* = 6.1 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.29 (d, *J* = 4.3 Hz, 4H), 7.26 – 7.17 (m, 3H), 6.87 (d, *J* = 2.9 Hz, 2H), 6.85 (d, *J* = 3.1 Hz, 2H), 6.25 (t, *J* = 5.2 Hz, 1H), 3.81 (d, *J* = 4.2 Hz, 6H), 3.61 – 3.56 (m, 2H), 3.52 (dd, *J* = 6.8, 4.8 Hz, 2H), 3.47 (s, 2H), 2.90 (dt, *J* = 11.4, 3.4 Hz, 2H), 2.10 (ddt, *J* = 11.2, 8.3, 4.3 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.85 – 1.72 (m, 4H).

6.2.29. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)-1-(4-chlorobenzyl)piperidine-4-carboxamide (101)

Compound **(101)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 4-chlorobenzyl chloride (**80,** 0.130 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**101,** 0.37 gm, 72%), m. p. 168-170 ºC.

Analysis:

TLC : R_f 0.51 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3326, 2936, 1737, 1702, 1642, 1519, 1244, 837.

Mass (m/z) : 602.5 $(M+H)^+$, 604 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 7.51 (t, *J* = 6.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 4.3 Hz, 4H), 7.21 – 7.17 (m, 2H), 6.87 (d, *J* = 3.6 Hz, 2H), 6.85 (d, *J* = 3.8 Hz, 2H), 6.17 (d, *J* = 6.2 Hz, 1H), 3.82 (d, *J* = 3.2 Hz, 6H), 3.64 – 3.57 (m, 2H), 3.53 (td, *J* = 6.5, 4.4 Hz, 2H), 3.43 (s, 2H), 2.90 – 2.83 (m, 2H), 2.07 (s, 1H), 2.02 – 1.93 (m, 2H), 1.83 – 1.72 (m, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.79, 160.06, 159.13, 151.91, 151.08, 137.10, 132.71, 130.33, 129.96, 129.79, 128.41, 127.62, 124.57, 124.31, 123.50, 114.14, 113.92, 62.40, 55.35, 53.10, 43.19, 40.18, 28.88.

6.2.30. Synthesis of 1-(2,6-difluorobenzyl)-*N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (102)

Compound **(102)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 2,6-difluorobenzyl bromide (**81,** 0.196 gm, 0.95 mM) using the procedure described for

the synthesis of compound **(100)** to obtain the desired product as off-white solid (**102,** 0.38 gm, 73%), m. p. 177-180 **º**C.

Analysis:

TLC : R_f 0.48 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3323, 2935, 2838, 1736, 1643, 1239, 1208, 837.

Mass (m/z) : 604.5 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 7.50 (t, *J* = 6.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.25 – 7.18 (m, 3H), 6.89 – 6.84 (m, 6H), 6.16 (d, *J* = 5.8 Hz, 1H), 3.83 (d, *J* = 1.1 Hz, 6H), 3.68 (t, *J* = 1.6 Hz, 2H), 3.59 (td, *J* = 6.7, 4.4 Hz, 2H), 3.50 (td, *J* = 5.8, 2.8 Hz, 2H), 2.96 (d, *J* = 11.5 Hz, 2H), 2.12 – 1.99 (m, 3H), 1.86 – 1.70 (m, 4H).

6.2.31. Synthesis of 1-(2-(trifluoromethyl)benzyl)-*N*-(2-(3,4-bis(4-methoxyphenyl)-*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (103)

Compound **(103)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 2-trifluoromethylbenzyl bromide (**82,** 0.152 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**103,** 0.38 gm, 70%), m. p. 170-173 **º**C.

Analysis:

TLC : R_f 0.48 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3374, 3294, 2938, 2918, 1727, 1633, 1514, 1239, 1139.

Mass (m/z) : 636.6 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.47 – 7.42 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.22 – 7.17 (m, 2H), 6.89 – 6.83 (m, 4H), 6.20 (t, *J* = 5.1 Hz, 1H), 3.82 (d, *J* = 4.0 Hz, 6H), 3.61 (d, *J* = 6.2 Hz, 4H), 3.56 – 3.51 (m, 2H), 2.87 (dt, *J* = 11.8, 3.6 Hz, 2H), 2.08 (dd, *J* = 22.6, 10.8, 4.1 Hz, 3H), 1.85 – 1.74 (m, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.90, 160.07, 159.12, 151.94, 151.10, 138.30, 131.88, 130.19, 129.98, 129.81, 128.61, 128.31, 127.64, 126.69, 125.96, 125.69, 125.63, 124.58, 124.32, 123.52, 123.24, 114.13, 113.94, 77.36, 58.35, 55.36, 53.40, 43.30, 40.25, 40.18, 29.10

6.2.32. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3,5-dimethylbenzyl)piperidine-4-carboxamide (104)

Compound **(104)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 3,5-dimethylbenzyl bromide (**83,** 0.189 gm, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**104,** 0.39 gm, 75%), m. p. 80-82 **º**C.

Analysis:

TLC : R_f 0.43 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3319, 3261, 2936, 1703, 1639, 1508, 1244, 838.

Mass (m/z) : 596.44 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.52 (t, *J* = 6.0 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.91 (bs, 2H), 6.87 (q, *J* = 2.4 Hz, 3H), 6.85 (d, *J* = 2.5 Hz, 2H), 6.18 (s, 1H), 3.82 (d, *J* = 3.3 Hz, 6H), 3.60 (td, *J* = 6.8, 4.4 Hz, 2H), 3.55 – 3.49 (m, 2H), 3.40 (s, 2H), 2.91 (dt, *J* = 11.6, 3.5 Hz, 2H), 2.29 (s, 6H), 2.15 – 2.07 (m, 1H), 1.96 (t, *J* = 11.3 Hz, 2H), 1.82 – 1.74 (m, 4H).

6.2.33. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(4-nitrobenzyl)piperidine-4-carboxamide (105)

Compound **(105)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 4-nitrobenzyl bromide (**84,** 0.205 gm, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**105,** 0.36 gm, 68%), m. p. 96-99 **º**C.

Analysis:

TLC : R_f 0.42 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3312, 2937, 1701, 1641,1509, 1243, 837.

Mass (m/z) : 613.42 $(M+H)^+$

HRMS (ESI+) m/z : Calculated, 613.2774 for $C_{33}H_{36}N_6O_6$ $[M+H]^+$; found, 613.2761.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 8.14 (d, *J* = 1.9 Hz, 1H), 7.54 (t, *J* = 6.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 1.8 Hz, 1H), 6.87 – 6.85 (m, 2H), 6.84 (d, *J* = 2.2 Hz, 1H), 6.24 (s, 1H), 3.82 (d, *J* = 4.2 Hz, 6H), 3.61 (td, *J* = 6.7, 4.3 Hz, 2H), 3.57 – 3.50 (m, 4H), 2.90 – 2.82 (m, 2H), 2.13 (m,1H), 2.05 (s, 2H), 1.87 – 1.74 (m, 4H)

6.2.34. Synthesis of 1-(2,4-dichlorobenzyl)-*N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (106)

Compound **(106)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 2,4-dichlorobenzyl chloride (**85,** 0.132 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**106,** 0.38 gm, 70%), m. p. 166-169 ºC.

Analysis:

TLC : R_f 0.45 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3347, 3301, 2937, 1738, 1642, 1518, 1241, 832.

HRMS (ESI+) m/z : Calculated, 636.2144 for $C_{33}H_{35}Cl_2N_5O_4$ $[M+H]^+$; found, 636.2126.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.52 (t, *J* = 6.1 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.19 (dt, *J* = 6.4, 1.9 Hz, 3H), 6.87 (d, *J* = 2.7 Hz, 2H), 6.85 (d, *J* = 2.7 Hz, 2H), 6.20 (t, *J* = 4.9 Hz, 1H), 3.82 (d, *J* = 3.0 Hz, 6H), 3.63 – 3.59 (m, 2H), 3.53 (d, *J* = 4.6 Hz, 4H), 2.88 (dt, *J* = 11.7, 3.6 Hz, 2H), 2.10 (qd, *J* = 11.4, 5.0 Hz, 3H), 1.85 – 1.74 (m, 4H).

6.2.35. Synthesis of 1-(4-methylbenzyl)-*N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (107)

Compound (**107)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 4-methylbenzyl chloride (**86,** 0.126 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**107,** 0.37 gm, 75%), m. p. 87-90 ºC.

Analysis:

TLC : R_f 0.48 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3314, 3274, 2937, 1724, 1642, 1515, 1243, 834.

HRMS (ESI+) m/z : Calculated, 582.3080 for $C_{34}H_{39}N_5O_4$ $[M+H]^+$; found, 582.3072.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.54 (t, *J* = 6.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.21 – 7.16 (m, 4H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.87 (d, *J* = 2.4 Hz, 2H), 6.85 (t, *J* = 2.3 Hz, 2H), 6.26 (t, *J* = 5.0 Hz, 1H), 3.82 (d, *J* = 2.7 Hz, 6H), 3.62 – 3.57 (m, 2H), 3.54 – 3.49 (m, 2H), 3.44 (s, 2H), 2.93 – 2.88 (m, 2H), 2.33 (s, 3H), 2.11 (ddt, *J* = 11.4, 7.2, 4.1 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.83– 1.71 (m, 4H).

6.2.36. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(4-methoxybenzyl)piperidine-4-carboxamide (108)

Compound **(108)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 3-methoxybenzyl chloride (**87,** 0.139 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**108,** 0.36 gm, 70%), m. p. 77-80 ºC.

Analysis:

TLC : R_f 0.45 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3326, 2924, 1520, 694.

HRMS (ESI+) m/z : Calculated, 598.3029 for $C_{34}H_{39}N_5O_5$ $[M+H]^+$; found, 598.3016.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.56 (t, *J* = 6.1 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.24 – 7.17 (m, 3H), 6.91 (s, 1H), 6.87 (ddd, *J* = 9.8, 6.0, 2.3 Hz, 5H), 6.80 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.33 (s, 1H), 3.82 (d, *J* = 4.5 Hz, 6H), 3.79 (s, 3H), 3.60 (td, *J* = 6.8, 4.4 Hz, 2H), 3.55 – 3.48 (m, 4H), 2.97 – 2.92 (m, 2H), 2.11 (d, *J* = 31.8 Hz, 3H), 1.88 – 1.74 (m, 4H).

6.2.37. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3-chlorobenzyl)piperidine-4-carboxamide (109)

Compound **(109)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 3-chlorobenzyl chloride (**88,** 0.120 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**109,** 0.38 gm, 74%), m. p. 83-86 ºC.

Analysis:

TLC : R_f 0.47 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3327, 2934, 1704, 1507, 1246, 1175, 838.

HRMS (ESI+) m/z : Calculated, 602.2533 for $C_{33}H_{36}ClN_5O_4$ $[M+H]^+$; found, 602.2533.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.53 (t, *J* = 6.0 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.23 – 7.17 (m, 5H), 6.88 – 6.84 (m, 4H), 6.22 (s, 1H), 3.82 (d, *J* = 3.1 Hz, 6H), 3.60 (td, *J* = 6.8, 4.5 Hz, 2H), 3.55 – 3.50 (m, 2H), 3.44 (s, 2H), 2.89 – 2.86 (m, 2H), 1.98 (d, *J* = 12.4 Hz, 3H), 1.84 – 1.71 (m, 4H).

6.2.38. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3,4-dichlorobenzyl)piperidine-4-carboxamide (110)

Compound **(110)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and 3,4-dichlorobenzyl chloride (**89,** 0.132 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**110,** 0.37 gm, 68%), m. p. 188-191 **º**C.

Analysis:

TLC : R_f 0.47 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3336, 1733, 1635, 1506, 1207, 834.

HRMS (ESI+) m/z : Calculated, 636.2144 for $C_{33}H_{35}Cl_2N_5O_4$ $[M+H]^+$; found, 636.2095.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 7.53 (t, *J* = 6.0 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.16 – 7.12 (m, 1H), 6.88 – 6.84 (m, 4H), 6.22 (t, *J* = 5.2 Hz, 1H), 3.82 (d, *J* = 3.4 Hz, 6H), 3.60 (td, *J* = 6.8, 4.4 Hz, 2H), 3.56 – 3.50 (m, 2H), 3.40 (s, 2H), 2.85 (dt, *J* = 11.9, 3.5 Hz, 2H), 2.16 – 2.06 (m, 1H), 2.03 – 1.94 (m, 2H), 1.81 – 1.68 (m, 4H).

6.2.39. Synthesis of *N*-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-phenethylpiperidine-4-carboxamide (111)

Compound **(111)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**77,** 0.5 gm, 0.86 mM) and phenethyl bromide (**90,** 0.129 ml, 0.95 mM) using the procedure described for the synthesis of compound **(100)** to obtain the desired product as off-white solid (**111,** 0.35 gm, 71%), m. p. 179-182 **º**C.

Analysis:

TLC : R_f 0.47 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3292, 2939, 1705, 1516, 1244, 698.

Mass (m/z) : 582.41 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.55 (t, *J* = 6.1 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.30 – 7.27 (m, 1H), 7.25 (s, 1H), 7.22 – 7.16 (m, 5H), 6.88 – 6.84 (m, 4H), 6.27 (s, 1H), 3.82 (d, *J* = 2.7 Hz, 6H), 3.64 – 3.58 (m, 2H), 3.53 (q, *J* = 5.3 Hz, 2H), 3.03 (dt, *J* = 11.9, 3.6 Hz, 2H), 2.83 – 2.77 (m, 2H), 2.58 (dd, *J* = 10.3, 6.1 Hz, 2H), 2.14 (d, *J* = 12.0 Hz, 2H), 1.90 (d, *J* = 12.7 Hz, 2H), 1.80 (td, *J* = 12.4, 3.7 Hz, 2H).

^{13}C NMR ($CDCl_3$) : δ 175.63, 160.10, 159.15, 152.01, 151.16, 130.01, 129.85, 128.83, 128.53, 127.68, 126.20, 124.59, 124.35, 123.58, 114.17, 113.98, 77.36, 55.40, 53.18, 40.34, 40.21, 33.66, 28.80.

HPLC purity : 96.59%.

6.2.40. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-benzylpiperidine-4-carboxamide (112)

In a 25 ml RBF, *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) was added in 10 ml DCM. Chilling was applied in ice bath and between 0-5 °C, 4 M HCl in dioxane (1ml) solution was added and reaction mixture was stirred for 1-2 hrs. The reaction was monitored with TLC. After completion of reaction, excess HCl dioxane was removed along with DCM under vacuum to obtain semi-solid *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide hydrochloride. In the RBF containing salt, 10 ml DCM and triethylamine (0.236 ml, 1.7 mM) were added and the reaction mixture was stirred for 30 min. Benzyl bromide (**79,** 0.110 ml, 0.93 mM) was added and the reaction was further continued for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice-cold water and extracted with DCM. The obtained solid was further purified through column chromatography using $CHCl_3$:CH_3OH (5%) mobile phase to obtain off-white solid (**112,** 0.38 gm, 75%), m. p. 163-166 **º**C (decomposed).

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3363, 3125, 1729, 1640, 1518, 1089, 831, 695.

HRMS (ESI+) m/z : Calculated, 576.1932 for $C_{31}H_{31}Cl_2N_5O_2$ $[M+H]^+$; found, 576.1895.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.23 (s, 1H), 7.58 (t, *J* = 5.9 Hz, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.30 – 7.23 (m, 9H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 6.18 (t, *J* = 5.4 Hz, 1H), 3.57 (td, *J* = 6.7, 4.4 Hz, 2H), 3.54 – 3.47 (m, 2H), 3.45 (s, 2H), 2.93 – 2.83 (m, 2H), 2.08 (tt, *J* = 11.3, 4.2 Hz, 2H), 1.95 (td, *J* = 11.5, 2.8 Hz, 1H), 1.83 – 1.65 (m, 4H).

6.2.41. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(4-chlorobenzyl)piperidine-4-carboxamide (113)

Compound **(113)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 4-chlorobenzyl chloride (**80,** 0.120 ml, 0.93 mM) using the procedure described for the

synthesis of compound **(112)** to obtain the desired product as off-white solid (**113,** 0.38 gm, 74%), m. p. 164-167 ºC.

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3125, 1729, 1644, 1519, 1088, 823.

HRMS (ESI+) m/z : Calculated, 610.1543 for $C_{32}H_{30}Cl_2F_3N_5O_2$ $[M+H]^+$, found, 610.1504, $[M+2H]^+$ 612.1504.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.55 (t, *J* = 6.4 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.35 – 7.26 (m, 8H), 7.20 – 7.17 (m, 2H), 6.09 (s, 1H), 3.61 (t, *J* = 6.1 Hz, 2H), 3.54 (q, *J* = 5.6 Hz, 2H), 3.45 (s, 2H), 2.88 (bs, 2H), 2.11 (bs, 1H), 1.99 (bs, 2H), 1.80 (bs, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.68, 150.68, 150.42, 138.15, 134.95, 133.72, 130.30, 130.14, 130.02, 129.81, 129.03, 128.84, 128.31, 127.66, 122.68, 62.53, 52.36, 46.20, 40.50, 39.68, 29.77, 27.82, 21.31.

6.2.42. Synthesis of 1-(2-(trifluoromethyl)benzyl)-*N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (114)

Compound **(114)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 2-trifluoromethylbenzyl bromide (**82,** 0.149 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**114,** 0.38 gm, 74%), m. p. 189-192 ºC.

Analysis:

TLC : R_f 0.42 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3329, 3129, 1734, 1638, 1519, 1310, 1112, 828.

HRMS (ESI+) m/z : Calculated, 644.1806 for $C_{32}H_{30}Cl_2F_3N_5O_2$ $[M+H]^+$, found, 644.1810.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 5H), 7.20 – 7.15 (m, 2H), 6.17 (s, 1H), 3.66 – 3.59 (m, 4H), 3.55 (dd, *J* = 6.9, 4.8 Hz, 2H), 2.92 – 2.83 (m, 2H), 2.20 – 2.02 (m, 3H), 1.86 – 1.75 (m, 4H).

6.2.43. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3,5-dimethylbenzyl)piperidine-4-carboxamide (115)

Compound **(115)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM)

and 3,5-dimethylbenzyl bromide (**83,** 0.185 gm, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**115,** 0.36 gm, 70%), m. p. 166-169 **º**C.

Analysis:

TLC : R_f 0.42 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3348, 2930, 1731, 1639, 1519, 831.

HRMS (ESI+) m/z : Calculated, 604.2245 for $C_{33}H_{35}Cl_2N_5O_2$ $[M+H]^+$, found, 604.2240.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.33 (s, 1H), 7.68 (t, *J* = 5.9 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 – 7.36 (m, 4H), 7.34 (s, 1H), 7.27 (d, *J* = 2.1, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.05 (bs, 1H), 7.00 (bs, 1H), 3.71 – 3.66 (m, 2H), 3.61 (dd, *J* = 7.5, 4.1 Hz, 4H), 3.20 (t, *J* = 7.3 Hz, 3H), 3.09 (bs, 2H), 2.41 (bs, 1H), 2.37 (s, 6H), 1.95 (bs, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 175.68, 150.68, 150.42, 138.15, 134.95, 133.72, 130.30, 130.14, 130.02, 129.81, 129.03, 128.84, 128.31, 127.66, 122.68, 62.53, 52.36, 46.20, 40.50, 39.68, 29.77, 27.82, 21.31.

6.2.44. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(4-nitrobenzyl)piperidine-4-carboxamide (116)

Compound **(116)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 4-nitrobenzyl bromide (**84,** 0.2 gm, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**116,** 0.41 gm, 78%), m. p. 173-176 **º**C.

Analysis:

TLC : R_f 0.42 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3321, 1733, 1638, 1510, 1347, 831, 736.

HRMS (ESI+) m/z : Calculated, 621.1783 for $C_{31}H_{30}Cl_2N_6O_4$ $[M+H]^+$, found, 621.1734.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 2H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 6.14 (s, 1H), 3.62 (m, 2H), 3.56 (m, 4H), 2.86 (dd, *J* = 9.7, 5.7 Hz, 2H), 2.12 (m, *J* = 5.1 Hz, 1H), 2.07 – 2.01 (m, 2H), 1.83 – 1.77 (m, 4H).

^{13}C NMR ($CDCl_3$) : δ 175.79, 150.82, 150.64, 147.21, 146.46, 135.04, 133.82, 130.21, 130.05, 129.99, 129.77, 129.53, 129.49, 129.09, 129.00, 128.88,

128.27, 123.62, 122.82, 77.36, 62.26, 53.18, 42.92, 40.46, 40.02, 38.80, 29.79, 28.79, 23.82, 23.08.

6.2.45. Synthesis of 1-(2,4-dichlorobenzyl)-*N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (117)

Compound **(117)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 2,4-dichlorobenzyl chloride (**85,** 0.13 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**117,** 0.38 gm, 68%), m. p. 196-199 **º**C.

Analysis:

TLC : R_f 0.38 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3348, 3264, 3124, 1731, 1640, 1519, 828.

Mass (m/z) : 644.30 $(M+H)^+$, 646.22 $(M+2H)^+$.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 2H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.33 (d, *J* = 1.6 Hz, 2H), 7.31 (d, *J* = 1.5 Hz, 2H), 7.21 – 7.17 (m, 3H), 6.11 (s, 1H), 3.61 (td, *J* = 6.8, 4.5 Hz, 2H), 3.57 – 3.52 (m, 4H), 2.91 – 2.86 (m, 2H), 2.09 (m, 3H), 1.83 – 1.73 (m, 4H).

6.2.46. Synthesis of 1-(4-methylbenzyl)-*N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethyl)piperidine-4-carboxamide (118)

Compound **(118)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 4-methylbenzyl chloride (**86,** 0.124 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**118,** 0.37 gm, 75%), m. p. 169-172 **º**C.

Analysis:

TLC : R_f 0.43 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3349, 3267, 3124, 1731, 1641, 1518, 829.

Mass (m/z) : 590.32 $(M+H)^+$, 592.27 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.56 (t, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.32 (s, 2H), 7.30 (d, *J* = 2.0 Hz, 2H), 7.19 (d, *J* = 1.9 Hz, 2H), 7.17 (s, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.11 (s, 1H), 3.63 – 3.59 (m, 2H), 3.54 (dd, *J* = 5.8, 3.7 Hz, 2H), 3.46 (s, 2H), 2.91 (d, *J* =

10.9 Hz, 2H), 2.33 (s, 3H), 2.11 (s, 1H), 2.00 (d, *J* = 10.5 Hz, 2H), 1.76 (td, *J* = 12.0, 3.5 Hz, 4H).

6.2.47. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3-methoxybenzyl)piperidine-4-carboxamide (119)

Compound **(119)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 3-methoxybenzyl chloride (**87,** 0.136 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**119,** 0.38 gm, 74%), m. p. 160-163 **º**C.

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3330, 1704, 1639, 1519, 1255, 1203, 829, 740.

Mass (m/z) : 606.35 $(M+H)^+$, 608.28 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.31 (dd, *J* = 8.3, 1.4 Hz, 4H), 7.23 – 7.16 (m, 3H), 6.87 (d, *J* = 7.5 Hz, 2H), 6.81 – 6.77 (m, 1H), 6.11 (s, 1H), 3.79 (s, 3H), 3.61 (td, *J* = 6.8, 4.4 Hz, 2H), 3.54 (dd, *J* = 7.8, 4.0 Hz, 2H), 3.46 (s, 2H), 2.91 (dt, *J* = 11.8, 3.5 Hz, 2H), 2.11 (dt, *J* = 11.3, 6.7 Hz, 1H), 2.00 (d, *J* = 10.0 Hz, 2H), 1.76 (td, *J* = 11.8, 3.5 Hz, 4H).

^{13}C-NMR ($CDCl_3$, δ): δ 176.01, 159.74, 150.84, 150.60, 139.87, 135.04, 133.79, 130.27, 130.14, 130.05, 129.81, 129.28, 129.08, 128.90, 128.32, 122.82, 121.50, 114.62, 112.66, 63.11, 55.30, 53.10, 43.22, 40.49, 39.95, 29.81, 28.86.

6.2.48. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethyl)-1-(3-chlorobenzyl)piperidine-4-carboxamide (120)

Compound **(120)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 3-chlorobenzyl chloride (**88,** 0.118 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**120,** 0.37 gm, 72%), m. p. 184-187 **º**C.

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3363, 3270, 2937, 1725, 1633, 1517, 827.

Mass (m/z) : 610.30 $(M+H)^+$, 612.26 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) :δ 8.26 (s, 1H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.33 – 7.30 (m, 5H), 7.23 (d, *J* = 4.6 Hz, 2H), 7.20 – 7.16 (m, 3H), 6.15 (s, 1H), 3.65 – 3.58 (m, 2H), 3.55 (t, *J* = 5.7 Hz, 2H), 3.48 (d, *J* = 6.2 Hz, 2H), 2.95 – 2.86 (m, 2H), 2.14 (s, 1H), 2.01 (s, 2H), 1.72 (s, 4H).

6.2.49. Synthesis of *N*-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethyl)-1-(3,4-dichlorobenzyl)piperidine-4-carboxamide (121)

Compound **(121)** was synthesized from *tert*-butyl-4-(2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamoyl)piperidine-1-carboxylate (**78,** 0.5 gm, 0.85 mM) and 3,4-dichlorobenzyl chloride (**89,** 0.13 ml, 0.93 mM) using the procedure described for the synthesis of compound **(112)** to obtain the desired product as off-white solid (**121,** 0.38 gm, 70%), m. p. 103-106 ºC.

Analysis:

TLC : R_f 0.41 Chloroform: Methanol (9:1)

IR (cm^{-1}) : 3336, 2940, 1729, 1642, 1518, 831.

HRMS (ESI+) m/z : Calculated, 644.1153 for $C_{31}H_{29}Cl_4N_5O_2$ $[M+H]^+$, found, 644.1112, $[M+2H]^+$ 646.1112;

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.56 (t, *J* = 6.0 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.32 (dd, *J* = 8.3, 1.6 Hz, 5H), 7.20 – 7.16 (m, 2H), 6.10 (s, 1H), 3.62 (q, *J* = 4.0 Hz, 2H), 3.55 (t, *J* = 5.9 Hz, 2H), 3.42 (s, 2H), 2.86 (d, *J* = 10.8 Hz, 2H), 2.12 (s, 1H), 1.99 (s, 2H), 1.78 (d, *J* = 15.5 Hz, 4H).

^{13}C-NMR ($CDCl_3$, δ) : 175.68, 150.60, 150.39, 134.84, 133.61, 132.22, 130.91, 130.64, 130.14, 130.09, 129.94, 129.84, 129.62, 128.90, 128.70, 128.19, 128.11, 122.60, 61.60, 52.78, 45.82, 40.33, 39.73, 28.53;

HPLC purity : 96.66%.

6.2.50. Synthesis of phenyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (130)

In a 25 ml RBF, *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) was added in 10 ml DCM. In ice-cold condition, triethylamine (0.304 ml, 2.44 mM) and dropwise phenyl chloroformate (**122,** 0.225 ml, 1.80 mM) was added and the reaction mixture was stirred for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice cold water and extracted with DCM. The obtained product was purified through column chromatography using Pet ether: Ethyl acetate (40%) as mobile phase to obtain the desired final product as a white solid (**130,** 0.52 gm, 75%), m. p. 148-150 ºC.

Analysis:

TLC : R_f 0.69 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3348, 3058, 1717, 1521, 1220, 694.

Mass (m/z) : 427.27 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.32 (s, 1H), 7.60 (t, *J* = 6.1 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.37 – 7.27 (m, 10H), 7.21 – 7.15 (m, 1H), 7.14 – 7.08 (m, 2H), 5.52 (d, *J* = 6.2 Hz, 1H), 3.68 (td, *J* = 6.6, 4.8 Hz, 2H), 3.57 (td, *J* = 6.6, 4.8 Hz, 2H).

6.2.51. Synthesis of isobutyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido) ethylcarbamate (131)

Compound **(131)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and isobutyl chloroformate (**123,** 0.234 ml, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**131,** 0.53 gm, 72%), m. p. 122-125 ºC.

Analysis:

TLC : R_f 0.53 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3334, 1714, 1694, 1524, 696.

Mass (m/z) : 407.28 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.30 (s, 1H), 7.57 – 7.51 (m, 2H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.36 – 7.27 (m, 8H), 5.06 (s, 1H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.61 (q, *J* = 6.0 Hz, 2H), 3.48 (dd, *J* = 8.5, 3.9 Hz, 2H), 1.89 (p, *J* = 6.7 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

6.2.52. Synthesis of ethyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (132)

Compound **(132)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and ethyl chloroformate (**124,** 0.172 ml, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**132,** 0.47 gm, 71%), m. p. 193-195 ºC.

Analysis:

TLC : R_f 0.45 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 696, 1252, 1693, 1726, 3345

Mass (m/z) : 379.23$(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.30 (s, 1H), 7.56 (s, 1H), 7.53 – 7.48 (m, 2H), 7.36 – 7.27 (m, 8H), 5.11 (d, *J* = 7.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.60 (q, *J* = 5.9 Hz, 2H), 3.46 (q, *J* = 6.0 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

6.2.53. Synthesis of methyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (133)

Compound **(133)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and methyl chloroformate (**125,** 0.141 ml, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**133,** 0.44 gm, 76%), m. p. 196-198 **º**C.

Analysis:

TLC : R_f 0.42 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3341, 1712, 1700, 1508, 1252, 698.

HRMS (ESI+) m/z : Calculated, 365.1613 for $C_{20}H_{20}N_4O_3$ $[M+H]^+$, found, 365.1595.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.25 (s, 1H), 7.51 (s, 1H), 7.48 – 7.44 (m, 2H), 7.34 – 7.27 (m, 4H), 7.26 – 7.19 (m, 4H), 5.12 (s, 1H), 3.63 (s, 3H), 3.55 (q, *J* = 6.0 Hz, 2H), 3.41 (q, *J* = 5.8 Hz, 2H).

6.2.54. Synthesis of pentyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (134)

Compound **(134)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and *n*-pentyl chloroformate (**126,** 0.256 ml, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**134,** 0.49 gm, 72%), m. p. 146-148 **º**C.

Analysis:

TLC : R_f 0.58 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3309, 3061, 1712, 1680, 1524, 1224, 763, 693.

HRMS (ESI+) m/z : Calculated, 421.2239 for $C_{24}H_{28}N_4O_3$ $[M+H]^+$, found, 421.2261.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.30 (s, 1H), 7.59 – 7.53 (m, 1H), 7.51 (dd, *J* = 7.1, 2.2 Hz, 2H), 7.36 – 7.28 (m, 8H), 5.08 (s, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 3.60 (q, *J* = 6.0 Hz, 2H), 3.51 – 3.41 (m, 2H), 1.65 – 1.59 (m, 2H), 1.30 (p, *J* = 3.8 Hz, 4H), 0.90 – 0.86 (m, 3H).

6.2.55. Synthesis of 2,2,2-trichloroethyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido) ethylcarbamate (135)

Compound **(135)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and 2,2,2-trichloroethyl chloroformate (**127,** 0.254 ml,

1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**135,** 0.57 gm, 73%), m. p. 160-162 ºC.

Analysis:

TLC : R_f 0.63 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3396, 3292, 3058, 1728, 1705, 1535, 1242, 692.

HRMS (ESI+) m/z : Calculated, 481.0600 for $C_{21}H_{19}Cl_3N_4O_3$ $[M+H]^+$, found, 481.0586.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.30 (s, 1H), 7.55 (d, *J* = 5.9 Hz, 1H), 7.50 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.37 – 7.28 (m, 8H), 5.47 (d, *J* = 6.3 Hz, 1H), 4.74 (s, 2H), 3.65 (td, *J* = 6.6, 4.8 Hz, 2H), 3.53 (td, *J* = 6.6, 4.8 Hz, 2H).

^{13}C-NMR ($CDCl_3$, δ) : δ 155.09, 152.22, 150.55, 132.07, 131.84, 128.88, 128.79, 128.71, 128.62, 128.55, 128.17, 127.59, 124.08, 95.61, 74.69, 41.35, 40.35

6.2.56. Synthesis of benzyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (136)

Compound **(136)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and benzyl chloroformate (**128,** 0.256 ml, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (0.50 gm, 70%), m. p. 105-108 ºC.

Analysis:

TLC : R_f 0.73 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3344, 3030, 1707, 1691, 1528, 1268, 694.

HRMS (ESI+) m/z : Calculated, 441.1926 for $C_{26}H_{24}N_4O_3$ $[M+H]^+$, found, 441.1926.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.24 (s, 1H), 7.53 (t, *J* = 6.0 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.31 – 7.26 (m, 8H), 7.26 – 7.20 (m, 5H), 5.22 (t, *J* = 4.3 Hz, 1H), 5.06 (s, 2H), 3.55 (q, *J* = 5.9 Hz, 2H), 3.42 (td, *J* = 6.5, 3.7 Hz, 2H).

6.2.57. Synthesis of (9*H*-fluore*n*-9-yl)methyl 2-(3,4-diphenyl-1*H*-pyrazole-1-carboxamido)ethylcarbamate (137)

Compound **(137)** was synthesized from *N*-(2-aminoethyl)-3,4-diphenyl-1*H*-pyrazole-1-carboxamide (**71,** 0.5gm, 1.63 mM) and (9*H*-fluore*n*-9-yl)methyl chloroformate (**129,** 0.465 gm, 1.80 mM) using the procedure described for the synthesis of compound **(130)** to obtain the desired product as a white solid (**137,** 0.56 gm, 65%), m. p. 174-176 ºC.

Analysis:

TLC : R_f 0.73 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3313, 1722, 1699, 1523, 1252, 696.

HRMS (ESI+) m/z : Calculated, 529.2239 for $C_{33}H_{28}N_4O_3$ $[M+H]^+$, found, 529.2228.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.54 (s, 1H), 7.51 – 7.47 (m, 2H), 7.38 – 7.29 (m, 10H), 7.26 – 7.21 (m, 2H), 5.21 (s, 1H), 4.41 (d, *J* = 6.9 Hz, 2H), 4.19 (t, *J* = 6.9 Hz, 1H), 3.64 – 3.58 (m, 2H), 3.49 (q, *J* = 4.5 Hz, 2H).

^{13}C-NMR ($CDCl_3$, δ) : δ 156.88, 152.09, 150.50, 143.96, 141.40, 132.10, 131.86, 128.80, 128.75, 128.66, 128.60, 128.50, 128.13, 127.77, 127.50, 127.12, 125.16, 123.93, 120.06, 66.93, 47.30, 41.01, 40.61.

6.2.58. Synthesis of phenyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (138)

In a 25 ml RBF, *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) was added in 10 ml DCM. In ice-cold condition, triethylamine (0.284 ml, 2.04 mM) and dropwise phenyl chloroformate (**122,** 0.188 ml, 1.50 mM) was added and the reaction mixture was stirred for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice cold water and extracted with DCM. The obtained product was purified through column chromatography using Pet ether: Ethyl acetate (40%) as mobile phase to obtain the desired final product as a white solid (**138,** 0.46 gm, 70%), m. p. 147-150 **º**C.

Analysis:

TLC : R_f 0.69 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3363, 3313, 1736, 1710, 1688, 1519, 1248, 1204, 1025.

Mass (m/z) : 487.27 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : 8.23 (s, 1H), 7.57 (t, *J* = 6.2 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.23 – 7.15 (m, 3H), 7.11 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.89 – 6.84 (m, 4H), 5.54 (t, *J* = 5.8 Hz, 1H), 3.82 (d, *J* = 1.4 Hz, 6H), 3.70 – 3.64 (m, 2H), 3.55 (q, *J* = 5.7 Hz, 2H).

^{13}C-NMR ($CDCl_3$, δ) : δ 160.03, 159.06, 155.18, 151.89, 151.03, 150.74, 129.96, 129.84, 129.37, 127.73, 125.43, 124.61, 124.33, 123.43, 121.69, 114.11, 113.93, 55.37, 55.34, 41.33, 40.39.

6.2.59. Synthesis of isobutyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (139)

Compound **(139)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and isobutyl chloroformate (**123,** 0.194 ml, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**139,** 0.47 gm, 75%), m. p. 133-136 **º**C.

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3423, 3374, 1706, 1611, 1507, 1243, 835, 1243.

HRMS (ESI+) m/z : Calculated, 467.2294 for $C_{25}H_{30}N_4O_5$ $[M+H]^+$, found, 467.2305.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.50 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.18 (m, 2H), 6.88 – 6.85 (m, 4H), 5.08 (s, 1H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.82 (s, 6H), 3.60 (q, *J* = 6.0 Hz, 2H), 3.49 – 3.43 (m, 2H), 1.89 (dt, *J* = 13.4, 6.7 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

^{13}C-NMR ($CDCl_3$, δ): δ 160.02, 159.06, 157.24, 151.78, 150.57, 129.97, 129.82, 127.69, 124.67, 124.41, 123.34, 114.11, 113.91, 71.33, 55.37, 55.34, 41.01, 40.61, 28.07, 19.14.

6.2.60. Synthesis of ethyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (140)

Compound **(140)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and ethyl chloroformate (**124,** 0.143 ml, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**140,** 0.45 gm, 75%), m. p. 191-194 **º**C.

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3370, 1705, 1613, 1506, 1242, 831.

HRMS (ESI+) m/z : Calculated, 439.1981 for $C_{23}H_{26}N_4O_5$ $[M+H]^+$, found, 439.1976.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.52 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.21 – 7.18 (m, 2H), 6.87 (t, 2H), 6.86 (t, *J* = 2.0 Hz, 2H), 5.11 (s, 1H), 4.15 – 4.10 (m, 2H), 3.82 (s, 6H), 3.59 (d, *J* = 6.0 Hz, 2H), 3.44 (dd, *J* = 11.0, 4.8 Hz, 2H), 1.24 (d, *J* = 7.1 Hz, 3H).

^{13}C-NMR ($CDCl_3$, δ): δ 160.04, 159.09, 157.07, 151.84, 150.60, 129.99, 129.84, 127.71, 124.68, 124.42, 123.38, 114.13, 113.94, 113.85, 61.15, 60.54, 55.39, 41.06, 40.62, 14.71, 14.32.

HPLC purity : 95.62 %

6.2.61. Synthesis of methyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (141)

Compound **(141)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (0.5gm, 1.36 mM) and methyl chloroformate (**125,** 0.118 ml,

1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**141,** 0.41 gm, 72%), m. p. 168-170 ºC.

Analysis:

TLC : R_f 0.44 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3346, 1705, 1613, 1504, 1245, 825.

HRMS (ESI+) m/z : Calculated, 425.1824 for $C_{22}H_{24}N_4O_5$ $[M+H]^+$, found, 425.1823.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.22 – 7.18 (m, 2H), 6.88 (s, 2H), 6.86 (d, *J* = 2.0 Hz, 2H), 5.15 (s, 1H), 3.82 (s, 6H), 3.68 (s, 3H), 3.59 (d, *J* = 6.1 Hz, 2H), 3.45 (d, *J* = 6.0 Hz, 2H).

6.2.62. Synthesis of pentyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (142)

Compound **(142)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and pentyl chloroformate (**126,** 0.213 ml, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**142,** 0.44 gm, 68%), m. p. 116-118 ºC.

Analysis:

TLC : R_f 0.47 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3361, 1728, 1685, 1513, 1242, 829.

Mass (m/z) : 481.30 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.51 (s, 1H), 7.47 – 7.43 (m, 2H), 7.22 – 7.18 (m, 2H), 6.88 (s, 2H), 6.86 (d, *J* = 2.0 Hz, 2H), 5.08 (s, 1H), 4.06 (t, *J* = 6.7 Hz, 2H), 3.82 (s, 6H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.45 (d, *J* = 6.3 Hz, 2H), 1.59 (d, *J* = 6.4 Hz, 2H), 1.31 (h, *J* = 3.2 Hz, 4H), 0.89 (q, *J* = 4.0 Hz, 3H).

6.2.63. Synthesis of 2,2,2-trichloroethyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamate (143)

Compound **(143)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and 2,2,2-trichloroethyl chloroformate (**127,** 0.211 ml, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**143,** 0.55 gm, 75%), m. p. 172-175 ºC.

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3368, 3285, 1726, 1702, 1239, 829, 728, 829.

HRMS (ESI+) m/z : Calculated, 541.0812 for $C_{23}H_{23}Cl_3N_4O_5$ $[M+H]^+$, found, 541.0800.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.49 (t, *J* = 6.2 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.22 – 7.18 (m, 2H), 6.89 – 6.85 (m, 4H), 5.46 (s, 1H), 4.73 (s, 2H), 3.82 (s, 6H), 3.65 (dd, *J* = 6.6, 4.9 Hz, 2H), 3.55 – 3.51 (m, 2H).

6.2.64. Synthesis of benzyl 2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (144)

Compound **(144)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and benzyl chloroformate (**128,** 0.213 ml, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**144,** 0.48 gm, 71%), m. p. 74-76 **º**C.

Analysis:

TLC : R_f 0.66 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3372, 2925, 1726, 1686, 1503, 1241, 1210, 1022.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.20 (s, 1H), 7.53 (d, *J* = 5.4 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.30 (m, 5H), 7.21 – 7.18 (m, 2H), 6.87 (d, *J* = 2.1 Hz, 2H), 6.85 (d, *J* = 2.1 Hz, 2H), 5.22 (s, 1H), 5.11 (s, 2H), 3.82 (d, *J* = 1.9 Hz, 6H), 3.60 (d, *J* = 6.0 Hz, 2H), 3.50 – 3.46 (m, 2H).

6.2.65. Synthesis of (9*H*-fluore*n*-9-yl)methyl-2-(3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamate (145)

Compound **(145)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (**72,** 0.5gm, 1.36 mM) and (9*H*-fluore*n*-9-yl)methyl chloroformate (**129,** 0.388 gm, 1.50 mM) using the procedure described for the synthesis of compound **(138)** to obtain the desired product as a white solid (**145,** 0.52 gm, 65%), m. p. 159-162 **º**C.

Analysis:

TLC : R_f 0.73 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3330, 1713, 1521, 1247.

Mass (m/z) : 589.39 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.19 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.51 (s, 1H), 7.43 – 7.40 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.18 – 7.14 (m, 2H), 6.86 – 6.82 (m, 4H), 5.22 (s, 1H), 4.40 (d, *J* = 7.0 Hz, 2H), 4.19 (t, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 5.4 Hz, 6H), 3.64 – 3.56 (m, 2H), 3.52 – 3.44 (m, 2H).

6.2.66. Synthesis of phenyl-2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (146)

In a 25 ml RBF, *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) was added in 10 ml DCM. In ice-cold condition, triethylamine (0.278 ml, 1.99 mM) and dropwise phenyl chloroformate (**122,** 0.185 ml, 1.46 mM) was added and the reaction mixture was stirred for 1-2 hrs. After completion of reaction, the reaction mixture was poured in ice cold water and extracted with DCM. The obtained product was purified through column chromatography using Pet ether: Ethyl acetate (40%) as mobile phase to obtain the desired final product as a white solid (**146,** 0.49 gm, 75%), m. p. 163-166 ºC.

Analysis:

TLC : R_f 0.71 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3349, 3296, 1717, 1598, 1518, 1202, 1090.

HRMS (ESI+) m/z : Calculated, 495.0990 for $C_{25}H_{20}Cl_2N_4O_3$ $[M+H]^+$, found, 495.0956.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.29 (s, 1H), 7.60 (t, *J* = 6.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.33 – 7.29 (m, 6H), 7.20 – 7.17 (m, 3H), 7.10 (dd, *J* = 7.7, 1.7 Hz, 2H), 5.50 (s, 1H), 3.68 (q, *J* = 5.8 Hz, 2H), 3.56 (q, *J* = 5.8 Hz, 2H).

6.2.67. Synthesis of isobutyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (147)

Compound **(147)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and isobutyl chloroformate (**123,** 0.188 ml, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**147,** 0.45 gm, 72%), m. p. 152-155 ºC.

Analysis:

TLC : R_f 0.61 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3377, 3334, 2960, 1726, 1680, 1508, 1401, 1239, 1214, 1091, 825.

HRMS (ESI+) m/z : Calculated, 475.1303 for $C_{23}H_{24}Cl_2N_4O_3$ $[M+H]^+$, found, 475.1291.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.56 (d, *J* = 6.2 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.29 (m, 4H), 7.20 – 7.17 (m, 2H), 5.09 (d, *J* = 6.5 Hz, 1H), 3.85 (d, *J* = 6.7 Hz, 2H), 3.61 (q, *J* = 5.9 Hz, 2H), 3.51 – 3.42 (m, 2H), 1.89 (dq, *J* = 13.4, 6.2 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

6.2.68. Synthesis of ethyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (148)

Compound **(148)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and ethyl chloroformate (**124,** 0.140 ml,

1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**148,** 0.42 gm, 71%), m. p. 186-189 ºC.

Analysis:

TLC : R_f 0.52 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3370, 3349, 1732, 1686, 1536, 1260, 831.

HRMS (ESI+) m/z : Calculated, 447.0990 for $C_{21}H_{20}Cl_2N_4O_3$ $[M+H]^+$, found, 447.0957.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.34 – 7.29 (m, 4H), 7.20 – 7.17 (m, 2H), 5.08 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.60 (q, *J* = 5.9 Hz, 2H), 3.46 (q, *J* = 6.2 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

6.2.69. Synthesis of methyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (149)

Compound **(149)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and methyl chloroformate (**125,** 0.115 ml, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**149,** 0.39 gm, 68%), m. p. 192-195 ºC.

Analysis:

TLC : R_f 0.45 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3328, 1736, 1695, 1545, 1261, 828.

Mass (m/z) : 433.19 $(M+H)^+$, 435.16 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.30 (m, 4H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.18 (d, *J* = 1.9 Hz, 1H), 5.10 (s, 1H), 3.68 (s, 3H), 3.60 (q, *J* = 6.0 Hz, 2H), 3.51 – 3.42 (m, 2H).

^{13}C-NMR ($CDCl_3$, δ): δ 157.39, 150.63, 150.04, 134.89, 133.62, 130.15, 130.00, 129.88, 129.67, 128.94, 128.82, 128.76, 128.22, 122.58, 52.29, 40.92, 40.63.

6.2.70. Synthesis of pentyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (150)

Compound **(150)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and pentyl chloroformate (**126,** 0.209 ml, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**150,** 0.51 gm, 78%), m. p. 131-134 ºC.

Analysis:

TLC : R_f 0.56 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3346, 3325, 1737, 1675, 1516, 1258, 1089, 827.

HRMS (ESI+) m/z : Calculated, 489.1459 for $C_{24}H_{26}Cl_2N_4O_3$ $[M+H]^+$, found, 489.1420.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.28 (s, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.33 – 7.30 (m, 4H), 7.20 – 7.17 (m, 2H), 5.05 (s, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 3.60 (q, *J* = 5.9 Hz, 2H), 3.47 (t, *J* = 6.0 Hz, 2H), 1.60 (d, *J* = 6.6 Hz, 2H), 1.30 (q, *J* = 3.4 Hz, 4H), 0.90 – 0.86 (m, 3H).

^{13}C-NMR ($CDCl_3$, δ): δ 157.16, 150.57, 150.01, 134.86, 133.59, 130.16, 130.01, 129.87, 129.66, 128.92, 128.74, 128.20, 122.54, 65.30, 40.73, 28.61, 27.92, 22.29, 13.94.

6.2.71. Synthesis of 2,2,2-trichloroethyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamate (151)

Compound **(151)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and 2,2,2-trichloroethyl chloroformate (**127,** 0.202 ml, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**151,** 0.47 gm, 65%), m. p. 182-185 **º**C.

Analysis:

TLC : R_f 0.61 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3370, 3290, 3061, 1726, 1705, 1535, 1243, 831, 727.

HRMS (ESI+) m/z : Calculated, 548.9821 for $C_{21}H_{17}Cl_5N_4O_3$ $[M+H]^+$, found, 548.9754, $[M+2H]^+$, 550.9754 .

^{1}H-NMR ($CDCl_3$, δ) : δ 8.21 (s, 1H), 7.49 (t, *J* = 6.1 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 2H), 6.86 (d, *J* = 2.1 Hz, 2H), 5.46 (s, 1H), 4.73 (s, 2H), 3.64 (td, *J* = 6.7, 4.8 Hz, 2H), 3.56 – 3.50 (m, 2H).

6.2.72. Synthesis of benzyl-2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido) ethylcarbamate (152)

Compound **(152)** was synthesized from *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and benzyl chloroformate (**128,** 0.209 ml, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**152,** 0.46 gm, 68%), m. p. 148-150 **º**C.

Analysis:

TLC : R_f 0.71 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3407, 3311, 3164, 1720, 1685, 1516, 1265, 1063, 733.

Mass (m/z) : 509.15 $(M+H)^+$, 511.99 $(M+2H)^+$

^{1}H-NMR ($CDCl_3$, δ) : δ 8.26 (s, 1H), 7.55 (d, *J* = 6.1 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.29 (m, 9H), 7.20 – 7.16 (m, 2H), 5.18 (s, 1H), 5.11 (s, 2H), 3.61 (q, *J* = 5.8 Hz, 2H), 3.49 (dd, *J* = 7.1, 4.7 Hz, 2H).

^{13}C-NMR ($CDCl_3$, δ): δ 156.94, 150.75, 150.18, 136.40, 135.02, 133.75, 130.31, 130.15, 130.02, 129.82, 129.07, 128.95, 128.88, 128.64, 128.37, 128.30, 128.22, 122.70, 67.05, 41.02, 40.78.

HPLC purity : 95.61 %

6.2.73. Synthesis of (9*H*-fluore*n*-9-yl)methyl 2-(3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamido)ethylcarbamate (153)

Compound **(153)** was synthesized from RBF, *N*-(2-aminoethyl)-3,4-bis(4-chlorophenyl)-1*H*-pyrazole-1-carboxamide (**73,** 0.5gm, 1.33 mM) and (9*H*-fluore*n*-9-yl)methyl chloroformate (**129,** 0.378 gm, 1.46 mM) using the procedure described for the synthesis of compound **(146)** to obtain the desired product as a white solid (**153,** 0.49 gm, 62%), m. p. 188-191 **º**C.

Analysis:

TLC : R_f 0.67 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3335, 1747, 1679, 1541, 1521, 1269, 730.

HRMS (ESI+) m/z : Calculated, 597.1459 for $C_{33}H_{26}Cl_2N_4O_3$ $[M+H]^+$, found, 597.1416.

^{1}H-NMR ($CDCl_3$, δ) : δ 8.22 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 5.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.39 – 7.32 (m, 4H), 7.29 – 7.24 (m, 6H), 7.10 (d, *J* = 8.2 Hz, 2H), 5.21 (t, *J* = 5.9 Hz, 1H), 4.38 (d, *J* = 7.0 Hz, 2H), 4.15 (t, *J* = 7.1 Hz, 1H), 3.61 (q, *J* = 5.8 Hz, 2H), 3.50 (q, *J* = 5.9 Hz, 2H).

6.2.74. Synthesis of ethyl 5-nitrobenzofuran-2-carboxylate (156)

2-Hydroxy-5-nitobenzaldehyde (**154**, 10g, 0.060 mM) and K_2CO_3 (20.7 g, 0.15 mM) were dissolved in dichloromethane at room temperature and stirred for 2 hrs. Diethyl 2-bromomalonate (**155**, 20.08 g, 0.08 mM) was added in reaction mixture and stirred at 85°C for 2 hrs. The reaction was monitored with TLC. After completion of reaction, the mixture was poured in ice water, stirred, filtered and washed with water. After that product was recrystallize in methanol to obtain desired product as off-white solid (**156,** 12.11 gm, 86%), m.p. 175-177 **º**C (Lit.[11]176.4-178.4**º**C)

TLC : R_f 0.33 (*n*-hexane : Ethyl acetate) 18:02

6.2.75. Synthesis of ethyl 5-aminobenzofuran-2-carboxylate (157)

Ethyl 5-nitro-1-benzofuran-2-carboxylate (**156**, 10 g, 0.042 mM) and ammonium formate (31.5 g, 0.5 mM) were dissolved in dichloromethane at room temperature. 10% Pd/C

(50% wet) (0.8 g) along with methanol were added in reaction mixture and stirred at 25°C for 2 hrs. After completion of reaction, the product was extracted, dried over Na_2SO_4 and distilled to get product (**157,** 7.9 g, 90%), m.p. 190-192 °C (Lit.[11]189.6-191.4 °C).

TLC : R_f 0.14 Chloroform : Methanol (9:1)

6.2.76. Synthesis of ethyl 5-(4-methylbenzamido)benzofuran-2-carboxylate (159)

In a 50ml RBF, ethyl 5-aminobenzofuran-2-carboxylate (**157,** 0.5g, 0.24mM) and triethylamine (1.01 ml, 0.73mM) were added in anhydrous DCM and chilled in ice bath. Dropwise 4-methylbenzoyl chloride **(158**, 0.483 ml, 0.36mM) was added and reaction mixture was stirred until the reaction was over. After completion of reaction, the reaction mixture was poured in ice cold water and extracted with DCM, dried over anhydrous Na_2SO_4 and vacuum distilled to produce desired product (**159,** 0.68g, 87%) which was considered without purification for the next stop produce **(160).**

TLC : R_f 0.14 *n*-Hexane: Ethyl acetate (12:08)

6.2.77. Synthesis of 5-(4-methylbenzamido)benzofuran-2-carbohydrazide (160)

In a 50 ml RBF, ethyl 5-(4-methylbenzamido)benzofuran-2-carboxylate (**159,** 1.57g, 0.48mM) and hydrazine hydrate (2.43 ml, 4.8mM) were added in methanol and refluxed for 3-4 hrs until the reaction was over. After completion of reaction, excess methanol was vacuum distilled and reaction mixture was poured in ice-cold water to obtain solid product which was recrystallised in methanol to produce desired brown solid (**160,** 1.28 g, 86%).

Analysis

TLC : R_f 0.14 Chloroform : Methanol (9:1)

IR (cm^{-1}) : 3324, 3031, 1651, 1594, 1442, 1261, 819, 743.

Mass (m/z) : 310.3 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 10.26 (s, 1H), 10.01 (s, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.72 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 0.9 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.65 – 4.52 (m, 2H), 2.39 (s, 3H).

6.2.78. Synthesis of *(E)-N*-(2-(2-(3-bromobenzylidene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (181)

In a 25ml RBF, *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.2gm,0.65mM) was added in 20 ml of methanol. Potassium carbonate (0.089 gm, 0.65 mM) and 3-bromo benzaldehyde (**161,** 0.108gm, 0.58mM) was added. Reaction mixture was refluxed and stirred for 4-5 hours on oil bath. After completion of reaction, excess methanol was distilled off using rota evaporator and was poured in ice-cold water. The obtained solid

was filtered and purified by recrystallization using methanol to get desired product. (**181,** 0.25gm, 81 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.52 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3399, 3321, 1678, 1657, 1539, 1275.

Mass (m/z) : 476.4 $(M+H)^+$, 478.4 $(M+2H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.34 (s, 1H), 10.32 (s, 1H), 8.50 (s, 1H), 8.34 (s, 1H), 7.94 – 7.90 (m, 3H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.68 (dd, *J* = 17.3, 7.9 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H).

6.2.79. Synthesis of *(E)*-*N*-(2-(2-(fura*n*-2-ylmethylene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (182)

Compound **(182)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.5gm,1.61mM) and furfuraldehyde (**162,** 0.1397gm, 1.45mM)) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**182,** 0.52, 83%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.40 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3247, 3032, 1656, 1644, 1583, 1226, 868, 737.

Mass (m/z) : 388.3 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.16 (s, 1H), 10.31 (s, 1H), 8.41 (s, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 7.90 (dd, *J* = 8.8, 7.0 Hz, 3H), 7.82 – 7.67 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 3.4 Hz, 1H), 6.66 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.40 (s, 3H).

6.2.80. Synthesis of *(E)*-4-methyl-*N*-(2-(2-(thiophe*n*-2-ylmethylene)hydrazine-1-carbonyl)benzofuran-5-yl)benzamide (183)

Compound **(183)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.5gm,1.61mM) and thiophene-2-carbaldehyde (**163,** 0.163gm, 1.45mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product (**183,** 0.551gm, 84.48 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.46 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3264, 1756, 1645, 1584, 1288, 869, 746.

Mass (m/z) : 404.4 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.18 (s, 1H), 10.31 (s, 1H), 8.72 (s, 1H), 8.31 (s, 1H), 7.95 – 7.88 (m, 2H), 7.78 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.70 (dd, *J* = 12.1, 8.0 Hz, 3H), 7.49 (d, *J* = 3.6 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.16 (dd, *J* = 5.0, 3.6 Hz, 1H), 2.40 (s, 3H).

6.2.81. Synthesis of *(E)*-*N*-(2-(2-([1,1'-biphenyl]-4-ylmethylene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (184)

Compound **(184)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.5gm,1.61mM) and [1,1'-biphenyl]-4-carbaldehyde (**164,** 0.265gm, 1.45mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**184,** 0.63gm, 82%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.58 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3316, 3256, 1665, 1642, 1531, 1062.

Mass (m/z) : 474.4 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.26 (s, 1H), 10.33 (s, 1H), 8.56 (s, 1H), 8.31 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.79 – 7.72 (m, 6H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H).

6.2.82. Synthesis of *(E)*-*N*-(2-(2-((1-*H*-imidazol-2-yl)methylene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (185)

Compound **(185)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 1*H*-imidazole-2-carbaldehyde (**165,** 0.084gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**185,** 0.32 gm, 85 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.15 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3309, 3236, 1663, 1640, 1277.

Mass (m/z) : 388.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.87 (s, 1H), 12.30 (s, 1H), 10.31 (s, 1H), 8.43 (s, 1H), 8.33 (s, 1H), 7.95 – 7.87 (m, 2H), 7.83 – 7.67 (m, 3H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.11 (s, 2H), 2.39 (s, 3H).

6.2.83. Synthesis of *(E)*-4-methyl-*N*-(2-(2-(naphthale*n*-2-ylmethylene)hydrazine-1-carbonyl)benzofuran-5-yl)benzamide (186)

Compound **(186)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 2-naphthaldehyde (**166,** 0.136gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**186,** 0.362gm, 83 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.55 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3329, 3267, 1664, 1648, 1536, 1281.

Mass (m/z) : 448.3 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.30 (s, 1H), 10.32 (s, 1H), 8.70 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.04 (dt, *J* = 7.0, 3.5 Hz, 1H), 8.00 (s, 2H), 7.97 (dd, *J* = 6.1, 3.5 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.79 (s, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.59 (dt, *J* = 6.3, 3.5 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 2.40 (s, 3H).

6.2.84. Synthesis of *(E)*-4-methyl-*N*-(2-(2-(1-phenylethylidene)hydrazine-1-carbonyl)benzofuran-5-yl)benzamide (187)

Compound **(187)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and acetophenone (**167,** 0.105gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**187,** 0.33gm, 82 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.62 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3333, 1676, 1644, 1537, 1281.

Mass (m/z) : 412.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 10.95 (s, 1H), 10.32 (s, 1H), 8.35 – 8.30 (m, 1H), 7.90 (dd, *J* = 11.3, 5.7 Hz, 4H), 7.82 – 7.77 (m, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.47 (dd, *J* = 5.5, 2.1 Hz, 3H), 7.36 (d, *J* = 7.8 Hz, 2H), 2.41 (d, *J* = 8.3 Hz, 6H).

6.2.85. Synthesis of *(E)*-*N*-(2-(2-benzylidenehydrazine-1-carbonyl)benzofuran-5-yl)-4-methylbenzamide (188)

Compound **(188)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and benzaldehyde (**168,** 0.093gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**188,** 0.331gm, 85 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.51 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3288, 3243, 1660, 1637, 1521, 1284.

Mass (m/z) : 398.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.32 (s, 1H), 10.42 (s, 1H), 8.65 (s, 1H), 8.44 (s, 1H), 7.94 (d, *J* = 62.3 Hz, 7H), 7.52 (d, *J* = 48.5 Hz, 5H), 2.61 (s, 3H).

6.2.86. Synthesis of *(E)*-*N*-(2-(2-(4-methoxybenzylidene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (189)

Compound **(189)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 4-methoxybenzaldehyde (**169,** 0.118gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**189,** 0.340gm, 82 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.65 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3351, 3290, 1664, 1650, 1251, 819.

Mass (m/z) : 428.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.05 (s, 1H), 10.31 (s, 1H), 8.47 (s, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.78 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.74 (s, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H).

6.2.87. Synthesis of *N*-(2-(2-(diphenylmethylene)hydrazine-1-carbonyl) benzofuran-5-yl)-4-methylbenzamide (190)

Compound **(190)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and benzophenone (**170,** 0.159gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**190,** 0.35gm, 76 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.74 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3340, 1667, 1468, 1343, 1157.

Mass (m/z) : 474.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 10.29 (s, 1H), 9.98 (s, 1H), 8.27 (d, *J* = 17.1 Hz, 1H), 7.90 (t, *J* = 8.1 Hz, 2H), 7.71 (dd, *J* = 21.3, 4.7 Hz, 5H), 7.60 – 7.51 (m, 3H), 7.47 (s, 5H), 7.34 (d, *J* = 7.7 Hz, 2H), 2.39 (s, 3H)

6.2.88. Synthesis of *(E)*-4-methyl-*N*-(2-(2-(4-nitrobenzylidene)hydrazine-1-carbonyl)benzofuran-5-yl)benzamide (191)

Compound **(191)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 4-nitrobenzaldehyde (**171,** 0.132gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**191,** 0.34gm, 79 %), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.50 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 2363, 1650, 1518, 1341, 746.

Mass (m/z) : 443.1 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.48 (s, 1H), 10.32 (s, 1H), 8.63 (s, 1H), 8.32 (d, *J* = 8.8 Hz, 3H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 11.3 Hz, 2H), 7.71 (d, *J* = 9.1 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 2.40 (s, 3H).

6.2.89. Synthesis of *(E)*-4-methyl-*N*-(2-(2-(4-methylbenzylidene)hydrazine-1-carbonyl) benzofuran-5-yl)benzamide (192)

Compound **(192)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 4-methylbenzaldehyde (**172,** 0.103ml, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**192,** 0.31gm, 77%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3300, 3236, 1659, 1604, 1507, 812.

Mass (m/z) : 412.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.13 (s, 1H), 10.32 (s, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.81 – 7.74 (m, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 2.38 (d, *J* = 15.6 Hz, 6H).

6.2.90. Synthesis of *(E)*-5-(4-methylbenzamido)-*N*-(1-(4-nitrophenyl)ethylidene) benzofuran-2-carbohydrazide (193)

Compound **(193)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 4-nitroacetophenone (**173,** 0.144gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**193,** 0.35gm, 79%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.57 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3362, 1662, 1506, 1470, 1341, 743.

Mass (m/z) : 457.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 11.13 (s, 1H), 10.32 (s, 1H), 8.37 – 8.28 (m, 3H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.95 – 7.86 (m, 3H), 7.79 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.48 (s, 3H), 2.40 (s, 3H).

6.2.91. Synthesis of *(E)*-5-(4-methylbenzamido)-*N*-(1-p-tolylethylidene) benzofuran-2-carbohydrazide (194)

Compound **(194)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm, 0.97mM) and 4-methylacetophenone (**174,** 0.116 ml, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**194,** 0.32gm, 78%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.65 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3333, 3027, 1674, 1644, 1537, 1204, 1159, 872, 748.

Mass (m/z) : 426.2 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : 10.88 (s, 1H), 10.30 (s, 1H), 8.32 (s, 1H), 7.90 (s, 2H), 7.74 (d, *J* = 21.7 Hz, 5H), 7.37 – 7.28 (m, 4H), 2.40 (s, 9H).

6.2.92. Synthesis of *(E)*-*N*'-(2-hydroxybenzylidene)-5-(4-methylbenzamido) benzofuran-2-carbohydrazide (195)

Compound **(195)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and salicyladehyde (**175,** 0.091ml, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**195,** 0.31gm, 77%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.69 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 1637, 1601, 1473, 1303, 746.

Mass (m/z) : 414.2 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 13.10 (s, 1H), 10.25 (s, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.45 (s, 1H), 7.37 (dd, *J* = 15.0, 7.6 Hz, 3H), 7.19 (t, *J* = 8.2 Hz, 1H), 6.86 – 6.78 (m, 2H), 2.39 (s, 3H).

6.2.93. Synthesis of *(E)*-*N*'-(3-nitrobenzylidene)-5-(4-methylbenzamido) benzofuran-2-carbohydrazide (196)

Compound **(196)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 4-nitrobenzaldehyde (**176,** 0.132gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**196,** 0.33gm, 76%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.64 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3288, 2349, 1657, 1604, 1516, 1469.

Mass (m/z) : 443.4 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.46 (s, 1H), 10.32 (s, 1H), 8.64 (s, 1H), 8.55 (t, *J* = 2.0 Hz, 1H), 8.34 (s, 1H), 8.27 (dd, *J* = 8.3, 2.4 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.83 – 7.72 (m, 3H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 2.39 (s, 3H).

6.2.94. Synthesis of *(E)*-*N*'-(2-nitrobenzylidene)-5-(4-methylbenzamido) benzofuran-2-carbohydrazide (197)

Compound **(197)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 2-nitrobenzaldehyde (**177,** 0.132 gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**197,** 0.34gm, 79%), m. p. >220 **º**C.

Analysis:

TLC : R_f 0.59 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3300, 3243, 1660, 1638, 1540, 1284.

Mass (m/z) : 443.4 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 12.55 (s, 1H), 10.32 (s, 1H), 8.95 (s, 1H), 8.37 – 8.32 (m, 1H), 8.18 – 8.07 (m, 2H), 7.94 – 7.77 (m, 5H), 7.75 – 7.66 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H).

6.2.95. Synthesis of *(E)*-5-(4-methylbenzamido)-*N*'-(cycloheptylmethylene)benzofuran-2-carbohydrazide (198)

Compound **(198)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm,0.97mM) and 2-phenylacetophenone (**178,** 0.171gm, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**198,** 0.38gm, 80 %).m. p. >220 **º**C.

Analysis:

TLC : R_f 0.58 *n*-Hexane: Ethyl acetate (4:6)

IR (cm^{-1}) : 3368, 3349, 1647, 1538, 1472.

Mass (m/z) : 488.2 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) **:** 11.26 (s, 1H), 10.30 (s, 1H), 8.26 (s, 1H), 7.94 – 7.83 (m, 4H), 7.78 – 7.72 (m, 1H), 7.70 – 7.60 (m, 2H), 7.37 (dd, *J* = 15.2, 7.7 Hz, 5H), 7.29 (q, *J* = 6.2 Hz, 4H), 7.20 – 7.15 (m, 1H), 4.45 (s, 2H), 2.40 (s, 3H).

6.2.96. Synthesis of *(E)*-5-(4-methylbenzamido)-*N*'-butylidenebenzofuran-2-carbohydrazide (199)

Compound **(199)** was synthesized from *N*-(2-(hydrazinecarbonyl)benzofuran-5-yl)-4-methylbenzamide (**160,** 0.3gm, 0.97mM) and *n*-butyraldehyde (**179,** 0.079 ml, 0.87mM) using the procedure described for the synthesis of compound **(181)** to obtain the desired product. (**199,** 0.28gm, 79%), m. p. >220 ºC.

Analysis:

TLC : R_f 0.64 *n*-Hexane: Ethyl acetate (4:6)

IR (cm-1) : 3301, 2923, 1659, 1538, 1275.

Mass (m/z) : 364.2 $(M+H)^+$

^{1}H-NMR (DMSO d6, δ) : 11.76 (s, 1H), 10.30 (s, 1H), 8.30 (s, 1H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.80 (dd, *J* = 24.0, 7.3 Hz, 2H), 7.66 (d, *J* = 10.0 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 2.40 (s, 3H), 2.26 (q, *J* = 6.9 Hz, 2H), 1.54 (p, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

6.2.97. Synthesis of ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (202)

In a 100 ml RBF, 3-nitro benzoic acid (**200,** 1.46 gm, 0.010 mM) and thionyl chloride (3.51ml, 0.048 mM) were transferred into RBF and reflux for 2-3 hrs. The reaction was monitor by TLC. After completion of reaction, excess of thionyl chloride was degassed and in another 100 ml RBF ethyl 5-aminobenzofuran-2-carboxylate (**157,** 2 gm, 0.0097 mM) and triethyl amine (4.05 ml, 0.029 mM) were dissolved in dichloromethane at room temperature. 3-Nitro benzoyl chloride was added drop wise into reaction mixture and stirred at 25ºC until reaction completion after which ethyl 5-((3-nitro)benzamido)benzofuran-2-carboxylate **(201)** and ammonium formate (7.33 g /0.12 mmole) were dissolved in dichloromethane at room temperature. 10% Pd/C (50% wet) (0.4 g) along with methanol were added in reaction mixture and stirred at 25°C. After completion of reaction, ice cold water was added and extracted with DCM, organic layer was collected, dried over anhydrous Na_2SO_4 and distilled off to obtain off-white solid (**202,** 2.8 gm, 92%) m.p. 148-150 ºC.

Analysis:

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (5:5)

IR (cm^{-1}) : 3408, 3330, 3118, 2931, 1710, 1639, 1202

Mass (m/z) : 325.08 $[M+H]^+$

^{1}H-NMR (DMSO, δ) : 10.19 (s, 1H), 8.28 (s, 1H), 7.74-7.72 (d, 2H), 7.66 (s, 1H), 7.12 (s, 1H), 7.07-7.05 (t, *J* = 2.1 Hz, 2H), 6.72-6.71 (d, *J* = 5.4 Hz, 1H), 5.29 (s, 2H), 4.32-4.31 (d, *J* = 7.1 Hz, 2H), 1.29 (s, 3H).

6.2.98. Synthesis of ethyl 5-((3-phenylcarbamate)benzamido)benzofuran-2-carboxylate (203)

Ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and triethylamine (0.257 ml, 0.183 mM) were dissolved in dichloromethane and stirred at 25 ºC. Phenylchloroformate (**122**, 0.092 ml, 0.073 mM) was added dropwise and reaction mixture was stirred at room temperature until the reaction was complete. After completion of reaction, the mixture was poured in ice cold water and extracted with 25ml X 3 $CHCl_3$. The organic layers were combined, dried over anhydrous Na_2SO_4 and purified through column chromatography using Pet. ether: Ethyl acetate (30 %) as mobile phase to obtain desired off-white solid (**203,** 0.25 gm, 92%), m.p. 218-220 ºC.

Analysis

TLC : R_f 0.51 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3321, 3142, 2986, 1746, 1706, 1647, 1189

Mass (m/z) : 445.25 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.45 (s, 1H), 10.43 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.80-7.78(d, 2H), 7.73 (bs, 1H), 7.68-7.66 (d, 1H), 7.52-7.48 (t, 1H), 7.46-7.43 (t, 2H), 7.29-7.24 (m, 3H), 4.37-4.36 (q, 2H), 1.36-1.33(t, 3H).

6.2.99. Synthesis of ethyl 5-((3-isobutylcarbamate)benzamido)benzofuran-2-carboxylate (204)

Compound **(204)** was synthesized from Ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and isobutylchloroformate (**123**, 0.095 ml, 0.073 mM) using the procedure described for the synthesis of compound **(203)** to obtain the desired product as white solid. (**204,** 0.23 gm, 88%) m.p. 176-178 °C.

Analysis

TLC : R_f 0.47 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3330, 3102, 2957, 1730, 1696, 1641, 1218

Mass (m/z) : 425.16 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) :10.39 (s, 1H), 9.84 (s, 1H), 8.34-8.33 (d, *J* = 2.2 Hz, 1H), 8.04 (s, 1H), 7.81 (s, 1H), 7.78-7.77 (d, *J* = 2.3 Hz, 1H), 7.73-7.72 (d, *J* = 9.0 Hz, 1H), 7.68 (s, *J* = 8.1 Hz, 1H), 7.60-7.58 (d, *J* = 7.9 Hz, 1H), 7.47-7.43 (t, *J* = 7.9 Hz, 1H), 4.40-4.37 (q, *J* = 7.1 Hz, 2H), 3.91-3.90 (d, *J* = 6.7 Hz, 2H), 2.45-2.41 (t, *J* = 8.1 Hz, 1H), 1.37-1.33 (t, *J* = 7.1 Hz, 3H), 0.96-0.94 (d, *J* = 6.7 Hz, 6H).

6.2.100. Synthesis of ethyl 5-((3-ethylcarbamate)benzamido)benzofuran-2-carboxylate (205)

Compound **(205)** was synthesized from Ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and ethylchloroformate (**125**, 0.080 ml, 0.073 mM) using the procedure described for the synthesis of compound **(203)** to obtain the desired product as off-white solid (**205,** 0.22 gm, 90%) m.p. 215-218 ^oC .

Analysis

TLC : R_f 0.45 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3324, 3086, 2981, 1731, 1690, 1658, 1230

Mass (m/z) : 397.13 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.39 (s, 1H), 9.83 (s, 1H), 8.33-8.32 (d, *J* = 2.2 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.78-7.77 (d, *J* = 2.2 Hz, 1H), 7.76-7.72 (t, *J* = 9.0 Hz, 1H), 7.67 (s, *J* = 7.8 Hz, 1H), 7.60-7.58 (d, *J* = 8.0 Hz, 1H), 7.46-7.42 (t, *J* = 7.9 Hz, 1H), 4.40-4.34 (m, *J* = 7.1 Hz, 2H), 4.18-4.13 (m, *J* = 7.1 Hz, 2H), 1.37-1.33 (t, *J* = 7.1 Hz, 3H), 1.28-1.24 (t, *J* = 7.1 Hz, 3H).

6.2.101. Synthesis of ethyl 5-((3-methylcarbamate)benzamido)benzofuran-2-carboxylate (206)

Compound **(206)** was synthesized from ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and ethylchloroformate (**126**, 0.056 ml, 0.073 mM) using the procedure described for the synthesis of compound **(203)** to obtain the desired product as off-white solid (**206,** 0.23 gm, 89%), m.p. 207-211^oC.

Analysis

TLC : R_f 0.42 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3363, 3267, 3141, 2954, 1705, 1652, 1244

Mass (m/z) : 383.20 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.39 (s, 1H), 9.86 (s, 1H), 8.33-8.32 (d, *J* = 2.3 Hz, 1H), 8.01 (s, 1H), 7.81 (s, 1H), 7.78-7.77 (d, *J* = 2.2 Hz, 1H), 7.73-7.71 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 1H), 7.61-7.59 (d, *J* = 8.0 Hz, 1H), 7.47-7.43 (t, *J* = 7.9 Hz, 1H), 4.40-4.35 (m, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 1.37-1.33 (t, *J* = 7.1 Hz, 3H).

6.2.102. Synthesis of ethyl 5-((3-pentylcarbamate)benzamido)benzofuran-2-carboxylate (207)

Compound **(207)** was synthesized from ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and *n*-pentyl chloroformate (**127**, 0.105 ml, 0.073 mM) using the procedure described for the synthesis of compound **(203)** to obtain the desired product as off-white solid (**207,** 0.24 gm, 88%) m.p. 184-187 ^{o}C.

Analysis

TLC : R_f 0.48 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3345, 2954, 2864, 1731, 1706, 1646, 1223

Mass (m/z) : 439.27 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.38 (s, 1H), 9.82 (s, 1H), 8.33-8.32 (d, *J* = 2.2 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.78-7.77 (d, *J* = 2.2 Hz, 1H), 7.73-7.70 (d, *J* = 9.1 Hz, 1H), 7.67 (s, *J* = 7.7 Hz, 1H), 7.60-7.58 (d, *J* = 7.9 Hz, 1H), 7.46-7.42 (t, *J* = 7.9 Hz, 1H), 4.40-4.34 (m, *J* = 7.1 Hz, 2H), 4.12-4.08 (t, *J* = 6.7 Hz, 2H), 1.66-1.60 (m, *J* = 6.9 Hz, 2H), 1.36-1.23 (m, 7H), 0.91-0.88 (t, 3H).

6.2.103. Synthesis of ethyl 5-((3-benzylcarbamate)benzamido)benzofuran-2-carboxylate (208)

Compound **(208)** was synthesized from ethyl 5-((3-amino)benzamido)benzofuran-2-carboxylate (**202**, 0.2 gm, 0.061 mM) and benzyl chloroformate (**128**, 0.104 ml, 0.073 mM) using the procedure described for the synthesis of compound **(203)** to obtain the desired product as white solid (**208,** 0.26 gm, 91%), m.p. 207-210 ^{o}C.

Analysis

TLC : R_f 0.52 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3319, 3105, 2962, 1730, 1696, 1643, 1220

Mass (m/z) : 459.21 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.39 (s, 1H), 9.99 (s, 1H), 8.32 (s, 1H), 8.04 (s, 1H), 7.80-7.78 (d, 1H), 7.77-7.76 (d, *J* = 2.2 Hz, 1H), 7.73-7.70 (d, *J* = 9.0 Hz, 1H), 7.68-7.66 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H),

7.47 – 7.33 (m, 6H), 5.18 (s, 2H), 4.39-4.34 (m, 2H), 1.36-1.33 (t, *J* = 7.1 Hz, 3H).

6.2.104. Synthesis of ethyl 5-((4-amino)benzamido)benzofuran-2-carboxylate (211)

Compound **(211)** was synthesized from 4-amino benzoic acid (**209**, 1.6 gm, 0.97 mM) using the procedure described for the synthesis of compound **(202)** to obtain the desired product as off-white solid (**211,** 2.94 gm, 92%) m.p. 194-196 ºC.

Analysis

TLC : R_f 0.54 *n*-Hexane: Ethyl acetate (5:5)

IR (cm^{-1}) : 3394, 3318, 3130, 2918, 1706, 1658, 1222

Mass (m/z) : 325.11 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 9.92 (s, 1H), 8.30 (s, 1H), 7.79-7.78 (d, *J* = 2.2 Hz, 1H), 7.78-7.76 (d, 2H), 7.73 (s, 1H), 7.68-7.66 (d, *J* = 9.1 Hz, 1H), 6.62-6.60 (d, *J* = 8.7 Hz, 2H), 5.77 (s, 2H), 4.39-4.34 (m, *J* = 7.1 Hz, 2H), 1.35-1.33 (t, 3H).

6.2.105. Synthesis of ethyl 5-((4-phenylcarbamate)benzamido)benzofuran-2-carboxylate (212)

Ethyl 5-((4-amino)benzamido)benzofuran-2-carboxylate (**211**, 0.2 gm, 0.61 mM) and triethylamine (0.257 ml, 0.183 mM) were dissolved in dichloromethane and stirred at 25 ºC. Phenylchloroformate (**122**, 0.092 ml, 0.073 mM) was added dropwise and reaction mixture was stirred at room temperature until the reaction was complete. After completion of reaction, the mixture was poured in ice cold water and extracted with 25ml X 3 $CHCl_3$. The organic layers were combined, dried over anhydrous Na_2SO_4 and purified through column chromatography using Pet. ether: Ethyl acetate (30 %) as mobile phase to obtain desired off-white solid (**212,** 0.25 gm, 92%) m.p. 210-212 ºC.

Analysis

TLC : R_f 0.51 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3377, 3314, 3146, 2949, 1756, 1698, 1655, 1199

Mass (m/z) : 445.18 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.58 (s, 1H), 10.29 (s, 1H), 8.36-8.32 (d, *J* = 15.1 Hz, 2H), 8.00-7.98 (d, *J* = 8.8 Hz, 1H), 7.80-7.78 (d, *J* = 7.3 Hz, 3H), 7.73 (s, 1H), 7.68-7.66 (d, *J* = 8.9 Hz, 1H), 7.48-7.44 (t, *J* = 7.9 Hz, 2H), 7.31-7.26 (t, *J* = 10.0 Hz, 3H), 4.40-4.34 (m, *J* = 7.1 Hz, 2H), 1.37-1.33 (t, 3H).

6.2.106. Synthesis of ethyl 5-((4-isobutylcarbamate)benzamido)benzofuran-2-carboxylate (213)

Compound **(213)** was synthesized from ethyl 5-((4-amino)benzamido)benzofuran-2-carboxylate (**211**, 0.2 gm, 0.61 mM) and isobutyl chloroformate (**123**, 0.095 ml, 0.73 mM) using the procedure described for the synthesis of compound **(212)** to obtain the desired product as off-white solid (**213,** 0.245 gm, 89%), m.p. 178-180 ^{o}C.

Analysis

TLC : R_f 0.47 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3326, 3275, 3111, 2956, 1714, 1696, 1642, 1223.

Mass (m/z) : 425.16 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.23 (s, 1H), 9.96 (s, 1H), 8.32-8.31 (d, *J* = 2.2 Hz, 1H), 7.95-7.93 (d, *J* = 8.9 Hz, 2H), 7.80 (s, 1H), 7.78-7.77 (d, *J* = 2.2 Hz, 1H), 7.72 (s, 1H), 7.63-7.60 (d, *J* = 8.8 Hz, 1H), 4.40-4.34 (m, *J* = 7.0 Hz, 2H), 3.92-3.90 (d, *J* = 6.7 Hz, 2H), 3.55-3.49 (m, 1H), 1.36-1.33 (t, *J* = 7.1 Hz, 3H), 0.96-0.94 (d, *J* = 6.7 Hz, 6H).

6.2.107. Synthesis of ethyl 5-((4-pentylcarbamate)benzamido)benzofuran-2-carboxylate (214)

Compound **(214)** was synthesized from ethyl 5-((4-amino)benzamido)benzofuran-2-carboxylate (**211**, 0.2 gm, 0.00061 mM) and *n*-pentyl chloroformate (**126**, 0.105 ml / 0.00073 mM) using the procedure described for the synthesis of compound **(212)** to obtain the desired product as off-white solid (**214,** 0.255 gm, 94%), m.p. 213-216 °C.

Analysis

TLC : R_f 0.48 *n*-Hexane: Ethyl acetate (9:1)

IR (cm^{-1}) : 3346, 3108, 2954, 1732, 1701, 1647, 1222

Mass (m/z) : 439.24 $[M+H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.20 (s, 1H), 9.92 (s, 1H), 8.27 (s, 1H), 7.90-7.88 (d, *J* = 8.8 Hz, 2H), 7.75-7.73 (d, *J* = 9.9 Hz, 2H), 7.67-7.65 (d, *J* = 9.2 Hz, 1H), 7.58-7.56 (d, *J* = 8.9 Hz, 2H), 4.34-4.30 (m, *J* = 7.1 Hz, 2H), 4.07-4.05 (t, *J* = 6.6 Hz, 2H), 1.59-1.60 (d, 2H), 1.30 (s, 7H), 0.85 (s, 3H).

6.2.108. Synthesis of ethyl 5-((4-2,2,2-trichloroethylcarbamate)benzamido)benzofuran-2-carboxylate (215)

Compound **(215)** was synthesized from ethyl 5-((4-amino)benzamido)benzofuran-2-carboxylate (**211**, 0.2 gm, 0.61 mM) and 2,2,2-trichloroethyl chloroformate (**127**, 0.100 ml, 0. 73 mM) using the procedure described for the synthesis of compound **(212)** to obtain the desired product as off-white solid (**215,** 0.285 gm, 92%), m.p. 190-193 °C.

Analysis

TLC : R_f 0.43 *n*-Hexane: Ethyl acetate (9:1)

IR(cm^{-1}) : 3344, 3312, 2984, 2872, 1712, 1640, 1230

Mass (m/z) : 499.14 $[M+H]^+$, 501.34 $[M+2H]^+$

^{1}H-NMR (DMSO d_6, δ) : 10.49 (s, 1H), 10.28 (s, 1H), 8.32 (s, 1H), 7.99-7.97 (d, *J* = 8.9 Hz, 1H), 7.80-7.78 (d, 2H), 7.73 (s, 1H), 7.68-7.66 (d, *J* = 8.2 Hz, 2H), 4.99 (s, 2H), 4.39-4.35 (m, 2H), 1.36-1.34 (t, 3H).

6.2.109. Synthesis of ethyl 5-(3-benzamidobenzamido)benzofuran-2-carboxylate (222)

In a 25 ml RBF, benzoic acid (**216,** 0.188gm, 1.54 mM) and phosphorus tribromide (0.292 ml, 3.08 mM) were added in 10 ml THF at room temperature and stirred for one hour. Reaction was monitored by TLC followed by addition of ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.54 mM) and triethylamine (0.428 ml, 3.08 mM). After completion of reaction, excess THF was distilled off and the reaction mixture was poured in ice cold water to obtain crude. The obtained product was purified through column chromatography using Pet ether: Ethyl acetate (40%) as mobile phase to obtain the desired final product as a white solid (**222,** 0.29 gm, 78%) m.p. 198-200 °C

Analysis

TLC : R_f 0.62 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3348, 3297, 2897, 1728, 1643, 1563, 1293, 1153, 200, 686.

Mass (m/z) : 429.3 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) : 10.46 (d, *J* = 12.3 Hz, 2H), 8.35 (d, *J* = 2.2 Hz, 2H), 8.06 – 7.99 (m, 3H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 9.6 Hz, 2H), 7.62 – 7.51 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

6.2.110. Synthesis of 3-(2-phenylacetamido)-*N*-(2-propionylbenzofuran-5-yl)benzamide (223)

Compound **(223)** was synthesized from phenylacetic acid (**217,** 0.220 gm, 1.62 mM) and ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.62 mM) using the procedure described for the synthesis of compound **(222)** to obtain the desired product as off-white solid (**223,** 0.52 gm, 78%) m.p. 198-200 °C.

Analysis

TLC **:** R_f 0.62 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3390, 3263, 2917, 2849, 1711, 1680, 1644, 1549, 1265, 1232, 1154.

Mass (m/z) : 443.25 $[M+H]^+$

^1H NMR ($CDCl_3$, δ) : 10.40 (d, *J* = 5.7 Hz, 2H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.12 (s, 1H), 7.88 – 7.62 (m, 5H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.23 (m, 5H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

6.2.111. Synthesis of ethyl 5-(3-(nicotinamido)benzamido)benzofuran-2-carboxylate (224)

Compound **(224)** was synthesized from nicotinic acid (**218,** 0.189 gm, 1.54 mM) and ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.62 mM) using the procedure described for the synthesis of compound **(222)** to obtain the desired product as off-white solid (**224,** 0.3 gm, 81%), m.p. 233-235 **º**C.

Analysis

TLC : R_f 0.59 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3395, 3265, 2917, 2849, 1715, 1688, 1654, 1240, 1160.

Mass (m/z) : 430.20 $(M+H)^+$

^1H-NMR (DMSO d_6, δ) : δ 10.40 (d, *J* = 5.7 Hz, 2H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.12 (s, 1H), 7.88 – 7.62 (m, 5H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.23 (m, 5H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

6.2.112. Synthesis of ethyl 5-(3-(2-(naphthale*n*-2-yl)acetamido)benzamido)benzofuran-2-carboxylate (225)

Compound **(225)** was synthesized from napthyl acetic acid (**219,** 0.286 gm, 1.54 mM) and ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.62 mM) using the procedure described for the synthesis of compound **(222)** to obtain the desired product as off-white solid (**225,** 0.26 gm, 81%), m.p. 230-232 **º**C

Analysis

TLC : R_f 0.59 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 2979, 2926, 2869, 2665, 1677, 1606, 1316, 1285, 747.

Mass (m/z) : 493.25 $[M+H]^+$

^1H-NMR (DMSO d_6, δ) :10.56 (s, 1H), 10.41 (s, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 2H), 7.97 – 7.93 (m, 2H), 7.86 (dd, *J* = 8.4, 3.9 Hz, 2H), 7.79 (d, *J* = 5.8 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.53 (td, *J* = 5.8, 3.8 Hz, 4H), 7.48 – 7.44 (m, 2H), 4.37 (t, *J* = 7.1 Hz, 2H), 4.19 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

6.2.113. Synthesis of ethyl 5-(3-(thiophene-2-carboxamido)benzamido)benzofuran-2-carboxylate (226)

Compound **(226)** was synthesized from thiophene-2-carboxylic acid (**220,** 0.197 gm, 1.54 mM) and ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.62 mM) using the procedure described for the synthesis of compound **(222)** to obtain the desired product as off-white solid (**226,** 0.30 gm, 83%) m.p. 233-235 **º**C.

Analysis

TLC : R_f 0.62 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3308, 3078, 2973, 2661, 1711, 1651, 1630, 1345, 1299, 748.

Mass (m/z) : 435.19 $(M+H)^+$

^{1}H-NMR (DMSO d_6, δ) : 10.45 (d, *J* = 3.1 Hz, 2H), 8.34 (d, *J* = 2.1 Hz, 1H), 8.27 (t, *J* = 1.9 Hz, 1H), 8.08 (dd, *J* = 3.8, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.89 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.75 – 7.71 (m, 2H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

6.2.114. Synthesis of ethyl 5-(3-(2-chloroacetamido)benzamido)benzofuran-2-carboxylate (227)

Compound **(227)** was synthesized from 2-chloroacetyl chloride (**221,** 0.122 ml, 1.54 mM) and ethyl 5-(3-aminobenzamido)benzofuran-2-carboxylate (**202,** 0.5gm, 1.62 mM) using the procedure described for the synthesis of compound **(222)** to obtain the desired product as off-white solid (**227,** (0.33 gm, 81%) m.p. 190-192 **º**C.

Analysis

TLC : R_f 0.63 *n*-Hexane: Ethyl acetate (6:4)

IR (cm^{-1}) : 3252, 3109, 3086, 2940, 1712, 1667, 1647, 1594, 1470, 1442, 1228, 807.

Mass (m/z) : 401.13 $(M+H)^+$, 403.17 $(M+3)^+$

^{1}H-NMR (DMSO d_6, δ) : δ 10.52 (s, 1H), 10.44 (s, 1H), 8.33 (d, *J* = 2.1 Hz, 1H), 8.12 (t, *J* = 2.0 Hz, 1H), 7.86 – 7.77 (m, 3H), 7.74 – 7.69 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 4.38 (t, *J* = 7.1 Hz, 2H), 4.29 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

6.3. Biological studies

6.3.1. AChE and BuChE inhibition assay

A modified version of Ellman's colorimetric assay[12] was adapted to a high-throughput assay for the measurement of the enzymatic activity of BuChE and AChE. The reagents were acquired from Sigma-Aldrich (St. Louis, MO, USA) and included butyryl thiocholine iodide (BTC), acetylthiocholine iodide (ATC), and 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB). The specifics of the updated test are as previously stated.[13,14] In order to apply the procedure as a high-throughput test in 384-well plates, it was further refined. In short, AChE activity was measured using 25µL/well of a 1:400 diluted solution of lysed pooled human RBC and 1:768 diluted (3.5 ng/ml final concentration) pure recombinant human AChE protein (Sigma, Cat no. C1682). Frozen RBC that had been centrifuged to remove the plasma was then lysed in an equivalent volume of phosphate buffer to create the lysed RBC solution, which served as the source of RBC AChE. This resulted in a four-fold diluted RBC stock solution, which was then further diluted with an equivalent amount of glycerol and kept in tiny volume aliquots at -20 ^{o}C.

For BuChE, 25µL/well of a 1:400 diluted solution of a pooled human plasma was used for activity measurement. During the first stage of in vitro screening, the wells were pre-incubated for 10–30 minutes at room temperature using 25µL/well of synthesized compounds (37-91) at a concentration of 30 µM. In each well, the final concentration of the compounds was 10 µM. Ultimately, each well received 25µL of a cocktail mix made in Na/K phosphate buffer. This cocktail mix contained DTNB (final concentration 0.4 mM), BTC (final concentration 1 mM), or ATC (final concentration 0.5 mM). The absorbance changes were tracked at a wavelength of 412 nm for 15-20 minutes at intervals of one minute, using a microplate spectrophotometer reader (Infinite M1000, Tecan). With SOFTmax PRO 3.1.2, the percentage inhibition of the enzyme activity was computed compared to the control wells containing the enzyme incubated with the compounds vehicle (DMSO) solution.

6.3.2. MAO-B inhibition assay

MAO-B activity in *STHdh*$^{Q7/Q7}$ cells was measured using the Amplex® Red Monoamine Oxidase Assay Kit (Invitrogen, USA). Cells were lysed in M-PER™ Mammalian Protein Extraction Reagent (Thermo Fisher Scientific) supplemented with a 1x protease inhibitor cocktail (Sigma-Aldrich). Following a 30-minute incubation on ice, the lysate was centrifuged at 14,000 rpm for 15 minutes at 4°C. The supernatant was collected for subsequent analysis. Protein concentration was determined by the Bradford assay (Bio-Rad Protein Assay Dye Reagent Concentrate, Bio-Rad), and 4 µg of protein was used per

well in the MAO-B activity assay. Benzylamine hydrochloride for MAO-B enzyme was used as substrate. Sodium phosphate buffer (0.05 M, pH 7.4) was used for all the enzyme reactions and dilutions. The final reaction volume was 200 µl, containing the substrate, 10 µM test inhibitor, and DMSO as the co-solvent. The effects of test compounds on MAO-B activity were evaluated by measuring H_2O_2 production from benzylamine using the Amplex® Red assay kit. Briefly, 0.1 ml of sodium phosphate buffer (0.05 M, pH 7.4) containing 10 µM test compound and 4 µg of protein (*STHdh*$^{Q7/Q7}$ cell lysate) were incubated for 1 hour at 37°C in a 96-well plate to ensure maximal binding and reaction equilibrium. After this incubation period, the reaction was initiated by adding 200 µM Amplex Red reagent, 1 U/mL horseradish peroxidase, and 1 mM benzylamine hydrochloride (final concentrations) for 1 hour at RT. Fluorescence intensity (excitation 560 nm, emission 590 nm), proportional to H_2O_2 production and, consequently, of resorufin, was measured using a Synergy HTX Multi-Mode Microplate Reader (BioTek Instruments).Control experiments were carried out simultaneously by replacing the test drugs (new compounds and reference inhibitors) with appropriate dilutions of the vehicles. Background fluorescence was subtracted, and data were normalized to wells containing no inhibitor (0 µM) to calculate %inhibition. Based on these results, the five most potent compounds (K12, K24, K32, K48, and K58) were selected for IC_{50} determination. IC_{50} values were calculated using the curvatures of log (inhibitor) vs normalized response with a variable slope in GraphPad Prism: version 6. Initial compound concentrations ranging from 0 to 10 µM were used for IC_{50} calculations.

6.3.3. Cytotoxicity assay (MTT assay)

The MTT assay was employed to assess the cytotoxic effects of compounds **K12, K24, K32, K48 and K58** at varying concentrations, specifically 10 nM, 100 nM, 1 µM, 2 µM, and 10 µM. These evaluations were conducted utilizing ST*Hdh*$^{Q7/Q7}$ (mouse striatal cells) cells as the experimental model.[15]

Material & Method

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out according to the protocol outlined by Mosmann (1983)[16]. A transgenic mouse striatal cell line expressing human huntingtin protein with a polyglutamine repeat of 7, known as STHdh$^{Q7/Q7}$ cells, was employed. These cells were cultured in complete Dulbecco's Modified Eagle's Medium (DMEM) (Gibco, Invitrogen, USA) supplemented with 10% Fetal Bovine Serum (FBS) (Gibco, Invitrogen, USA) and 1% penicillin and streptomycin (Pe*n*-Strep) antibiotic mixture (Gibco, Invitrogen, USA) at 37°C with 5% CO_2 atmosphere.

Initially, $5x10^3$ cells were seeded in each well of a 96-well plate. Subsequently, the media was replaced, and test compounds were introduced in triplicates at specified concentrations, followed by an additional 24-hour incubation period. An equal volume of dimethyl sulfoxide (DMSO) in complete media served as the untreated control. After replacing the media, 10 µl of MTT solution (5mg/ml in 1x Phosphate-Buffered Saline) was added to each well, and the plates were kept in the dark for 4 hours at 37°C. Thereafter, the media was removed, and 100µl of DMSO was added to dissolve the formazan crystals formed. Following a 30-minute incubation in the dark, the absorbance was measured at 570 nm using Synergy HTX Multi-Mode Microplate Reader (BioTek Instruments). A lower intensity of the purple colour in the wells indicates reduced cell viability after treatment with test compounds. The percentage viability of each sample was calculated relative to the untreated control samples serving as a reference.

6.3.4. Metal chelating activity

In order to determine whether the selected compounds have significant metal chelating ability, metal chelating assay was carried out using ferrozine and ferrous chloride as described previously by Dinis *et.al,* 1994[17] Ferrozine can quantitatively chelate with Fe^{2+} and form a purple-coloured complex. This reaction is limited in the presence of other chelating agents and results in a decrease of the purple colour of the ferrozine-Fe^{2+} complex. Measurement of the colour reduction estimates the chelating activity to compete with ferrozine for the ferrous ions[18].

Material and Methods:

In this modified assay, solutions of ferrous chloride (2mM) and ferrozine (5 mM) were prepared in distilled water. The compounds (10uM final concentration, dissolved in DMSO) were mixed and incubated with 5µl of 2mM Ferrous Chloride for 20 minutes. 10µM EDTA was used as standard. Subsequently, a ferrozine solution (0.2 mL, 5 mM) was added. After allowing the mixtures to equilibrate for 10 minutes at room temperature, their absorbances were measured spectrophotometrically at 562 nm. The ability of each compound to inhibit the formation of the ferrous iron–ferrozine complex, expressed as its Fe^{2+} chelating activity (%), was then calculated using a specific equation.

% MCA = ((*Abs control - Abs sample*)/ *Abs control*) x 100

Where, MCA is the Metal chelation Activity; *Abs control* is the absorbance of Ferrous chloride + Ferrozine + DMSO; *Abs sample* is the absorbance of Ferrous chloride + Ferrozine + compounds.

Metal-chelating studies of the five compounds with different biological metals were performed. For the assay, all five compounds (50 μM, final concentration) alone or in the presence of $CuSO_4$, $FeCl_2$, or $ZnCl_2$ (50 μM, final concentration) in a buffer (20 mM HEPES, 150 mM NaCl, pH 7.4) were mixed. Following a 1-hour incubation period at room temperature, UV-Vis absorption spectra of the samples were acquired within the wavelength range of 230 to 360 nm, maintaining room temperature conditions.

6.3.5. Antioxidant (DPPH) assay:

DPPH (2,2-diphenyl-1-picrylhydrazyl) assay have been widely used to determine the antioxidant activities of synthetic and natural products. In order to explore the antioxidant potential of the compounds, DPPH assay was conducted using 10μM final concentrations of the selected compounds in a 96-well format as per established protocols[19].

Material and Methods: The DPPH radical scavenging assay was carried out using a Synergy Multimode reader (Bio-Tek Instruments, USA)[20]. Briefly, 10μM final concentration of all compounds is used for the assay. 180μL of freshly prepared DPPH solution (0.1mM in methanol) was mixed with 10μM of sample (dissolved in DMSO) in a 96-well plate. Pure MeOH + DMSO was used as a negative control and 10uM ascorbic acid (Vitamin C) was used as a positive control. The mixtures were shaken and left for 30 min in dark. The absorbance of the resulting solutions was measured at λ = 570 nm. The % radical scavenging activity of the compounds was calculated using the following formula,

$$\% \text{ RSA} = ((Abs\ control - Abs\ sample)/\ Abs\ control) \times 100$$

Where, RSA is the Radical Scavenging Activity; *Abs control* is the absorbance of the DPPH radical + methanol & DMSO; *Abs sample* is the absorbance of the DPPH radical + compound.

6.4. References

(1) RCSB PDB: Homepage https://www.rcsb.org/ (accessed 2024 -04 -26).

(2) Armarego, W. L.; Chai, C. L. L. Purification of Biochemicals and Related Products. *Purif. Lab. Chem.* **2009**, 577–708.

(3) No Title https://www.sigmaaldrich.com/IN/en/product/aldrich/d4369?icid=sharepdp-clipboard-copy-productdetailpage (accessed 2024 -01 -04).

(4) Kilic, B.; Erdogan, M.; Gulcan, H. O.; Aksakal, F.; Oruklu, N.; Bagriacik, E. U.; Dogruer, D. S. Design, Synthesis and Investigation of New Diphenyl Substituted Pyridazinone Derivatives as Both Cholinesterase and Aβ-Aggregation Inhibitors. *Med. Chem. (Los. Angeles).* **2019**, *15* (1), 59–76.

(5) Schneider, M. R.; Von Angerer, E.; Schoenenberger, H.; Michel, R. T.; Fortmeyer, H. P. 1, 1, 2-Triphenylbut-1-Enes: Relationship between Structure, Estradiol Receptor Affinity, and Mammary Tumor Inhibiting Properties. *J. Med. Chem.* **1982**, *25* (9), 1070–1077.

(6) Nilsson, P.; Larhed, M.; Hallberg, A. Highly Regioselective, Sequential, and Multiple Palladium-Catalyzed Arylations of Vinyl Ethers Carrying a Coordinating Auxiliary: An Example of a Heck Triarylation Process. *J. Am. Chem. Soc.* **2001**, *123* (34), 8217–8225.

(7) Rynbrandt, R. H.; Nishizawa, E. E.; Balgoyen, D. P.; Mendoza, A. R.; Annis, K. A. Synthesis and Platelet Aggregation Inhibitory Activity of 4,5-Bis(Aryl)-2-Substituted-Thiazoles. *J. Med. Chem.* **1981**, *24* (12), 1507–1510. https://doi.org/10.1021/jm00144a026.

(8) Padwa, A.; Dharan, M.; Smolanoff, J.; Wetmore, S. I. Photochemical Transformations of Small Ring Heterocyclic Compounds. XLVII. Electronic Details of the Photocycloaddition of Arylazirines. *J. Am. Chem. Soc.* **1973**, *95* (6), 1954–1961.

(9) Domínguez, E.; de Marigorta, E. M.; Olivera, R.; SanMartin, R. A Short and Efficient Synthesis of 4, 5-Diarylpyrimidines. *Synlett* **1995**, *1995* (09), 955–956.

(10) TANAKA, A.; MOTOYAMA, Y.; TAKASUGI, H. Studies on Anti-Platelet Agents. IV. A Series of 2-Substituted 4, 5-Bis (4-Methoxyphenyl) Pyrimidines as Novel Anti-Platelet Agents. *Chem. Pharm. Bull.* **1994**, *42* (9), 1828–1834.

(11) Renuka, J.; Reddy, K. I.; Srihari, K.; Jeankumar, V. U.; Shravan, M.; Sridevi, J. P.; Yogeeswari, P.; Babu, K. S.; Sriram, D. Design, Synthesis, Biological Evaluation of Substituted Benzofurans as DNA GyraseB Inhibitors of Mycobacterium Tuberculosis. *Bioorg. Med. Chem.* **2014**, *22* (17), 4924–4934.

(12) Ellman, G. L.; Courtney, K. D.; Andres Jr, V.; Featherstone, R. M. A New and Rapid Colorimetric Determination of Acetylcholinesterase Activity. *Biochem. Pharmacol.* **1961**, *7* (2), 88–95.

(13) Darreh-Shori, T.; Kadir, A.; Almkvist, O.; Grut, M.; Wall, A.; Blomquist, G.; Eriksson, B.; Långström, B.; Nordberg, A. Inhibition of Acetylcholinesterase in CSF versus Brain Assessed by 11C-PMP PET in AD Patients Treated with Galantamine. *Neurobiol. Aging* **2008**, *29* (2), 168–184.

(14) Darreh-Shori, T.; Brimijoin, S.; Kadir, A.; Almkvist, O.; Nordberg, A. Differential CSF Butyrylcholinesterase Levels in Alzheimer's Disease Patients with the ApoE E4 Allele, in Relation to Cognitive Function and Cerebral Glucose Metabolism. *Neurobiol. Dis.* **2006**, *24* (2), 326–333.

(15) Frederick, N. M.; Bertho, J.; Patel, K. K.; Petr, G. T.; Bakradze, E.; Smith, S. B.; Rosenberg, P. A. Dysregulation of System Xc− Expression Induced by Mutant Huntingtin in a Striatal Neuronal Cell Line and in R6/2 Mice. *Neurochem. Int.* **2014**, *76*, 59–69.

(16) Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol. Methods* **1983**, *65* (1–2), 55–63.

(17) Dinis, T. C. P.; Madeira, V. M. C.; Almeida, L. M. Action of Phenolic Derivatives (Acetaminophen, Salicylate, and 5-Aminosalicylate) as Inhibitors of Membrane Lipid Peroxidation and as Peroxyl Radical Scavengers. *Arch. Biochem. Biophys.* **1994**, *315* (1), 161–169.

(18) Soler-Rivas, C.; Espín, J. C.; Wichers, H. J. An Easy and Fast Test to Compare Total Free Radical Scavenger Capacity of Foodstuffs. *Phytochem. Anal. An Int. J. Plant Chem. Biochem. Tech.* **2000**, *11* (5), 330–338.

(19) Chang, S.-T.; Wu, J.-H.; Wang, S.-Y.; Kang, P.-L.; Yang, N.-S.; Shyur, L.-F. Antioxidant Activity of Extracts from Acacia Confusa Bark and Heartwood. *J. Agric. Food Chem.* **2001**, *49* (7), 3420–3424.

(20) Yurchenko, E. A.; Menchinskaya, E. S.; Pislyagin, E. A.; Chingizova, E. A.; Girich, E. V; Yurchenko, A. N.; Aminin, D. L.; Mikhailov, V. V. Cytoprotective Activity of P-Terphenyl Polyketides and Flavuside B from Marine-Derived Fungi against Oxidative Stress in Neuro-2a Cells. *Molecules* **2021**, *26* (12), 3618.

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