5.0 EXPERIMENTAL

5.1 Chemical Work

5.2 Biological Evaluation

5.1 Chemical work

All the chemicals, solvents and reagents were obtained commercially from Sigma-Aldrich or Fischer Scientific and used as such unless otherwise specified. All chemical reactions were controlled by thin-layer chromatography (TLC) using pre-coated silica gel G plates observed under ultraviolet light, ninhydrin reagent or iodine vapors. The compounds were purified by either re-crystallization or column chromatography over silica gel (100-200 mesh) stationary phase. Melting points of the synthesized compounds were determined on Veego programmable apparatus and are uncorrected. The IR spectra (in cm^{-1}) were recorded using KBr pellets on Bruker ALPHA-T (Germany) FT-IR instrument. The target compounds were characterized by proton NMR and carbon-NMR spectra recorded on Bruker AVANCE II (400, 500 and 100 Hz) spectrometer using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 solvents. The chemical shifts (δ) are expressed in parts per million (ppm) with reference to the standard TMS and signal multiplicities are given as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), broad singlet (bs) and multiplet (m) while coupling constants (*J)* are expressed in Hz. Mass spectra were recorded on Thermoscientific DSQ II instrument with ESI ion source and micrOTOF-Q II spectrometer with ESI ion source.

5.1.1 2-(Hydroxyimino)-*N*-(4-methoxyphenyl)acetamide (159)

Chloral hydrate (1.47 g, 8.93 mmol) was mixed in water (20 ml) and then added to sodium sulphate (9.22 g, 65.19 mmol) in water (18 ml). 4-Methoxyaniline (**156,** 1.0 g, 8.12 mmol) was dissolved in a solution of water (5 ml) and conc. HCl (0.8 ml) and added to the first mixture, a layer of brown oil was formed on the top of the mixture. Hydroxylamine hydrochloride (1.78 g, 24.3 mmol) was dissolved in water (8 ml) and added to the reaction mixture. The mixture was heated at 40 °C and then upto 50°C. Finally the mixture was heated to reflux for 10 min and then again heated to 130°Cfor 20 min. The mixture was cooled to RT and transferred to ice bath. The precipitate so obtained was collected under suction and washed with

some quantity of cold water. The light brown colored solid so obtained was dried in a vacuum oven(72 %); m.p.180-182 °C (Lit.184-185 °C). [1, 2]

Anal.:

TLC : R_f0.38 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) :1660, 1616, 1562, 1512, 1249, and 1002.

5.1.2 2-(Hydroxyimino)-*N*-(3,4-dimethoxyphenyl)acetamide (160)

Compound (**160**) was synthesized from 3,4-dimethoxyaniline (**157**,1.0 g, 6.52 mmol) following the method described for compound (**159)** to get a brown solid (70 %); m.p.168-170 °C.

Anal.:

TLC : R_f0.34 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 3388, 1656, 1622, 1257, and 1026

5.1.3 2-(Hydroxyimino)-*N*-(4-chlorophenyl)acetamide (161)

Compound (**161)** was synthesized from 4-chloroaniline (**158**, 1.0 g, 7.83 mmol) following the method described for compound (**159)** to get a grey coloured solid (78%); m.p. 177-179 °C.

Anal.:

TLC : R_f0.48 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 3300, 1664, 1615, 1552, 1248, and 1007.

5.1.4 5-Methoxyindoline-2,3-dione (162)

Concentrated sulphuric acid (5.0 ml) in 0.5 ml water was warmed to 60°C and compound (**159**, 1.0 g, 5.14 mmol) was mixed with this acid solution in one portion. The mixture was stirred and heated to 85°C for 10 min. and allowed to cool at RT. The mixture was poured into ice (50 g) and extracted by ethyl acetate (3x50 ml). The ethyl acetate layer was dried from anhydrous sodium sulphate and concentrated to give a dark red solid (**162**, 50 %); m.p.198-200 °C (Lit.201-203 °C).[1, 2]

Anal.:

TLC : R_f0.36 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 1745, 1633, 1489, and 1032.

5.1.5 5,6-Dimethoxyindoline-2,3-dione (163)

Compound (**163**) was synthesized from2-(hydroxyimino)-*N*-(3,4-dimethoxyphenyl)-acetamide (**160**, 1.0 g, 5.14 mmol) following the method described for compound (**162)** to obtain a red solid (42%); m.p.235-237 °C (Lit.240-241 °C).[3]

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 3300, 1758, 1714, 1622, 1496, and 1006.

5.1.6 5-Chloroindoline-2,3-dione (164)

Compound (**164**) was synthesized from 2-(hydroxyimino)-*N*-(4-chlorophenyl)acetamide **(161,** 1.0 g,5.0 mmol**)** following the method described for compound (**162)** to obtain an orange solid (60%); m.p. 244-248 °C.

Anal.:

TLC : R_f0.40 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 3183, 1755, 1709, 1615, and 1450.

5.1.7 2-Amino-5-methoxybenzoic acid (165)

5-Methoxyindoline-2,3-dione, (**162**,2.0 g, 11.28 mmol) was dissolved in aqueous sodium hydroxide solution (5 %, 40 ml) with continuous stirring. A solution of H_2O_2 (30 %, 30 ml, 28.20 mmol) in water was added to the above mixture dropwise in cold conditions during 30 min. The mixture was heated at 50°C for 2 hrs and then cooled at RT. HCl (2M, ~20ml) was added to the the mixture till acidic *p*H, 2.0 to afford a solid which was filtered under suction and dried in a vacuum oven to get a grey colored solid (**165**,52 %); m.p. 146-148 °C (Lit.148-150 °C).[2]

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) :3399, 3311, 1660, 1602, and 1030.

5.1.8 2-Amino-4,5-dimethoxybenzoic acid (166)

Compound (**166**) was synthesized from 5,6-dimethoxyindoline-2,3-dione (**163**, 2.0 g, 9.65 mmol) following the method described for compound (**165)** to get a grey solid (54 %); m.p.152-155°C (Lit.156-157 °C).[4]

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) :3487, 3372, 1655, 1420 and 996.

5.1.9 2-Amino-5-chlorobenzoic acid (167)

Compound (**167**) was synthesized from 5-chloroindoline-2,3-dione (**164**, 2.0 g, 11.01 mmol) following the method described for compound (**165)** to obtain an off-white solid (70 %); m.p. 208-210°C.

Anal.:

TLC : R_f0.35 (*n*-Hexane: ethyl acetate; 5:5)

IR (KBr, cm^{-1}) : 3468, 3357, 1675, and 1238.

5.1.10 2-(4-Chlorophenyl)-6-methoxy-4*H*-benz[*d*][1,3]oxazin-4-one (168)

4-Chlorobenzoic acid (0.95 g, 6.0 mmol) and thionyl chloride (1.44 g, 0.88 ml, 12.17 mmol) were taken in a 100 ml dry RBF and refluxed for 3-4 hrs. under anhydrous conditions. After completion of the reaction, excess of thionyl chloride was removed under vacuum. 2-Amino-5-methoxybenzoic acid, (**165**, 1.0 g, 5.828 mmol) dissolved in dry pyridine (4.6 g, 4.69 ml, 50.71 mmol) was added drop-wise to the above acid chloride at 0-5 °C with continuous stirring. After completion of the reaction, the reaction mixture was mixed with crushed ice. The precipitated product was filtered out and washed with the saturated solution of $NaHCO_3$. The dry solid was recrystallized from acetone to afford a pure off white compound[5] (**168**; 68 %); m.p. 195-196 °C.

Anal.:

TLC : R_f0.74 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1759, 1625, 1497, and 1030.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ 7.65-7.64 (m, 1H, Ar-*H*), 7.55-7.53 (m, 4H, Ar-*H*), 7.51-7.49 (d, 1H, *J* = 7.2 Hz, Ar-*H*), 7.44-7.42 (dd, 1H, *J* = 2.4 Hz; 7.2 Hz, Ar-*H*), 3.96 (s, 3H).

5.1.11 2-(4-Chlorophenyl)-6,7-dimethoxy-4*H*-benz[*d*][1,3]oxazin-4-one (169)

Compound (**169**) was synthesized from compound (**166**, 1.0 g, 5.071 mmol) and 4-chlorobenzoic acid (0.95 g, 6.085 mmol) following the method described for compound (**168)** to get light yellow solid (78 %); m.p. 212-215 °C (Lit.210-212 °C).[6]

Anal.:

TLC : R_f0.72 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1759, 1602, 1505, and 1016.

5.1.12 6-Chloro-2-(4-chlorophenyl)-4*H*-benz[*d*][1,3]oxazin-4-one (170)

Compound (**170**) was synthesized from compound (**167**, 1.0 g, 5.828 mmol) and 4-chlorobenzoic acid (1.0 g, 6.99 mmol) following the method described for (**168)** to obtain a white solid (71%); m.p. 144-146 °C (Lit.147 °C). [7]

Anal.:

TLC : R_f0.78 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1751, 1612, 1467, and 1255.

5.1.13 2-(5-Chlorothiophen-2-yl)-6-methoxy-4*H*-benz[*d*][1,3]oxazin-4-one (171)

Compound (**171)** was synthesized from compound (**165**, 1.0 g, 5.828 mmol) and 5-chlorothiophene-2-carboxylic acid (1.13 g, 6.993 mmol) following the method described for compound (**168)** to get a white solid (64 %); m.p. 180-182 °C.

Anal.:

TLC : R_f0.73 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1761, 1612, 1489, 1040.

PMR (400 MHz, $CDCl_3$) : δ 7.71-7.70 (m, 1H, Ar-*H*), 7.62-7.61(m, 1H, Ar-*H*), 7.58-7.56 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.41-7.39 (dd, *J* = 2.2 Hz, *J* = 7.2 Hz, 1H, Ar-*H*), 7.00 (d, *J* = 3.2 Hz, 1H, Ar-*H*), 3.94 (s, 3H, OCH_3).

5.1.14 2-(5-Chlorothiophen-2-yl)-6,7-dimethoxy-4*H*-benz[*d*][1,3]oxazin-4-one (172)

Compound (**172**) was synthesized from compound (**166**, 1.0 g, 5.071 mmol) and 5-chlorothiophene-2-carboxylic acid (0.98 g, 6.085 mmol) following the method described for (**168)** to geta light yellow solid (73 %); m.p. 225-228 °C.

Anal.:

TLC : R_f0.70 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1760, 1602, 1506, and 1015.

PMR (400 MHz, $CDCl_3$) : δ 7.69-7.68 (d, *J* = 3.2 Hz, 1H, Ar-*H*,), 7.52 (s, 1H, Ar-*H*) 7.03 (s, 1H, Ar-*H*), 6.98-6.97 (d, *J* = 3.2 Hz, 1H, Ar-*H*), 4.02 (s, 3H), 3.99 (s, 3*H*).

5.1.15 6-Chloro-2-(5-chlorothiophen-2-yl)-4H-benz[*d*][1,3]oxazin-4-one (173)

Compound (**173**) was synthesized from compound (**167**, 1.0 g, 5.828 mmol) and 5-chlorothiophene-2-carboxylic acid (1.13 g, 6.993 mmol) following the method described for (**168)** to get white solid (76 %); m.p. 166-168 °C.

Anal.:

TLC : R_f0.78 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1767 (C=O stretch), 1615, 1430 and 1028.

PMR (400 MHz, $CDCl_3$) : δ 8.19-8.18 (m, 1H, Ar-*H*), 7.77-7.75 (m, 2H, Ar-*H*), 7.59-7.57 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 7.03-7.02 (d, *J* = 3.2 Hz, 1H, Ar-*H*).

5.1.16 2-(6-Chloropyridin-3-yl)-6,7-dimethoxy-4*H*-benz[*d*][1,3]oxazin-4-one (174)

Compound (**174)** was synthesized from compound (**166**, 1.0 g, 5.071 mmol) and 6-chloronicotinic acid (0.95 g, 6.085 mmol) following the method described for (**168)** to get alight yellow solid (68 %); m.p.: 201-203 °C.

Anal.:

TLC : R_f0.68 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1749, 1602, 1508, and 1015.

PMR (400 MHz, $CDCl_3$) : δ 9.27 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.50-8.48 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 1H, Ar-*H*), 7.59 (s, 1H, Ar-*H*), 7.51-7.49 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 7.14 (s, 1H, Ar-*H*), 4.07 (s, 3H), 4.03 (s, 3*H*).

5.1.17 6-Chloro-2-(6-chloropyridin-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (175)

Compound (**175**) was synthesized from compound (**167**, 1.0 g, 5.828 mmol) and 6-chloronicotinic acid (0.95 g, 6.085 mmol) following the method described for (**168)** to get light yellow solid (70%); m.p. 216-218 °C.

Anal.:

TLC : R_f0.73 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1765, 1623, 1474, and 1132.

PMR (400 MHz, $CDCl_3$) : δ 9.29-9.28 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.52-8.50 (dd, *J* = 2.0 and 6.8 Hz, 1H, Ar-*H*), 8.25-8.24 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.84-7.82 (dd, *J* = 2.0 and 6.8 Hz, 1H, Ar-*H*), 7.70-7.68 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 7.53-7.51(d, 1H, *J* = 6.8 Hz, Ar-*H*).

5.1.18 4-Chloro-*N*-(2-(4-(2-chlorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-benzamide (177)

Compound (**168**, 0.20 g, 0.69 mmol) and 1-(2-chlorophenyl)piperazine (0.27 g, 1.39 mmol) were mixed in a 100 ml dry RBF and stirred at 100 ^oC for 6 hrs. After completion of reaction, crushed ice was added to the reaction mixture. The solid product was isolated out and washed with cold water. The crude dry product was purified by column chromatography to afford a pure white solid, (**177**, 58 %); m.p. 151-153 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 2923, 1664, 1641, 1596, and 1288.

PMR (400 MHz, $CDCl_3$) : δ 9.66 (s, 1H, N*H*CO), 8.21-8.19 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.87-7.85 (d, *J* = 8.55 Hz, 2H, Ar-*H*), 7.46-7.44 (d, *J* =

8.55 Hz, 2H, Ar-*H*), 7.37-7.35 (dd, *J* =1.4 and 7.8 Hz, 1H, Ar-*H*), 7.21-7.17 (m, 1H, Ar-*H*), 7.00-6.97 (m, 2H, Ar-*H*), 6.93-6.91 (dd, *J* =1.4 and 7.8 Hz, 1H, Ar-*H*), 6.84-6.83 (d, *J* = 2.8 Hz, 1H, Ar-*H*), 3.95 (bs, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.73 (bs, 2H, CH_2), 3.02 (bs, 4H, CH_2).

MS (ESI) *m/z* : 484.2 $[M+H]^+$.

5.1.19 4-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-benzamide (178)

Using method described for the compound (**177**), compound (**168**, 0.20 g, 0.69 mmol) and 1-(2-fluorophenyl)piperazine (0.25 g, 1.39 mmol) furnished compound (**178**) as white solid (64 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.33 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1664, 1598, 1288, and 1218.

PMR (400 MHz, $CDCl_3$) : δ 10.08 (s, 1H, N*H*CO), 8.09 (s,1H, Ar-*H*), 7.96-7.94 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 7.49-7.47 (d, *J* = 8.4 Hz, Ar-*H*), 7.07-6.99 (m, 3H, Ar-H), 6.97-6.94 (m, 1H, Ar-*H*), 6.89-6.86 (m, 2H, Ar-*H*), 3.82 (s, 3H, OCH_3), 3.77 (bs, 2H, CH_2), 3.54 (bs, 2H, CH_2), 3.0 (bs, 4H, 2×CH_2).

MS (ESI) *m/z* : 468.4 $[M+H]^+$.

5.1.20 4-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-benzamide (179)

Following the method described for the compound (**177**), compound (**168**, 0.20 g, 0.69 mmol)and 1-(4-fluorophenyl)piperazine (0.25 g, 1.39 mmol) yielded compound (**179**) as white solid (59 %); m.p. 177-179 °C.

Anal.:

TLC : R_f0.27 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3318, 1678, 1617, 1528, and 1281.

PMR (500 MHz, $CDCl_3$) : δ 9.66 (s, 1H, N*H*CO), 8.28-8.26 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.87-7.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.47-7.46 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.06-7.04 (dd, *J* = 3.0, *J* = 9.0 Hz, 1H, Ar-*H*), 7.00-6.97 (m, 2H, Ar-*H*), 6.89-6.85 (m, 3H, Ar-*H*), 3.85 (m, 7H, OCH_3 & 2×CH_2), 3.11 (bs, 4H, CH_2).

5.1.21 4-Chloro-*N*-(2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-benzamide (180)

Using the method described for the compound (**177**), compound (**168**, 0.20 g, 0.69 mmol) and 1-(4-methoxyphenyl)piperazine (0.26 g, 1.39 mmol) offered compound (**180**) as white solid (72 %); m.p. 173-175 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3313, 1666, 1612, 1514, and 1278.

PMR (500 MHz, $CDCl_3$) : δ 9.63 (s, 1H, N*H*CO), 8.28-8.26 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.87-7.85 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.47-7.45 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.06-7.02 (m, 4H, Ar-*H*), 6.89-6.86 (m, 1H, Ar-*H*), 6.85-6.84 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 3.93 (bs, 2H, CH_2), 3.83 (s, 6H, 2×OCH_3), 3.74 (bs, 2H, CH_2), 3.06 (s, 4H, CH_2).

5.1.22 4-Chloro-*N*-(2-(4-(4-cyanophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-benzamide (181)

Using the method described for the compound (**177)**, compound (**168**, 0.20 g, 0.69 mmol) and 1-(4-cyanophenyl)piperazine (0.26 g, 1.39 mmol) furnished compound (**181)** as off white solid (58 %); m.p. 218-220 °C.

Anal.:

TLC : R_f0.23 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3241, 2209, 1640, 1600, 1515, 1242, and 1012.

PMR (500 MHz, $CDCl_3$) : δ 9.58 (s, 1H, N*H*CO), 8.23-8.21 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.84-7.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.52-7.50 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.45-7.43 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.05-7.04 (dd, *J* = 3.0 and 9.0 Hz, 1H, Ar-*H*), 6.85-6.82 (m, 3H, Ar-*H*), 3.83-3.82 (m, 7H, 2×CH_2& OCH_3), 3.35 (bs, 4H, CH_2).

MS (ESI) *m/z* : 475.4 $[M+H]^+$.

5.1.23 4-Chloro-*N*-(2-(4-(4-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) benzamide (182)

Using the method described for the compound (**177**), compound (**169**, 0.20 g, 0.62 mmol) and 1-(4-methylphenyl)piperazine (0.22 g, 1.25 mmol) furnished compound (**182)** as off white solid (55 %); m.p. 148-150 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1668, 1595, 1516, and 1097.

PMR (500 MHz, $CDCl_3$) : δ 10.37 (s, 1H, N*H*CO), 8.19 (s, 1H, Ar-*H*), 7.89-7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.47-7.45 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.09-7.07 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.84-6.80 (m, 3H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.16 (bs, 4H, 2×CH_2), 2.27 (s, 3H, CH_3).

5.1.24 4-Chloro-*N*-(2-(4-(2-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) benzamide (183)

In a 100 ml single necked dry RBF, 1-(2-methylphenyl)piperazine hydrochloride (0.22 g, 1.24 mmol) and *N*,*N*-diisopropylethylamine (0.32 g; 0.43 ml, 2.49 mmol) were mixed in a dry DMF and stirred at RT for 30 min. After formation of free piperazine base, compound (**169**, 0.20 g, 0.62 mmol) was added and mixture was heated at 100 °C for 6 hrs. After completion, crushed ice was added to the reaction mixture. The solid product was isolated and washed with cold

water. The crude dry product was purified to afford compound (**183**) as off white solid (68 %); m.p. 171-173 °C.

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3318, 1661, 1606, 1512, and 1219.

PMR (500 MHz, $CDCl_3$) : δ 10.32 (s, 1H, N*H*CO), 8.17 (s, 1H, Ar-*H*), 7.91-7.90 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.49-7.48 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.19-7.16 (m, 2H, Ar-*H*), 7.01 (m,1H, Ar-*H*), 6.94-6.92 (dd, *J* = 1.2 and 8.0 Hz, 1H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 3.97 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.81 (bs, 4H, 2×CH_2), 2.91(bs,4H, 2×CH_2), 2.31 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.96, 164.12, 151.15, 150.51, 144.57, 138.26, 132.83, 132.78, 132.69, 131.21, 129.09, 128.61, 126.69, 123.97, 119.19, 114.65, 111.02, 106.23, 56.40, 56.12, 52.04, 17.74.

HR-MS (ESI)*m/z* : 494.1826 $[M+H]^+$.

5.1.25 4-Chloro-*N*-(2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (184)

Using the method described for the compound (**177**), compound (**169**, 0.20g, 0.62 mmol) and 1-(2-methoxyphenyl)piperazine (0.24 g, 1.24 mmol) furnished compound (**184**) as white solid (62 %); m.p. 197-199 °C.

Anal:

TLC : R_f0.18 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3307, 1667, 1615, 1511, and 1238.

PMR (500 MHz, $CDCl_3$) : δ 10.39 (s, 1H, -N*H*CO), 8.22 (s, 1H, Ar-*H*), 7.92-7.91 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.50-7.49 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.08-7.04 (m, 1H, Ar-*H*), 6.95-6.90 (m, 3H, Ar-*H*),

6.84 (s, 1H, Ar-*H*), 4.00 (s, 3H, OCH_3), 3.91-3.86 (m, 10H, 2×CH_2& 2×OCH_3), 3.10 (s, 4H, 2×CH_2).

5.1.26 4-Chloro-*N*-(2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (185)

Using the method described for the compound (**177)**, compound (**169**, 0.20 g, 0.62 mmol) and 1-(4-methoxyphenyl)piperazine (0.24g, 1.24 mmol) furnished compound (**185**) as white solid (72 %); m.p. 173-175 °C.

Anal.:

TLC : R_f0.13 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3313, 1666, 1612, 1514, and 1278.

PMR (400 MHz, $CDCl_3$) : δ 10.34 (s, 1H, N*H*CO), 8.18 (s, 1H, Ar-*H*), 7.88-7.86 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.47-7.45 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.89-6.80 (m, 5H, Ar-*H*),3.97 (s, 3H, -OCH_3), 3.87(s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.75 (s, 3H, OCH_3), 3.07 (bs, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.93, 164.07, 154.55, 151.23, 144.94, 144.52, 138.23, 132.92, 132.81, 129.07, 128.58, 118.91, 114.55, 114.34, 111.03, 106.18, 56.41, 56.12, 55.52, 51.24.

HR-MS (ESI) *m/z* : 510.1790 $[M+H]^+$.

5.1.27 4-Chloro-*N*-(2-(4-(4-chlorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (186)

Using the method described for the compound (**183)**, compound **(169**, 0.20 g, 0.62 mmol) and 1-(4-chlorophenyl)piperazine dihydrochloride (0.33 g, 1.24 mmol) furnished compound **(186**) as off white solid (64%); m.p. 177-179 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3318, 1667, 1609, 1508, and 1228.

PMR (400 MHz, $CDCl_3$) : δ 10.31 (s, 1H, N*H*CO), 8.18 (s, 1H, Ar-*H*), 7.88-7.86 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.48-7.46 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.24-7.22 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.88-6.86 (d, *J* = 8.4 Hz, 2*H*, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.85 (bs, 4*H*, 2×CH_2), 3.18 (bs, 4*H*, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.09, 151.39, 149.29, 138.30, 133.11, 132.79, 129.16, 129.10, 128.58, 117.87, 111.05, 106.33, 56.47, 56.15, 49.73.

MS (ESI) *m/z* : 514.5 $[M+H]^+$.

5.1.28 4-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (187)

Using the method described for the compound (**177)**, compound (**169**, 0.20 g, 0.62 mmol) and 1-(4-fluorophenyl)piperazine (0.22 g, 1.24 mmol) furnished compound (**187)** as white solid (70 %); m.p. 218-220 °C.

Anal.:

TLC : R_f0.18 (*n*-Hexane: Ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1666, 1623, 1510, and 1095.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ 10.35 (s, 1H, N*H*CO), 8.18 (s, 1H, Ar-*H*), 7.89-7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.48-7.46 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.99-6.95 (m,2H, Ar-*H*), 6.88-6.85 (m, 2H, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.83 (bs, 4H, 2×CH_2), 3.11 (bs, 4H, 2×CH_2).

HR-MS (ESI) *m/z* : 498.1590 $[M+1]^+$, 499.1624 $[M+2]^+$

5.1.29 4-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (188)

Using the method described for the compound (**177)**, compound **(169**, 0.20 g, 0.62 mmol) and 1-(4-fluorophenyl)piperazine (0.22 g, 1.24 mmol) furnished compound (**188**) as white solid (73 %). m.p. 191-193 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3314, 1683, 1593, and 1018.

PMR (500 MHz, $CDCl_3$) : δ 10.40 (s, 1H, N*H*CO), 8.21 (s, 1H, Ar-*H*), 7.92-7.91 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.50-7.49 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.09-7.06 (m, 2H, Ar-*H*), 7.04-6.97 (m, 1H, Ar-*H*), 6.94-6.90 (m, 1H, Ar-*H*), 6.83 (s, 1H, Ar-*H*), 4.00 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.88 (bs, 4H, 2×CH_2), 3.12 (bs, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.91, 164.08, 154.73, 151.18, 144.52,139.27, 139.21, 138.24, 132.87, 132.78, 129.07, 128.59, 124.55, 123.38, 123.32, 119.20, 116.37, 116.21, 110.92, 106.16, 56.37, 56.12, 50.78.

5.1.30 4-Chloro-*N*-(2-(4-(2-cyanophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (189)

Using the method described for the compound (**177)**, compound **(169**, 0.20 g, 0.62 mmol) and 1-(2-cyanophenyl)piperazine (0.23 g, 1.24 mmol) furnished compound (**189)** as white solid (58 %); m.p. 202-204 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3304, 2220, 1670, 1606, and 1267.

PMR (500 MHz, $CDCl_3$) : δ 10.41 (s, 1H, -N*H*CO), 8.18 (s, 1H, Ar-*H*), 7.92-7.90 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.62-7.60 (m, 1H, Ar-*H*), 7.53-7.48

(m, 3H, Ar-*H*), 7.09 (m, 1H, Ar-*H*), 6.99-6.97 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 4.00 (s, 3H, OCH_3), 3.94 (s, 4H, 2×CH_2), 3.91 (s, 3H, OCH_3), 3.21 (bs, 4H, 2×CH_2).

5.1.31 4-Chloro-*N*-(2-(4-(4-cyanophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (190)

Using the method described for the compound (**177)**, compound (**169**, 0.20 g, 0.62 mmol) and 1-(4-cyanophenyl)piperazine (0.23 g, 1.24 mmol) furnished compound (**190**) as light yellow solid (60 %); m.p. 183-185 °C.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3312, 2210, 1683, 1600, 1523, and 1251.

PMR (500 MHz, $CDCl_3$) : δ 10.39 (s, 1H, -N*H*CO), 8.21 (s, 1H, Ar-*H*), 7.90-7.89 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.55-7.53 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.50-7.48 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.89-6.87 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 4.01 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.86 (bs, 4H, 2×CH_2), 3.40 (bs, 4H, 2×CH_2).

5.1.32 4-Chloro-*N*-(2-(4-(4-nitrophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (191)

Using the method described for the preparation of (**177**), compound (**169**, 0.20 g, 0.62 mmol) and 1-(4-nitrophenyl)piperazine (0.26 g, 1.24 mmol) furnished compound (**191**) as light yellow solid (63 %); m.p. 232-234 °C.

Anal.:

TLC : R_f0.48 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1668, 1594, 1521, 1325, and 1234.

PMR (500 MHz, $CDCl_3$) : δ 10.40 (s, 1H, -N*H*CO), 8.20 (s, 1H, Ar-*H*), 8.17-8.15 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.91-7.89 (d, *J* = 8.5 Hz, 2H, Ar-*H*),

7.50-7.48 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.85-6.83 (m, 3H, Ar-*H*), 4.01 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.89 (bs, 4H, 2×CH_2), 3.51 (bs, 4H, 2×CH_2).

5.1.33 4-Chloro-*N*-(2-(4-(4-aminophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-benzamide (192)

In a two necked 100 ml dry RBF, compound (**191**, 0.3 g, 0.57 mmol) was mixed in 5 ml methanol and heated on water bath for few min. Iron powder (0.12 g, 2.28 mmol) and 5 ml aqueous ammonium chloride was then added simultaneously in portions during half an hour and reaction mixture was refluxed on water bath for 4-6 hrs.[8] After completion of reaction, mixture was filtered in hot condition through a hyflo bed, which was prepared using methanol in hot buchner funnel. The filterate was collected and concentrated. The reaction mixture was then basified with 10 % NaOH. The precipitated solid was isolated and washed with cold water. The crude dry solid was purified by column chromatography to afford a pure compound (**192**) as light brown solid (46 %); m.p. 205-208 °C.

Anal.:

TLC : R_f0.23 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3350, 2928, 1667, 1601, 1519, and 1265.

^{1}H-NMR (500 MHz, $CDCl_3$) : δ 10.38 (s, 1H, -N*H*CO), 8.21 (s, 1H, Ar-*H*), 7.91-7.89 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.49-7.48 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.83-6.79 (m, 3H, Ar-*H*), 6.67-6.65 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.00 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.83 (bs, 4H, 2×CH_2), 3.06 (bs, 4H, 2×CH_2).

5.1.34 4-Chloro-*N*-(4-chloro-2-(4-(2-methylphenyl)-1-piperazinylcarbonyl)-phenyl)-benzamide (193)

Following the method for the compound (**183**), compound **(170**, 0.20 g, 0.68 mmol) and 1-(2-methylphenyl)piperazine hydrochloride (0.29 g, 1.36 mmol) furnished compound (**193**) as a white solid (68 %); m.p. 135-138 °C.

Anal.:

TLC : R_f0.48 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1673, 1604, 1552, and 1230.

PMR (400 MHz, $CDCl_3$) : δ 10.03 (s, 1H, N*H*CO), 8.44-8.42 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.88-7.86 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.49-7.43 (m, 3H, Ar-*H*), 7.30 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.20-7.13 (m, 2H, Ar-*H*), 7.01 (m, 1H, Ar-*H*), 6.95-6.93 (m, 1H, Ar-*H*), 3.81 (bs, 4H, 2×CH_2), 2.92 (bs, 4H, 2×CH_2), 2.31 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 168.21, 164.11, 150.40, 138.54, 136.15, 132.71, 132.48, 131.24, 131.11, 129.15, 128.81, 128.69, 127.56, 126.73, 124.37, 124.20, 124.07, 119.25, 52.00, 17.74.

5.1.35 4-Chloro-*N*-(4-chloro-2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-phenyl)-benzamide (194)

Following the method described for the compound (**177**), compound **(170**, 0.20 g, 0.68 mmol) and 1-(2-methoxyphenyl)piperazine (0.26 g, 1.36 mmol) furnished compound (**194**) as a white solid (65 %)' m.p. 162-164 °C.

Anal.:

TLC : R_f0.34 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3239, 1674, 1593, 1499, and 1238.

PMR (500 MHz, $CDCl_3$) : δ 10.08 (s, 1H, N*H*CO), 8.46-8.44 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.90-7.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.50-7.45 (m, 3H, Ar-*H*), 7.32 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.08-7.04 (m, 1H, Ar-*H*), 6.94-6.88 (m, 3H, Ar-H), 3.97 (bs, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.77 (bs, 2H, CH_2), 3.10 (bs, 4H, 2×CH_2).

5.1.36 4-Chloro-*N*-(4-chloro-2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-phenyl)-benzamide (195)

Using the method described for the compound (**177)**, compound **(170,** 0.20 g, 0.68 mmol) and 1-(4-methoxyphenyl)piperazine (0.26 g, 1.36 mmol) furnished compound (**195**) as white solid (72 %); m.p. 184-186 °C.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3269, 1683, 1628, 1513, and 1235.

PMR (400 MHz, $CDCl_3$) : δ 10.02 (s, 1H, N*H*CO), 8.44-8.42 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.86-7.84 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.47-7.43 (m, 3H, Ar-*H*), 7.29-7.28 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.89-6.82 (m, 4H, Ar-*H*), 3.80-3.76 (m, 7H, OCH_3&2×CH_2), 3.07 (s, 4H, 2×CH_2).

HR-MS (ESI) *m/z* : 484.1189 $[M+H]^+$.

5.1.37 4-Chloro-*N*-(4-chloro-2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-phenyl)-benzamide (196)

Using the method described for the compound (**177**), compound **(170**, 0.20 g, 0.68 mmol) and 1-(4-fluorophenyl)piperazine (0.24 g, 1.36 mmol) furnished compound (**196)** as white solid (65 %); m.p. 180-182 °C.

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3317, 1681, 1624, 1510, and 1298.

PMR (500 MHz, $CDCl_3$) : δ 10.03 (s, 1H, N*H*CO), 8.46-8.44 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.87-7.85 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.48-7.45 (m, 3H, Ar-*H*), 7.29 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 6.99-6.96 (m, 2H, Ar-*H*), 6.88-6.86 (m, 2H, Ar-*H*), 3.82 (bs, 4H, 2×CH_2), 3.12 (s, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 168.21, 164.11, 138.57, 136.23, 132.42, 131.27, 129.14, 128.66, 128.55, 127.53, 124.55, 124.28, 118.81, 118.73, 115.90, 115.68, 50.82.

MS (ESI) *m/z* : 472.4 $[M+H]^+$.

5.1.38 4-Chloro-*N*-(4-chloro-2-(4-(4-cyanophenyl)-1-piperazinylcarbonyl)-phenyl)-benzamide (197)

Using the method described for the compound (**177)**, compound **(170**, 0.20 g, 0.68 mmol) and 1-(4-cyanophenyl)piperazine (0.25 g, 1.36 mmol) furnished compound **(197**) as off white solid (68 %); m.p. 223-225 °C.

Anal.:

TLC : R_f0.26 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3212, 2211, 1639, 1600, and 1245.

PMR (400 MHz, $CDCl_3$) : δ 10.02 (s, 1H, N*H*CO), 8.38-8.34 (m, 1H, Ar-*H*), 7.84-7.82 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.52-7.50 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.46-7.43 (m, 3H, Ar-*H*), 7.28-7.27 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.86-6.85 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 3.83 (bs, 4H, 2×CH_2), 3.37 (s, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 168.50, 164.17, 152.73, 138.61, 136.21, 133.66, 132.30, 131.45, 129.14, 128.75, 128.69, 127.49, 124.61, 119.59, 114.76, 101.75, 48.70.

5.1.39 5-Chloro-*N*-(2-(4-(2-methylphenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-thiophene-2-carboxamide (198)

Using the method described for the compound (**183**), compound (**171**, 0.20 g, 0.68 mmol) and 1-(2-methylphenyl)piperazine hydrochloride (0.28 g, 1.36 mmol) furnished compound (**198)** as off white solid (60 %); m.p.194-196 °C.

Anal.:

TLC : R_f0.38 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3291, 1652, 1613, 1505, 1226, and 1023.

PMR (500 MHz, $CDCl_3$) : δ 9.60 (s, 1H, N*H*CO), 8.20-8.18 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.43 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 7.22-7.16 (m, 2H, Ar-*H*), 7.05-7.00 (m, 2H, Ar-*H*), 6.97-6.95 (m, 2H, Ar-*H*), 6.86 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 3.84 (s, 3H, OCH_3), 3.74 (bs, 4H, CH_2), 2.93 (bs, 4H, CH_2), 2.34 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.98, 158.87, 155.53, 150.55, 138.24, 136.11, 132.73, 131.23, 129.62, 127.55, 127.25, 126.74, 125.67, 124.79, 123.99, 119.27, 115.79, 113.49, 55.69, 17.79

5.1.40 5-Chloro-*N*-(2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-thiophene-2-carboxamide (199)

Using the method described for the compound (**177**), compound (**171**, 0.20 g, 0.68 mmol) and 1-(4-methoxyphenyl)piperazine (0.26 g, 1.36 mmol) furnished compound (**199)** as white solid (65 %); m.p. 186-188 °C.

Anal.:

TLC : R_f0.16 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3267, 1658, 1613, 1513, 1254, and 1025.

PMR (500 MHz, $CDCl_3$) : δ 9.59 (s, 1H, N*H*CO), 8.19-8.18 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.03-7.01 (dd, *J* = 3.0 and 9.0 Hz, 1H, Ar-*H*), 6.95-6.94 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.91-6.84 (m, 5H, Ar-*H*), 3.95 (bs, 4H, 2×CH_2), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.08 (bs, 4H, 2×CH_2).

5.1.41 5-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-thiophene-2-carboxamide (200)

Using the method described for the compound (**177**), compound **(171**, 0.20 g, 0.68 mmol) and 1-(2-fluorophenyl)piperazine (0.24g, 1.36 mmol) furnished compound (**200**) as white solid (62 %); m.p. 206-208 °C.

Anal.:

TLC : R_f0.33 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3313, 1666, 1607, 1495, and 1234.

PMR (500 MHz, $CDCl_3$) : δ 9.65 (s, 1H, N*H*CO), 8.30-8.29 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.89-7.87 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.49-7.47 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.07-7.04 (m, 2H, Ar-*H*),6.92-6.88 (m, 1H, Ar-*H*), 6.87-6.86 (d, J = 3.0 Hz, 1H, Ar-*H*), 3.96-3.77 (m, 7H, 2×CH_2& OCH_3), 3.09 (s, 4H, 2× CH_2).

5.1.42 5-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-thiophene-2-carboxamide (201)

Using the method described for the compound (**177)**, compound **(171**,0.20 g, 0.68 mmol) and 1-(4-fluorophenyl)piperazine (0.24g, 1.36 mmol) furnished compound (**201**) as white solid (65 %); m.p. 197-198 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3306, 1651, 1613, 1505, and 1225.

PMR (500 MHz, $CDCl_3$) : δ 9.58 (s, 1H, N*H*CO), 8.20-8.18 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.41-7.40 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 7.03-6.97 (m, 3H, Ar-*H*), 6.95-6.94 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.90-6.87 (m, 2H, Ar-*H*), 6.84 (d, *J* = 3.5 Hz, 1H, Ar-*H*), 3.84 (m, 7H, -CH_2-CH_2&OCH_3), 3.13 (bs, 4H, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 169.04, 159.00, 158.70, 156.79, 155.73, 147.40, 138.17, 136.06, 129.27, 127.69, 127.24, 126.11, 125.26, 118.78, 115.84, 115.80, 115.67, 113.39, 55.68, 50.76

HR-MS (ESI)*m/z* : 474.1049 $[M+1]^+$, 475.1082 $[M+2]^+$

5.1.43 5-Chloro-*N*-(2-(4-(4-chlorophenyl)-1-piperazinylcarbonyl)-4-methoxyphenyl)-thiophene-2-carboxamide (202)

Using the method described for the compound (**183**), compound **(171**, 0.20 g, 0.68 mmol) and 1-(4-chlorophenyl)piperazine dihydrochloride (0.36 g, 1.36 mmol) furnished compound (**202**) as white solid (60 %); m.p. 134-136 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3297, 1650, 1613, 1502, and 1228.

PMR (500 MHz, $CDCl_3$) : δ 9.57 (s, 1H, N*H*CO), 8.20-8.18 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.40-7.39 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.25-7.24 (m, 2H, Ar-*H*), 7.04-7.02 (dd, *J* = 3.0 and 9.0 Hz, 1H, Ar-*H*), 6.95-6.94 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.86-6.83 (m, 3H, Ar-*H*), 3.84 (m, 7H, 2×CH_2& OCH_3), 3.18 (bs, 4H, CH_2).

HR-MS (ESI)*m/z* : 490.0753 $[M+H]^+$.

5.1.44 5-Chloro-*N*-(2-(4-(4-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (203)

Using the method described for the compound (**177)**, compound (**172**, 0.20 g, 0.61 mmol) and 1-(4-methylphenyl)piperazine (0.21 g, 1.23 mmol) furnished compound (**203**) as off white solid (58 %); m.p. 155-157 °C.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) :3282, 1647, 1600, 1510, and 1265.

PMR (400 MHz, $CDCl_3$) : δ 10.31 (s, 1H, N*H*CO), 8.08 (s, 1H, Ar-*H*), 7.43-7.42 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.10-7.08 (d, *J* = 8.3 Hz, 2H, Ar-*H*), 6.94-6.93 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.85-6.82 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.79 (s,1H, Ar-*H*), 3.95 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.16 (bs, 4H, 2×CH_2), 2.27 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 170.04, 158.95, 151.34, 148.60, 144.52, 138.36, 136.32, 132.74, 130.49, 129.83, 127.63, 127.33, 117.07, 113.86, 111.12, 105.97, 56.43, 56.15, 50.35, 20.45.

HR-MS (ESI)*m/z* : 500.1405 $[M+H]^+$.

5.1.45 5-Chloro-*N*-(2-(4-(2-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (204)

Using the method described for the compound (**183**), compound **(172**, 0.20 g, 0.61 mmol) and 1-(2-methylphenyl)piperazine hydrochloride (0.26 g, 1.23 mmol) furnished compound **(204**) as white solid (62 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.31 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) :3281, 1655, 1613, 1510, and 1261.

PMR (500 MHz, $CDCl_3$) : δ 10.34 (s, 1H, N*H*CO), 8.13 (s, 1H, Ar-*H*), 7.46 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.23-7.17 (m, 2H, Ar-*H*), 7.06-7.03 (m, 1H, Ar-*H*), 7.00-6.98 (m, 2H, Ar-*H*), 6.84 (s,1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.85 (bs, 4H, 2×CH_2), 2.96 (bs, 4H, 2×CH_2), 2.35 (s, 3H, CH_3).

5.1.46 5-Chloro-*N*-(2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (205)

Using the method described for the compound (**177)**, compound (**172**, 0.20 g, 0.61 mmol) and 1-(4-methoxyphenyl)piperazine (0.21 g, 1.23 mmol) furnished compound (**205**) as white solid (68 %); m.p. 166-168 °C.

Anal.:

TLC : R_f0.14 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3289, 1653, 1607, 1517, and 1247.

PMR (400 MHz, $CDCl_3$) : δ 10.30 (s, 1H, N*H*CO), 8.06 (s, 1H, Ar-*H*), 7.44-7.43 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.94-6.93 (d, *J* = 4.0 Hz, 1H, Ar-*H*),

6.90-6.83 (m, 4H, Ar-*H*), 6.79 (s, 1H, Ar-*H*), 3.95 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.76 (s, 3H, OCH_3), 3.08 (bs, 4H, 2×CH_2).

MS (ESI) *m/z* : 516.3 $[M+H]^+$.

5.1.47 5-Chloro-*N*-(2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (206)

Using the method described for the compound (**177)**, compound (**172**, 0.20 g, 0.61 mmol) and 1-(2-methoxyphenyl)piperazine (0.21 g, 1.23 mmol) furnished compound (**206**) as white solid (65 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3281, 1655, 1612, 1510, and 1262.

PMR (400 MHz, $CDCl_3$) : δ 10.32 (s, 1H, N*H*CO), 8.07 (s,1H, Ar-*H*), 7.44 (m, 1H, Ar-*H*), 7.04-7.02 (d, *J* = 7.1 Hz, 1H, Ar-*H*), 6.94-6.87 (m, 4H, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 3.95 (s, 3H, OCH_3), 3.87-3.86 (m, 10H, 2×CH_2& 2×OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.08 (bs, 4H, 2×CH_2).

HR-MS (ESI) *m/z* : 516.1354 $[M+H]^+$.

5.1.48 5-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (207)

Using the method described for the compound (**177)**, compound (**172**, 0.20 g, 0.61 mmol) and 1-(2-fluorophenyl)piperazine (0.22 g, 1.23 mmol) furnished compound (**207)** as white solid (63 %); m.p.: 177-179 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3273, 1650, 1608, 1511, and 1225.

PMR (500 MHz, $CDCl_3$) : δ 10.34 (s, 1H, N*H*CO), 8.14 (s,1H, Ar-*H*), 7.45-7.44 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.09-7.08 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.03-7.00 (m, 1H, Ar-*H*), 6.98-6.97 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.94-6.92 (m, 1H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.89-3.88 (m, 7H, OCH_3; 2×CH_2), 3.13 (bs, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 169.94, 158.94, 151.25, 144.52, 138.32, 136.30, 132.58, 127.62, 127.33, 124.58, 123.41, 119.23, 116.39, 116.23, 113.90, 111.0, 105.96, 56.37, 56.11, 50.78.

HR-MS (ESI)*m/z* : 504.1155 $[M+H]^+$.

5.1.49 5-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (208)

Using the method described for the compound (**177**), compound (**172**, 0.20 g, 0.61 mmol) and 1-(4-fluorophenyl)piperazine (0.22 g, 1.23 mmol) furnished compound (**208)** as white solid (66 %); m.p. 142-144 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3252, 1656, 1611, 1513, and 1230.

PMR (500 MHz, $CDCl_3$) : δ 10.34 (s, 1H), 8.01 (s, 1H, Ar-*H*), 7.49-7.48 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.01-6.97 (m, 2H, Ar-*H*), 6.96 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.90-6.87 (m, 2H, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 3.96 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84 (bs, 4H, 2×CH_2), 3.13 (bs, 4H, 2×CH_2).

5.1.50 5-Chloro-*N*-(2-(4-(2-chlorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (209)

Using the method described for the compound (**177)**, compound (**172**, 0.20 g, 0.61 mmol) and 1-(2-chlorophenyl)piperazine (0.24 g, 1.23 mmol) furnished compound (**209**) as white solid (58 %); m.p.184-186 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3274, 1649, 1605, 1512, and 1221.

PMR (400 MHz, $CDCl_3$) : δ 10.34 (s, 1H, N*H*CO), 7.99 (s, 1H, Ar-*H*), 7.48-7.47 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.38-7.36 (dd, *J* = 1.12 and 7.8 Hz, 1H, Ar-*H*), 7.23-7.19 (m, 1H, Ar-*H*), 7.02 -6.94 (m, 3H, Ar-*H*), 6.78 (s, 1H, Ar-*H*), 3.94 (s, 3H, OCH_3), 3.85 (m, 7H, 2×CH_2& OCH_3), 3.05 (bs, 4H, 2×CH_2).

5.1.51 5-Chloro-*N*-(2-(4-(4-chlorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (210)

Using the method described for the compound (**183**), compound **(172**, 0.20 g, 0.61 mmol) and 1-(4-chlorophenyl)piperazine hydrochloride (0.33 g, 1.23 mmol) furnished compound (**210**) as off white solid (64 %); m.p. 148-150 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3292, 1654, 1607, 1509, and 1226.

PMR (400 MHz, $CDCl_3$) : δ 10.28 (s, 1H, N*H*CO), 8.05 (s, 1H, Ar-*H*), 7.42-7.41 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.23-7.21 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.93-6.92 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.84-6.82 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.78 (s, 1H, Ar-*H*), 3.94 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.17 (bs, 4H, 2×CH_2).

5.1.52 5-Chloro-*N*-(2-(4-(4-cyanophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (211)

Using the method described for the compound (**177)**, compound **(172**, 0.20 g, 0.61 mmol) and 1-(4-cyanophenyl)piperazine (0.23 g, 1.23 mmol) furnished compound (**211)** as light brown solid (60 %); m.p. 172-174 °C.

Anal.:

TLC : R_f0.16 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 2922, 2206, 1670, 1604, and 1517.

PMR (500 MHz, $CDCl_3$) : δ 9.56 (s, 1H, N*H*CO), 8.06 (s, 1H, Ar-*H*), 7.65-7.64 (m, 1H, Ar-*H*), 7.54-7.52 (d, *J* = 9,0 Hz, 2H, Ar-*H*), 7.35-7.33 (m, 1H, Ar-*H*), 6.87-6.85 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.76 (s, 1H, Ar-*H*), 3.99 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.82 (bs, 4H, 2×CH_2), 3.35 (bs,4H, 2×CH_2).

5.1.53 5-Chloro-*N*-(2-(4-(2-cyanophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (212)

Using the method described for the compound (**177)**, compound **(172**, 0.20 g, 0.61 mmol) and 1-(2-cyanophenyl)piperazine (0.23 g, 1.23 mmol) furnished compound (**212)** as white solid (63 %); m.p. 198-199 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 2923, 2221, 1652, 1604, 1521, and 1431.

PMR (400 MHz, $CDCl_3$) : δ 10.33 (s, 1H, N*H*CO), 8.09 (s, 1H, Ar-*H*), 7.61-7.59 (dd, *J* = 1.5 Hz, *J* = 8.0 Hz, 1H, Ar-*H*), 7.52-7.49 (m, 1H, Ar-*H*), 7.43-7.42 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.10-7.06 (m, 1H, Ar-*H*), 6.99-6.98 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.96-6.95 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.79 (s, 1H, Ar-*H*), 3.96 (s, 3H, OCH_3), 3.92 (bs, 4H, 2×CH_2), 3.88 (s, 3H, OCH_3), 3.20 (bs, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 170.09, 144.58, 136.32, 134.33, 133.93, 132.80, 127.59, 127.32, 122.89, 119.06, 113.68, 111.05, 106.89, 105.99, 56.44.

MS (ESI) *m/z* : 511.4 $[M+H]^+$.

5.1.54 5-Chloro-*N*-(2-(4-(4-nitrophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (213)

Using the method described for the compound (**177)**, compound **(172**, 0.20 g, 0.61 mmol) and 1-(4-nitrophenyl)piperazine (0.25 g, 1.23 mmol) furnished compound (**213**) as light yellow solid (55 %); m.p. 202-204 °C.

Anal.:

TLC : R_f0.44 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1668, 1596, 1502, 1322, 1234, and 1113.

PMR (500 MHz, $CDCl_3$) : δ 10.34 (s, 1H, -N*H*CO), 8.15-8.13 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 8.02 (s, 1H, Ar-*H*), 7.46 (s, 1H, Ar-*H*), 6.96-6.95 (d, *J* = 4.5 Hz, 1H, Ar-*H*), 6.89-6.82 (m, 3H, Ar-*H*), 3.97 (s, 3H, OCH_3), 3.90-3.88 (m, 7H, 2×CH_2& OCH_3), 3.52-3.49 (m, 4H, 2×CH_2).

5.1.55 5-Chloro-*N*-(2-(4-(4-aminophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-thiophene-2-carboxamide (214)

Using the method described for the compound (**192**), compound **(213**, 0.3 g, 0.56 mmol) offered compound (**214**) as light yellow solid (45 %); m.p. 168-170 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) :3435, 3353, 2926, 1651, 1604, 1516, and 1264.

PMR (500 MHz, $CDCl_3$) : δ 10.33 (s, 1H, N*H*CO), 8.05 (s, 1H, Ar-*H*), 7.47 (s, 1H, Ar-*H*), 6.96-6.95 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.84-6.81 (m, 3H, Ar-*H*), 6.68-6.66 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 3.97 (s, 3H, OCH_3), 3.87-3.83 (m, 7H, 2×CH_2& OCH_3), 3.08 (bs, 4H, 2×CH_2).

5.1.56 5-Chloro-*N*-(2-(4-(4-methylphenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (215)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(4-methylphenyl)piperazine (0.23 g, 1.34 mmol) furnished compound (**215**) as off white solid (63 %); m.p. 174-176 °C.

Anal.:

TLC : R_f0.40 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1658, 1585, 1425, and 1238.

PMR (400 MHz, $CDCl_3$) : δ 10.40 (s, 1H, N*H*CO), 7.83-7.82 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.53-7.47 (m, 2H, Ar-*H*), 7.42-7.41 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.14-7.13 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 7.09-7.04 (m, 2H, Ar-*H*), 6.99-6.89 (m, 2H, Ar-*H*), 3.73 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 3.0 (bs, 4H, 2×CH_2), 2.57 (s, 3H, CH_3).

5.1.57 5-Chloro-*N*-(2-(4-(4-methoxyphenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (216)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(4-methoxyphenyl)piperazine (0.25 g, 1.34 mmol) furnished compound (**216**) as a white solid (66 %); m.p. 186-188 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3273, 1663, 1619, and 1035.

PMR (500 MHz, $CDCl_3$) : δ 9.97 (s, 1H, N*H*CO), 8.34-8-32 (d, *J* = 9.0 Hz, 1H, Ar-*H)*, 7.43-7.38 (m,2H, Ar-*H*), 7.28-7.27 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 6.94-6.93 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.90-6.83 (m, 4H, Ar-*H*), 3.77-3.75 (m, 7H, 2×CH_2& OCH_3), 3.09 (bs, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 168.15, 158.86, 154.65, 144.36, 137.76, 136.70, 135.82, 131.19, 128.53, 127.93, 127.56, 127.30, 124.48, 124.10, 119.06, 114.58, 55.53, 51.24.

5.1.58 5-Chloro-*N*-(2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (217)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(2-methoxyphenyl)piperazine (0.25 g, 1.34 mmol) furnished compound (**217**) as a white solid (72 %); m.p.: 153-155 °C.

Anal.:

TLC : R_f0.34 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3224, 1658, 1592, 1241, and 1019.

PMR (500 MHz, $CDCl_3$) : δ 10.02 (s, 1H, N*H*CO), 8.29-8.28 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.45-7.41 (m, 2H, Ar-*H*), 7.30 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.08-7.05 (m, 1H,Ar-*H*), 6.96-6.90 (m, 4H, Ar-*H*), 3.90 (s, 3H, OCH_3), 3.77 (bs, 4H, 2×CH_2), 3.11 (bs, 4H, 2×CH_2).

5.1.59 5-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (218)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(2-fluorophenyl)piperazine (0.24 g, 1.34 mmol) furnished compound (**218**) as white solid (70 %); m.p.192-194 °C.

Anal.:

TLC : R_f0.42 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3274, 1651, 1607, 1512, and 1226.

PMR (400 MHz, $CDCl_3$) : δ 9.97 (s, 1H, N*H*CO), 8.29-8.27 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.42-7.39 (m, 2H, Ar-*H*), 7.27 (d, *J* = 2.8 Hz, 1H, Ar-*H*), 7.08-6.97 (m, 3H, Ar-H), 6.93-6.89 (m, 2H, Ar-*H*), 3.84 (bs, 4H, 2×CH_2), 3.11 (s, 4H, 2×CH_2).

5.1.60 5-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (219)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(4-fluorophenyl)piperazine (0.24 g, 1.34 mmol) furnished compound (**219)** as a white solid (66 %); m.p. 208-210 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1664, 1618, 1508, and 1423.

PMR (400 MHz, $CDCl_3$) : δ 10.35 (s, 1H, N*H*CO), 7,78 (s, 1H, Ar-*H*), 7.57-7.55 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 7.47-7.45 (m, 1H, Ar-*H*), 7.38 (s, 1H, Ar-*H*), 7.06 (s, 1H, Ar-*H*), 6.97-6.95 (d, 2H, *J* = 7.8Hz, Ar-*H*), 6.89 (bs, 2H, Ar-*H*), 3.74 (bs, 2H, CH_2), 3.49 (bs, 2H, CH_2), 3.08 (bs, 4H, 2×CH_2).

MS (ESI) *m/z* : 478.3 $[M+H]^+$.

5.1.61 5-Chloro-*N*-(2-(4-(2-cyanophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (220)

Using the method described for the compound (**177)**, compound **(173**, 0.20 g, 0.67 mmol) and 1-(2-cyanophenyl)piperazine (0.25 g, 1.34 mmol) furnished compound (**220**) as white solid (62 %); m.p. 210-212 °C.

Anal.:

TLC : R_f0.33 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3207, 2221, 1658, 1604, 1433.

PMR (500 MHz, $CDCl_3$) : δ 10.01 (s, 1H, N*H*CO), 8.31-8,29 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.64-7.62 (dd, *J* = 2.0 and 8.5 Hz, 1H, Ar-*H*), 7.55-7.52 (m, 1H, Ar-*H*), 7.45-7.43 (m, 2H, Ar-*H*), 7.30-7.29 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.13-7.10 (m, 1H, Ar-H), 7.03-7.01 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 6.96 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 3.93 (bs, 4H, 2×CH_2), 3.25 (bs, 4H, 2×CH_2).

5.1.62 5-Chloro-*N*-(2-(4-(4-cyanophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (221)

Using the method described for the compound (**177)**, compound **(173,** 0.20 g, 0.67 mmol) and 1-(4-cyanophenyl)piperazine (0.25 g, 1.34 mmol) furnished compound (**221**) as off white solid (65 %); m.p. 175-177 °C.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3230, 2216, 1658, 1510, 1240, and 1014.

PMR (400 MHz, $CDCl_3$) : δ 9.98 (s, 1H, N*H*CO), 8.14-8.12 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.53-7.51 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.40-7.37 (m, 2H, Ar-*H*), 7.24 (s, 1H, Ar-*H*), 6.89-6.85 (m, 3H, Ar-*H*), 3.83 (bs, 4H, 2×CH_2), 3.40 (s, 4H, 2×CH_2).

5.1.63 5-Chloro-*N*-(2-(4-(4-nitrophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)thiophene-2-carboxamide (222)

Using the method for the compound (**177)**, compound **(173,** 0.20 g, 0.67 mmol) and 1-(4-nitrophenyl)piperazine (0.23 g, 1.34 mmol) furnished compound (**222**) as a yellow solid (54 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.58 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3206, 1647, 1593, 1507, 1323, and 1237.

PMR (500 MHz, $CDCl_3$) : δ 10.03 (s, 1H, N*H*CO), 8.22-8.21 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 8.18-8.16 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 7.45-7.42 (m, 2H, Ar-*H*), 6.94-6.93 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.87-6.83 (m, 3H, Ar-H), 3.90 (bs, 4H, 2×CH_2), 3.54 (bs, 4H, 2×CH_2).

5.1.64 5-Chloro-*N*-(2-(4-(4-aminophenyl)-1-piperazinylcarbonyl)-4-chlorophenyl)-thiophene-2-carboxamide (223)

Using the method described for the compound (**192)**, compound **(222**, 0.3 g, 0.59 mmol) offered compound (**223**) as light brown solid (44 %); m.p. 173-176 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3447, 3359, 2918, 1662, 1621, 1511, and 1236

PMR (500 MHz, $CDCl_3$) : δ 9.99 (s, 1H, N*H*CO), 8.35-8.33 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.43-7.42 (m, 1H, Ar-*H*), 7.30-7.29 (d, *J* = 2.5 Hz, 2H, Ar-*H*), 6.96-6.95 (d, *J* = 4.0 Hz, 1H, Ar-*H*), 6.83-6.82 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.68-6.67 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.27-3-25 (m, 4H, 2×CH_2), 3.08 (bs, 4H, 2×CH_2).

5.1.65 6-Chloro-*N*-(2-(4-(4-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-nicotinamide (224)

Using the method described for the compound (**177)**, compound **(174**, 0.20 g, 0.62 mmol) and 1-(4-methylphenyl)piperazine (0.22 g, 1.24 mmol) furnished compound (**224**) as off white solid (55 %); m.p. 170-172 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1658, 1585, 1425, and 1238.

PMR (500 MHz, $CDCl_3$) : δ 10.15 (s, 1H, N*H*CO), 8.79 (d, 1H, *J* = 2.5 Hz, Ar-*H*), 8.21(s, 1H, Ar-*H*), 8.02-8.00 (dd, *J* = 2.5 and 9.0 Hz, 1H, Ar-*H*), 7.08 (s, 1H, Ar-*H*), 6.90-6.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.83-6.82 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.71-6.69 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.86-3.84 (m, 4H, 2×CH_2), 3.25-3.23 (m, 4H, 2×CH_2), 2.88 (s, 3H, CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 163.97, 151.16, 149.02, 148.64, 148.45, 136.57, 133.28, 129.82, 129.78, 117.05, 116.83, 110.93, 106.19, 105.69, 56.14, 50.36, 49.76, 44.79, 20.47.

5.1.66 6-Chloro-*N*-(2-(4-(2-methylphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) nicotinamide (225)

Using the method described for the compound (**183)**, compound **(174**, 0.20 g, 0.62 mmol) and 1-(2-methylphenyl)piperazine dihydrochloride (0.26 g, 1.24 mmol) furnished compound (**225)** as off white solid (48 %); m.p. 184-186 °C.

Anal.:

TLC : R_f0.26 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3324, 2945, 2828, 1666, 1600, 1497, 1331, and 1243.

PMR (500 MHz, $CDCl_3$) : δ 10.18 (s, 1H, -N*H*CO), 8.85 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.24 (s, 1H, Ar-*H*), 8.06-8.04 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.23-7.21 (m, 2H, Ar-*H*), 7.06-7.04 (m, 2H, Ar-*H*), 6.99-6.97 (m, 1H, Ar-*H*), 6.83 (s, 1H, Ar-*H*), 4.01 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.86 (bs, 4H, 2×CH_2), 3.05 (m, 4H, 2×CH_2), 2.39 (s, 3H, CH_3).

5.1.67 6-Chloro-*N*-(2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-nicotinamide (226)

Using the method described for the compound (**177)**, compound **(174**, 0.20 g, 0.62 mmol) and 1-(2-methoxyphenyl)piperazine (0.24 g, 1.24 mmol) furnished compound (**226)** as white solid (60 %); m.p. 165-168 °C.

Anal.:

TLC : R_f0.15 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3309, 1667, 1595, 1241, and 1023.

PMR (500 MHz, $CDCl_3$) : δ 10.13 (s, 1H, N*H*CO), 8.81 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 8.20 (s, 1H, Ar-*H*), 8.03-8.02 (m, 1H, Ar-*H*), 7.06-7.01 (m, 4H, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 6.72-6.70 (d, *J*= 9.0 Hz, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.88-3.86 (m, 7H, 2×CH_2& OCH_3), 3.17 (m, 4H, 2×CH_2).

MS (ESI) *m/z* : 511.4 $[M+H]^+$.

5.1.68 6-Chloro-*N*-(2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) nicotinamide (227)

Using the method described for the compound (**177**), compound **(174**, 0.20 g, 0.62 mmol) and 1-(2-fluorophenyl)piperazine (0.22 g, 1.24 mmol) furnished compound (**227)** as white solid (63 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 2924, 1669, 1600, 1511, and 1236.

PMR (500 MHz, $CDCl_3$) : δ 10.16 (s, 1H, N*H*CO), 8.99-8.98 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 8.18 (s, 1H, Ar-*H*), 8.03-8.01 (dd, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H, Ar-*H*), 7.47-7.46 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.06-7.04 (m, 3H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 6.73-6.71 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.98 (s,3H, OCH_3), 3.88-3.87 (m, 7H, 2×CH_2, OCH_3), 3.19 (m, 4H, 2×CH_2).

5.1.69 6-Chloro-*N*-(2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) nicotinamide (228)

Using the method described for the compound (**177)**, compound **(174**, 0.20 g, 0.62 mmol) and 1-(4-fluorophenyl)piperazine (0.22 g, 1.24 mmol) furnished compound (**228**) as white solid (60 %); m.p. 185-187 °C.

Anal.:

TLC : R_f0.15 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1656, 1598, 1506, and 1213.

PMR (500 MHz, $CDCl_3$) : δ 10.16 (s, 1H, N*H*CO), 8.79 (d, 1H, *J* = 2.5 Hz, Ar-*H*), 8.21 (s, 1H, Ar-*H*), 8.03-8.01 (dd, *J* = 2.5 and 9.0 Hz, 1H, Ar-*H*), 6.99 (s, 1H, Ar-*H*), 6.98-6.93 (m, 2H, Ar-*H*), 6.88-6.85 (m, 2H, Ar-*H*), 6.72-6.70 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.98 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.84 (m, 4H, 2×CH_2), 3.21 (m, 4H, 2×CH_2).

MS (ESI) *m/z* : 499.4 $[M+H]^+$

5.1.70 6-Chloro-*N*-(2-(4-(4-chlorophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl) nicotinamide (229)

Using the method described for the compound (**183)**, compound **(174**, 0.20 g, 0.62 mmol) and 1-(4-chlorophenyl)piperazine dihydrochloride (0.33g, 1.24 mmol) furnished compound (**229**) as off white solid (57 %); m.p. 174-176 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3301, 1660, 1602, 1514, and 1220.

PMR (400 MHz, $CDCl_3$) : δ 9.06 (s, 1H, Ar-*H*), 8.29-8.27 (d, J = 8.4 Hz, 1H, Ar-*H*), 7.53 (s, 1H, Ar-*H*), 7.25-7.22 (m, 3H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 6.89-6.87 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.73-6.70 (m, 1H, Ar-*H*), 4.03-3.99 (m, 6H, 2×OCH_3), 3.88 (bs, 4H, 2×CH_2), 3.28 (bs, 4H, 2×CH_2).

HR-MS (ESI) *m/z* : 515.1247 $[M+1]^+$, 516.1281 $[M+2]^+$

5.1.71 6-Chloro-*N*-(2-(4-(4-nitrophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-nicotinamide (230)

Using the method described for the compound (**177**), compound **(174**, 0.20 g, 0.62 mmol) and 1-(4-nitrophenyl)piperazine (0.26 g, 1.25 mmol) furnished compound (**230**) as a yellow solid (56 %); m.p. 212-215 °C.

Anal.:

TLC : R_f0.42 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1658, 1595, 1516, 1324, 1238, and 1115.

PMR (500 MHz, $CDCl_3$) : δ 10.23 (s, 1H, N*H*CO), 8.99-8.98 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.82 (s, 1H, Ar-*H*), 8.20-8.18 (m, 3H, Ar-*H*), 8.08-8.06 (dd, *J* = 2.5 & 9.0 Hz, 1H, Ar-*H*), 7.49-7.47 (d, *J* = 8.5 Hz,

1H, Ar-*H*), 6.85-6.84 (m, 2H, Ar-*H*), 4.02 (s, 3H, OCH_3), 3.90-3.88 (m, 7H, 2×CH_2& OCH_3), 3.64 (m, 4H, 2×CH_2).

5.1.72 6-Chloro-*N*-(2-(4-(4-aminophenyl)-1-piperazinylcarbonyl)-4,5-dimethoxyphenyl)-nicotinamide (231)

Using the method described for the preparation of compound (**192**), compound **(230**, 0.3 g, 0.57 mmol) offered compound (**231**) as a grey solid (42 %); m.p. 181-183 °C.

Anal.:

TLC : R_f0.20 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3361, 2923, 1667, 1602, 1516, and 1268.

PMR (500 MHz, $CDCl_3$) : δ 10.63 (s, 1H, N*H*CO), 9.01 (s, 1H, Ar-*H*), 8.20-8.18 (m, 2H, Ar-*H*), 7.49-7.47 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.85-6.82 (m, 2H, Ar-*H*), 6.74 (s, 1H, Ar-*H*), 6.69-6.67 (m, 2H, Ar-H), 4.28 (bs, 2H, NH_2), 4.01 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.22-3.13 (m, 4H, 2×CH_2), 3.10 (bs, 4H, 2×CH_2).

5.1.73 6-Chloro-*N*-(4-chloro-2-(4-(4-methylphenyl)-1-piperazinylcarbonyl)-phenyl)-nicotinamide (232)

Using the method described for the compound (**177)**, compound **(175**, 0.20 g, 0.68 mmol) and 1-(4-methylphenyl)piperazine (0.24 g, 1.36 mmol) furnished compound (**232)** as light yellow solid (54 %). m.p. 202-204 °C.

Anal.:

TLC : R_f0.40 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3294, 1673, 1608, 1552, and 1233.

PMR (500 MHz, $CDCl_3$) : δ 9.82 (s, 1H, N*H*CO), 8.76-8.75 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.46-8.44 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 8.0-7.97 (dd, *J* = 2.5 and 9.0 Hz, 1H, Ar-*H*), 7.44-7.42 (dd, *J* = 2.5 and 8.5 Hz, 1H, Ar-*H*), 7.27-7.26 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 6.90-6.88 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.84-6.82 (d, *J* = 8.5 Hz,

2H, Ar-*H*), 6.70-6.68 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.85 (m, 4H, 2×CH_2), 3.24 (m, 4H, 2×CH_2), 2.28 (s, 3H, CH_3).

MS (ESI) *m/z* : 469.4 $[M+H]^+$.

5.1.74 6-Chloro-*N*-(4-chloro-2-(4-(2-methoxyphenyl)-1-piperazinylcarbonyl)-phenyl)-nicotinamide (233)

Using the method described for the compound (**177)**, compound **(175**, 0.20 g, 0.68 mmol) and 1-(2-methoxyphenyl)piperazine (0.26 g, 1.36 mmol) furnished compound (**233**) as off white solid (64 %); m.p. 156-158 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: Ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 2922, 1670, 1596, 1498, and 1238.

PMR (400 MHz, $CDCl_3$) : δ 9.81 (s, 1H, N*H*CO), 8.77 (s, 1H, Ar-*H*), 8.46-8.44 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 8.00-7.98 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 7.43-7.40 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 7.25 (s, 1H, Ar-*H*), 6.95-6.88 (m, 4H, Ar-*H*), 6.71-6.68 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 3.90 (s, 4H, 2×CH_2), 3.86 (s, 3H, OCH_3), 3.17 (m, 4H, 2×CH_2).

MS (ESI) *m/z* : 484.2 $[M]^+$.

5.1.75 6-Chloro-*N*-(4-chloro-2-(4-(4-fluorophenyl)-1-piperazinylcarbonyl)-phenyl)-nicotinamide (234)

Using the method described for the compound (**177)**, compound **(175**, 0.20 g, 0.68 mmol) and 1-(4-fluorophenyl)piperazine (0.24 g, 1.36 mmol) furnished compound (**234)** as a white solid (58 %); m.p. 204-206 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3298, 1675, 1608, and 1229.

PMR (500 MHz, $CDCl_3$) : δ 9.84 (s, 1H, N*H*CO), 8.76-8.75 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 8.45-8.43 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 8.01-8.00 (dd, *J* = 2.5, 9.0 Hz, 1H, Ar-*H*), 7.45-7.44 (dd, *J* = 2.5, 9.0 Hz, 1H, Ar-*H*), 7.27-7.26 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 6.93-6.87 (m, 4H, Ar-*H*), 6.71-6.69 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 3.84 (m, 4H, 2×CH_2), 3.20 (m, 4H, 2×CH_2).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 168.20, 163.85, 160.24, 158.43, 156.77, 156.52, 148.36, 136.74, 136.37, 131.09, 128.08, 127.36, 124.33, 118.67, 118.28, 115.83, 115.74, 115.65, 115.56, 105.67, 50.77, 50.14, 44.72.

5.1.76 6-Chloro-*N*-(4-chloro-2-(4-(2-fluorophenyl)-1-piperazinylcarbonyl)-phenyl)-nicotinamide (235)

Following the method described for the preparation of compound (**177)**, compound **(175**, 0.20 g, 0.68 mmol) and 1-(2-fluorophenyl)piperazine (0.24 g, 1.36 mmol) furnished compound (**235)** as white solid (63 %); m.p. 168-170 °C.

Anal.:

TLC : R_f0.44 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 1673, 1603, 1497, and 1238.

PMR (400 MHz, $CDCl_3$) : δ 9.84 (s, 1H, N*H*CO), 8.76 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 8.30-8.28 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 8.01-8.00 (dd, *J* = 2.4, 9.0 Hz, 1H, Ar-*H*), 7.44-7.41 (m, 2H, Ar-*H*), 7.29-7.28 (d, *J* = 2.4 Hz, 2H, Ar-*H*), 6.93-6.89 (m, 2H, Ar-*H*), 6.70-6.68 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 3.86 (m, 4H, 2×CH_2), 3.19 (m, 4H, 2×CH_2).

5.1.77 Diethyl 2-amino-5-methylfuran-3,4-dicarboxylate (238)

Ethyl cyanoacetate (**236**, 1.0 g, 0.94 ml, 8.84 mmol) and triethylamine (1.78 g, 17.68 mmol) mixed in isopropyl alcohol (8 ml) and stirred at RT for 15-20 minutes. Later ethyl-2-chloroacetoacetate, (**237**, 1.45 g, 1.21 ml, 8.84 mmol) was added dropwise with continuous

stirring at 0-5 ^{o}C. Once addition was complete, the mixture was stirred at RT for 4 hrs and was monitored. After completion, the mixture was added to the crushed ice. The precipitated product was filtered and washed with cold water to get compound (**238)** as a yellow solid (80 %); m.p. 82-83 °C (Lit.81-84 °C).[9]

Anal.:

TLC : R_f0.52 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3429, 3325, 1708, 1673, 1554, and 1219.

5.1.78 Ethyl-2-(chloromethyl)-3,4-dihydro-6-methyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (239)

A mixture of diethyl 2-amino-5-methylfuran 3,4-dicarboxylate (**238**, 1.0 g,4.14 mmol) and chloroacetonitrile (0.93 g, 12.43mmol) was stirred at RT for 30 mins. To the above mixture, dry HCl in dry dioxane solution (6 ml) was added dropwise at 0-5 °C with continuous stirring which resulted clear orange colour solution which was stirred for 5-6 hrs at cold conditionand reaction was monitored. After reaction completion, the mixture was poured into crushed ice and excess HCl was neutralized by liquid ammonia till neutral pH and the precipitated product was filtered under reduced pressure to obtain compound (**239),** (70 %); m.p.201-203 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3430, 1719, 1676, 1310, and 1246.

PMR (400 MHz, DMSO-d^6) : δ 12.24 (bs, 1H, N*H*), 4.53 (s, 2H, -CH_2Cl), 4.32-4.28 (q, *J* = 7.0 Hz, 2H,CH_2CH$_3$), 2.63 (s, 3H, Ar-CH_3), 1.34 (t, *J* = 7.0 Hz, 3H, CH$_2$CH_3).

MS (ESI) *m/z* : 271 $[M]^+$, 273 $[M+2]^+$

5.1.79 Ethyl-2-(chloromethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (240)

A mixture of ethyl 2-(chloromethyl)-1,4-dihydro-6-methyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (**239**, 1.0 g, 3.69 mmol) and sodium hydrogen carbonate (0.62 g, 7.38 mmol) in dry acetone (30 ml) was stirred at RT under nitrogen in 2-necked RBF for 30 mins. Then,

dimethyl sulphate (0.69 g, 5.54 mmol) was added slowly at 0-5 °C and the reaction mixture was refluxed at 65 °C under nitrogen and monitored. After completion, the mixture was poured on crushed ice and the solid was isolated under reduced pressure and washed with cold water to get compound (**240**), (62 %); m.p.120-122 °C.

Anal.:

TLC	: R_f0.48 (*n*-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 1727, 1689, 1581, 1547, 1350, and 1223.
PMR (400 MHz, DMSO-d^6)	: δ 4.59 (s, 2H, -CH_2Cl), 4.40 (q, *J* = 7.1 Hz, 2H, CH_2CH$_3$), 3.72 (s, 3H,-NCH_3), 2.66 (s, 3H, Ar-CH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3).
MS (ESI) *m/z*	: 284 $[M]^+$, 286 $[M+2]^+$

5.1.80 Ethyl-2-((4-chlorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (242)

A mixture of ethyl-2-(chloromethyl)-1,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (**240**, 1.0 g, 3.51 mmol) and 4-chloroaniline (0.89 g, 7.02 mmol) in dry dioxane (20 ml) was refluxed overnight and monitored. After completion, the reaction mixture was poured on crushed ice and the solid was isolated under reduced pressure and washed with cold water to get light yellow solid compound (**242**, 64 %); m.p.185-187 °C.

Anal.:

TLC	: R_f0.38 (*n*-Hexane: ethyl acetate; 1:1)
IR (KBr, cm^{-1})	: 3377, 1732, 1683, 1586, and 1090.
PMR (500 MHz,$CDCl_3$)	: δ 7.19-7.17 (d, *J* = 9.0 Hz, 2H, Ar-*H*),6.68-6.66 (d, *J* = 8.5 Hz,2H, Ar-*H*), 5.11(s, 1H, -N*H*), 4..41-4.39 (q, *J* = 7.0 Hz, 2H,CH_2CH$_3$), 4.33 (s, 2H, CH_2NH), 3.63 (s, 3H, -NCH_3), 2.68 (s, 3H, ArCH_3), 1.43 (t, *J* = 7.5 Hz, 3H,CH$_2$CH_3).
MS (ESI) *m/z*	: 376 $[M+1]^+$,377 $[M+2]^+$

5.1.81 Ethyl-2-((4-fluorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (243)

Following the method of preparation described for compound (**242**), compound **(240**,1.0 g, 3.51 mmol) and 4-fluoroaniline (0.78 g, 7.02 mmol) furnished compound (**243)** as light brown solid (58 %); m.p. 157-159 ^{o}C.

Anal.:

TLC	: R_f0.41 (*n*-Hexane: ethyl acetate; 1:1)
IR (KBr, cm^{-1})	: 3371, 1734, 1681, 1584, and 1084.
PMR (500 MHz,$CDCl_3$)	: δ 6.98-6.95 (m, 2H, Ar-*H*), 6.72-6.69 (m, 2H, Ar-*H*), 4.92 (s, 1H, -N*H*), 4.45-4.44 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 4.36 (s, 2H, C*H*$_2$NH), 3.66 (s, 3H, -NC*H*$_3$), 2.69 (s, 3H, Ar-C*H*$_3$), 1.44 (t, *J* = 7.0 Hz, 3H, CH$_2$C*H*$_3$).
^{13}C-NMR ($CDCl_3$)	: δ162.66, 161.82, 158.22, 157.33, 155.43, 143.13, 116.03, 115.86, 114.26, 114.20, 111.07, 103.36, 61.10, 47.05, 41.01, 29.53, 14.32, 13.93.
MS (ESI) *m/z*	: 360 $[M+1]^+$,361 $[M+2]^+$.

5.1.82 Ethyl-2-((3-chloro-4-fluorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (244)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 3-chloro-4-fluoroaniline (1.02 g, 7.02 mmol) furnished compound (**244)** as a grey solid (63 %); m.p. 174-175 ^{o}C.

Anal.:

TLC	: R_f0.40 (*n*-Hexane: ethyl acetate; 1:1)
IR (KBr, cm^{-1})	: 3389, 1722, 1678, 1586, and 1084.
PMR (400 MHz,$CDCl_3$)	: δ 7.07-6.98 (m, 1H, ArH), 6.75 (d, 1H, Ar-*H*), 6.62 (d, 1H, Ar-*H*), 5.07 (s, 1H, N*H*),4.44 (q, 2H,

C*H*$_2$CH$_3$), 4.34 (d, 2H, C*H*$_2$NH), 3.65 (s, 3H, NC*H*$_3$), 2.69 (s, 3H, ArC*H*$_3$), 1.44 (t, 3H, CH$_2$C*H*$_3$).

MS (ESI) *m/z* : 394 $[M+1]^+$, 395 $[M+2]^+$.

5.1.83 Ethyl-2-((4-cyanophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (245)

Following the method of preparation described for compound **(242)**, compound **(240**,1.0 g, 3.51 mmol) and 4-aminobenzonitrile (0.82 g, 7.02 mmol) furnished compound (**245)** as yellow solid (56 %); m.p. 234-237 ^oC.

Anal.:

TLC : R_f0.24 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3366, 2212, 1724, 1680, and 1098

PMR (400 MHz,$CDCl_3$) : δ 7.51-7.49 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 6.73-6.71 (d, *J* = 8.6 Hz, 2H, Ar-*H*), 5.70 (s, 1H, NH), 4.44-4.38 (m, 4H, C*H*$_2$CH$_3$ & C*H*$_2$NH), 3.64 (s, 3H, NC*H*$_3$), 2.68 (s, 3H, ArC*H*$_3$), 1.42 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$).

MS (ESI) *m/z* : 367 $[M+1]^+$,368 $[M+2]^+$

5.1.84 Ethyl-2-((4-ethylphenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (246)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 4-ethylaniline (0.85 g, 7.02 mmol) furnished compound (**246)** as off white solid (55 %); m.p. 165-167 ^oC.

Anal.:

TLC : R_f0.42 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3398, 1730, 1690, 1580, and 1106.

PMR (400 MHz,$CDCl_3$) : δ 7.11-7.07 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.73-6.69 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 4.88 (s, 1H, -N*H*), 4.48-

4.37 (m, 4H, -C*H*$_2$CH$_3$& -C*H*$_2$NH), 3.66 (s, 3H, NC*H*$_3$), 2.69 (s, 3H, Ar-C*H*$_3$), 2.63-2.59 (q, 2H, Ar-C*H*$_2$CH$_3$), 1.44 (t, 3H, CH$_2$C*H*$_3$), 1.21 (t, 3H, CH$_2$C*H*$_3$).

MS (ESI) *m/z* : 370 $[M+1]^+$, 371 $[M+2]^+$.

5.1.85 Ethyl-2-((4-methoxyphenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxylate (247)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 4-methoxyaniline (0.86g, 7.02 mmol) furnished compound (**247**), (60 %); m.p. 176-178 ^{o}C.

Anal.:

TLC : R$_f$0.24 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3401, 1725, 1514, 1377, and 1228.

PMR (400 MHz, CDCl$_3$) : δ 6.86-6.84 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.76-6.73 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.46-4.44 (q, *J* = 7.2 Hz, 2H, Ar-*H*), 4.38 (s, 2H, C*H*$_2$NH), 3.78 (s, 3H, OC*H*$_3$), 3.67 (s, 3H, -NC*H*$_3$), 2.70 (s, 3H, Ar-C*H*$_3$), 1.45 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$).

5.1.86 Ethyl-2-((5-chloropyridin-2-ylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro-[2,3*d*]pyrimidine-5-carboxylate (248)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 2-amino-5-chloropyridine (0.9 g, 7.02 mmol) furnished compound (**248**) as yellow solid (42 %); m.p. 158-160 ^{o}C.

Anal.:

TLC : R$_f$0.24 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3413, 1732, 1703, 1597, and 1099.

PMR (500 MHz,$CDCl_3$) : δ 8.08-8.07 (d, *J* = 2.5 Hz, 1H, Ar-*H*),7.44-7.42 (dd, *J* = 2.5 & 7.5 Hz,1H, Ar-*H*), 6.63-6.61 (m, 1H, Ar-*H*), 5.73 (s, 1H, -CH_2N*H*), 4.68 (d, *J* = 4.5 Hz, 2H,C*H*$_2$NH), 4.44-4.42 (q, *J* = 7.0 Hz, 2H, C*H*$_2$$CH_3$), 3.68 (s, 3H, NC*H*$_3$), 2.68 (s, 3H,ArC*H*$_3$), 1.45 (t, *J* = 7.5 Hz, 3H, CH_2C*H*$_3$).

MS (ESI) *m/z* : 377 $[M+1]^+$,378 $[M+2]^+$

5.1.87 Ethyl-2-((4-chlorophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (249)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 4-chlorophenol (0.90 g, 7.02 mmol) furnished compound (**249**), (58 %); m.p. 142-144 ^oC.

Anal.:

TLC : R_f0.35 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 2984, 1738, 1695, 1550, 1384, and 1232.

PMR (400 MHz,$CDCl_3$) : δ 7.27-7.25 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.97-6.95 (d, *J* = 8.8 Hz, 2H, Ar-*H*),4.43-4.42 (q, *J* = 7.2 Hz, 2H, C*H*$_2$$CH_3$), 3.72 (s, 3H, NC*H*$_3$), 2.68 (s, 3H, ArC*H*$_3$), 1.42 (t, *J* = 6.8 Hz, 3H, CH_2C*H*$_3$).

5.1.88 Ethyl-2-((4-fluorophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (250)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 4-fluorophenol (0.78 g, 7.02 mmol) furnished compound (**250),** (65 %); m.p. 131-132 ^oC.

Anal.:

TLC : R_f0.38 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 1739, 1701, 1506, 1381, and 1210.

PMR (400 MHz,$CDCl_3$) : δ 6.99-6.96 (m, 4H, Ar-*H*), 5.12 (s, 2H, CH_2-O), 4.43-4.41 (q, *J* = 6.8 Hz, 2H, CH_2CH_3), 3.73 (s, 3H, -NCH_3), 2.67 (s, 3H, ArCH_3), 1.42 (t, *J* = 7.2 Hz, 3H, CH_2CH_3).

5.1.89 Ethyl-2-((4-cyanophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3*d*]-pyrimidine-5-carboxylate (251)

Following the method of preparation described for compound (**242)**, compound **(240**, 1.0 g, 3.51 mmol) and 4-cyanophenol (0.83 g, 7.02 mmol) furnished compound (**251**); (63 %); m.p. 161-163ºC.

Anal.:

TLC : R_f0.23 (*n*-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3401, 2221, 1723, 1686, 1550, and 1246.

PMR (400 MHz,$CDCl_3$) :δ 7.64-7.62 (d, *J* = 7.0 Hz, 2H, Ar-*H*), 7.14-7.12 (d, *J* = 7.0 Hz, 2H, Ar-*H*), 5.24 (s, 2H,CH_2-O), 4.44-4.42 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.73 (s, 3H, NCH_3), 2.69 (s, 3H, Ar-CH_3), 1.42 (t, *J* = 7.2 Hz, 3H, CH_2CH_3).

5.1.90 2-((4-Chlorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethylfuro-[2,3-*d*]pyrimidine-5-carboxamide (253)

To a 50 ml dry two necked-round bottomed flask, β-phenethylamine (0.38 gm, 3.19 mmol) was added, followed by 3 ml ethylene dichloride under nitrogen conditions. Trimethyl aluminium, (0.34 gm; 2.46 ml, 4.78 mmol) 2.0 M solution in toluene was added dropwise with a syringe to the mixture at 0ºC during 15 min. and was stirred for next 30 min. at same temperature.[10] Then, solution of ethyl-2-((4-chlorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxylate, (**242**, 0.2 gm, 0.53 mmol) in 3 ml ethylene dichloride was added to this mixture and stirred overnight at RT. After completion, the reaction was hydrolysed by addition of 2 M hydrochloric acid and continued stirring for 30 min. to ensure complete hydrolysis. The mixture was then extracted with methylene chloride and solvent layer

was dried using anhydrous sodium sulphate and concentrated. The crude product was finally purified to get compound (**253)** as a light brown solid (52 %); m.p. 178-180 °C.

Anal.:

TLC	: R_f0.26 (*n*-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3251, 2922, 1665, 1639, 1595, and 1251.
PMR (500 MHz,$CDCl_3$)	: δ 10.03 (t, *J* = 5.0 Hz, 1H, CON*H*), 7.33-7.28 (m, 5H, Ar-*H*), 7.24-7.21 (m, 2H, Ar-*H*), 6.71-6.69 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 4.40 (s, 2H, CH_2-NH), 3.70-3.67 (m, 5H, CH_2-CH_2-NH & N-CH_3), 2.98 (t, *J* = 8.0 Hz, 2H, CH_2-CH_2), 2.85 (s, 3H, Ar-CH_3).
MS (ESI) *m/z*	: 451.3 $[M+H]^+$.

5.1.91 2-((4-Chlorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-(2-(pyridin-2-yl)ethyl)furo[2,3-*d*]pyrimidine-5-carboxamide (254)

Following the method of preparation described for compound (**253**),compound **(242**, 0.2 g, 0.53 mmol) and 2-(2-pyridyl)ethylamine (0.39 g, 3.19 mmol) provided compound (**254)** as light brown solid (45 %); m.p. 198-200 °C.

Anal.:

TLC	: R_f0.12 (*n*-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3390, 3257, 1668, 1591, and 1316.
PMR (400 MHz,$CDCl_3$)	: δ 10.15 (t, *J* = 5.4 Hz, 1H, CON*H*), 8.51-8.50 (m, 1H, Ar-*H*), 7.72-7.70 (d, *J* =7.7 Hz, 1H, Ar-*H*), 7.31-7.29 (d, *J* =7.7 Hz, 1H, Ar-*H*), 7.24-7.22 (m, 1H, Ar-*H*), 7.11-7.09 (m, 2H, Ar-*H*), 6.74-6.72 (m, 2H, Ar-*H*), 6.38 (t, *J* = 6.0 Hz, 1H, N-*H*), 4.51-4.50 (d, *J* = 5.9 Hz, 2H, CH_2-NH), 3.69-3.67 (q, *J* = 7.0 Hz, 2H, CH_2-CH_2-NH), 3.61 (s, 3H, N-CH_3), 2.99 (t, *J* =7.3 Hz, 2H, CH_2-CH_2), 2.68 (s, 3H, Ar-CH_3).

HR-MS(ESI) *m/z* : 452.1484 $[M+H]^+$.

5.1.92 2-((4-Chlorophenylamino)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxamide (255)

Following the method of preparation described for compound (**253)**, compound **(242**, 0.2 g, 0.53 mmol) and 2-(4-fluoro)phenethylamine (0.44g, 3.19 mmol) furnished yellow solid compound (**255**), (58 %); m.p. 154-156 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3375, 3239, 1659, 1600, 1506, and 1382.

PMR (500 MHz,$CDCl_3$) : δ 10.03 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.28-7.21 (m, 4H, Ar-*H*), 6.99-6.96 (m, 2H, Ar-*H*), 6.73-6.70 (m, 2H, Ar-*H*), 4.40 (s, 2H, CH_2-NH), 3.69-3.64 (m, 5H, -N-CH_3& -CH_2-CH_2-NH), 2.95 (t, *J* = 7.5 Hz, 2H, CH_2-CH_2), 2.84 (s, 3H, Ar-CH_3).

MS(ESI) *m/z* : 469.3 $[M+1]^+$, 470 $[M+2]^+$

5.1.93 2-((4-Chlorophenylamino)methyl)-*N*-(4-methoxyphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-*d*]pyrimidine-5-carboxamide (256)

Following the method of preparation describbed for compound (**253)**, compound **(242**, 0.2 g, 0.53 mmol) and 2-(4-methoxy)phenethylamine (0.48 g, 3.19 mmol) furnished yellow solid compound (**256**), (55 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3396, 3250, 1674, 1601, 1505, and 1243.

PMR (400 MHz, $CDCl_3$) : δ 9.97 (t, *J* = 5.6 Hz,1H, CON*H*), 7.20-7.18 (d, *J* = 8.0 Hz,4H, Ar-*H*), 6.84-6.82 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.68-6.66 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 4.38 (s, 2H, CH_2-NH), 3.78 (s, 3H, OCH_3), 3.67-3.60 (m,

5H, CH_2-C*H*$_2$-NH& -N-C*H*$_3$), 2.89 (t, *J* = 8.4 Hz, 2H,C*H*$_2$-CH_2), 2.82 (s, 3H, Ar-C*H*$_3$).

5.1.94 2-((4-Chlorophenylamino)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (257)

Following the method of preparation described for compound (**253)**, compound **(242**, 0.2 g, 0.53 mmol) and 2-(4-methyl)phenethylamine (0.43 g, 3.19 mmol) furnished yellow solid compound (**257),** (52 %); m.p. 179-181 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3250, 2923, 1672, 1639, and 1547.

PMR (500 MHz,$CDCl_3$) : δ 10.02 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.23-7.19 (m, 4H, Ar-*H*), 7.13-7.12 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 6.72-6.71 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 4.41 (d, *J* = 4.5Hz, 2H, C*H*$_2$-NH), 3.70 (s, 3H, N-C*H*$_3$), 3.68-3.67 (q, *J* = 7.5 Hz, 2H,CH_2-C*H*$_2$-NH), 2.95 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$), 2.34 (s, 3H, Ar-C*H*$_3$).

MS (ESI) *m/z* : 465.4 $[M+1]^+$, 466 $[M+2]^+$

5.1.95 2-((4-Fluorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethylfuro[2,3-d]pyrimidine-5-carboxamide (258)

Following the method of preparation described for compound (**253)**, compound **(243**, 0.2 g, 0.55 mmol) and 2-phenethylamine (0.40 g,3.33 mmol) furnished yellow solid compound (**258**), (60 %); m.p. 196-198°C.

Anal.:

TLC : R_f0.27 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3310, 3044, 1668, 1609, 1515, and 1382.

PMR (400 MHz,$CDCl_3$) : δ 10.02 (t, *J* = 5.2 Hz, 1H, CON*H*), 7.31-7.27 (m, 4H, Ar-*H*), 7.23-7.18 (m, 1H, Ar-*H*), 6.96-6.91 (m, 2H, Ar-*H*), 6.70-6.67 (m, 2H, Ar-*H*), 4.36 (s, 2H, C*H*$_2$-NH), 3.68-3.62 (m, 5H, CH_2-C*H*$_2$-NH), 2.95 (t, *J* = 7.9 Hz, 2H, C*H*$_2$-CH_2), 2.81 (s, 3H, O-C-C*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ162.12, 161.27, 160.32, 158.71, 154.70, 143.0, 139.31, 128.81, 128.44, 126.25, 116.09, 115.91, 114.34, 114.28, 112.44, 102.92, 47.17, 41.01, 35.89, 29.84, 14.04.

MS (ESI) *m/z* : 435.3 $[M+H]^+$

5.1.96 2-((4-Fluorophenylamino)methyl)-*N*-(4-chlorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (259)

Following the method of preparation described for compound (**253)**, compound **(243**, 0.2 g, 0.55 mmol) and 2-(4-chloro)phenethylamine (0.51 g, 3.33 mmol) furnished brown solid compound (**259)** as light brown solid (48 %); m.p. 162-164 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3390, 3253, 1677, 1648, 1518, 1381, and 1219.

PMR (400 MHz,$CDCl_3$) : δ 9.99 (t, *J* = 5.2 Hz, 1H, CON*H*), 7.24-7.19 (m, 4H, Ar-*H*), 6.95 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.71-6.67 (m, 2H, Ar-*H*), 4.85 (s, 1H, N*H*), 4.38 (s, 2H, C*H*$_2$-NH), 3.78 (s, 3H, -N-C*H*$_3$), 3.67-3.61 (m, 2H, -CH_2-C*H*$_2$-NH), 2.90 (t, *J* = 7.2 Hz, 2H, C*H*$_2$-CH_2), 2.81 (s, 3H, Ar-C*H*$_3$).

MS (ESI) m/z : 469.3 $[M+H]^+$, 470 $[M+2]^+$

5.1.97 2-((4-Fluorophenylamino)methyl)-*N*-(4-methoxyphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (260)

Following the method of preparation described for compound (**253)**, compound **(243**, 0.2 g, 0.55 mmol) and 2-(4-methoxy)phenethylamine (0.50 g, 3.19 mmol) furnished yellow compound (**260**), (55 %); m.p. 192-194 °C.

Anal.:

TLC : R_f0.23 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3387, 3258, 1673, 1514, 1381, and 1247.

PMR (400 MHz,$CDCl_3$) : δ 9.98 (s, *J* = 5.2 Hz, 1H, CON*H*), 7.20-7.18 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.97-6.95 (t, *J* = 8.8 Hz, 2H, Ar-*H*), 6.84-6.82 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.71-6.68 (m, 2H, Ar-*H*), 4.85 (s, 1H), 4.38 (s, 2H, CH_2-NH), 3.78 (s, 3H), 3.68 (s, 3H, CH_2-CH_2-NH), 3.63 (m, 2H), 2.90 (t, *J* = 8.0 Hz, 2H, CH_2-CH_2), 2.82 (s, 3H, O-C-CH_3).

HR-MS (ESI) *m/z* : 465.1933 $[M+1]^+$, 466.1966 $[M+2]^+$

5.1.98 2-((4-Fluorophenylamino)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (261)

Following the method of preparation described for compound **(253**), compound **(243**, 0.2 g, 0.53 mmol) and 2-(4-methyl)phenethylamine (0.45 g, 3.33 mmol) furnished brown compound (**261**), (50 %); m.p. 147-148 °C.

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3399, 3256, 1668, 1593, 1514, 1381, and 1222.

PMR (400 MHz,$CDCl_3$) : δ 10.03 (t, *J* = 5.6 Hz, 1H, CON*H*), 7.21-7.19 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.13-7.11 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.00-6.95 (m, 2H, Ar-*H*), 6.73-6.70 (m, 2H, Ar-*H*), 4.40 (s, 2H, CH_2-NH), 3.70 (s, 3H, NCH_3),

3.69-3.67 (q, *J* = 7.6 Hz, 2H,CH_2-C*H*$_2$-NH), 2.94 (t, *J* = 7.2 Hz, 2H, C*H*$_2$-CH_2), 2.84 (s, 3H, O-C-C*H*$_3$), 2.34 (s, 3H, Ar-C*H*$_3$).

MS (ESI) *m/z* : 449.3 $[M+H]^+$

5.1.99 2-((3-Chloro-4-fluorophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethylfuro[2,3-d]pyrimidine-5-carboxamide (262)

Following the method of preparation described for compound (**253)**, compound **(244**, 0.2 g, 0.50 mmol) and β-phenethylamine (0.36 g, 3.04 mmol) furnished yellow compound (**262**), (46 %); m.p. 180-182 °C.

Anal.:

TLC : R_f0.29 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3384, 3246, 1672, 1503, 1380, and 1131.

PMR (500 MHz,$CDCl_3$) : δ 10.03 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.33-7.30 (m, 4H, Ar-*H*), 7.24-7.23 (m, 1H, Ar-*H*), 7.04 (t, *J* = 9.0 Hz, 1H, Ar-*H*), 6.77-6.75 (m,1H, Ar-*H*), 6.64-6.61 (m, 1H, Ar-*H*), 5.05 (s, 1H), 4.38 (d, *J* = 3.5 Hz, 2H, C*H*$_2$-NH), 3.70-3.68 (m, 5H, -N-C*H*$_3$&-CH_2-C*H*$_2$-NH), 3.0-2.97 (m,2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$).

5.1.100 2-((3-Chloro-4-fluorophenylamino)methyl)-*N*-(4-chlorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (263)

Following the method of preparation described for compound (**253)**, compound **(244,** 0.2 g, 0.50 mmol) and 2-(4-chloro)phenethylamine (0.47 g, 3.04 mmol) furnished solid compound (**263)**, (50 %); m.p. 194-196 °C.

Anal.:

TLC : R_f0.26 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3394, 3237, 1682, 1641, 1515, and 1382.

PMR (500 MHz,$CDCl_3$) : δ 10.00 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.28-7.22 (m, 4H, Ar-*H*), 7.04 (t, *J* = 9.0 Hz, 1H, Ar-*H*), 6.77-6.75 (m, 1H,Ar-*H*), 6.64-6.61 (m, 1H, Ar-*H*), 5.04 (s, 1H), 4.38 (s, 2H, C*H*$_2$-NH), 3.69-3.65 (s, 5H, N-C*H*$_3$&CH_2-C*H*$_2$-NH), 2.95 (t, *J* =7.5 Hz, 2H, C*H*$_2$-CH_2), 2.84 (s, 3H, O-C-C*H*$_3$).

MS (ESI) *m/z* : 503.2 $[M+H]^+$

5.1.101 2-((3-Chloro-4-fluorophenylamino)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (264)

Following the method of preparation described for compound (**253)**, compound **(244**,0.2 g, 0.50 mmol) and 2-(4-methoxy)phenethylamine (0.42 g, 3.04 mmol) furnished yellow colored compound (**264**), (48 %); m.p. 190-192 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3385, 3250, 1674, 1645, 1505, and 1380.

PMR (500 MHz,$CDCl_3$) : δ 10.0 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.26-7.24 (m, 2H, Ar-*H*), 7.06-6.97 (m, 3H, Ar-*H*), 6.77-6.75 (m, 1H, Ar-*H*), 6.64-6.61 (m, 1H, Ar-*H*), 5.04 (s, 1H), 4.38-4.37 (d, *J* = 4.0 Hz, 2H, C*H*$_2$-NH), 3.69-3.64 (m, 5H, N-C*H*$_3$&-CH_2-C*H*$_2$-NH), 2.95 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$).

HR-MS (ESI) *m/z* : 487.1343 $[M+1]^+$, 488.1376 $[M+2]^+$.

5.1.102 2-((3-Chloro-4-fluorophenylamino)methyl)-*N*-(4-methoxyphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (265)

Following the method of preparation described for compound (**253)**, compound **(244**, 0.2 g, 0.50 mmol) and 2-(4-methoxy)phenethylamine (0.46 g, 3.04 mmol) furnished yellow compound (**265**), (56 %); m.p. 185-187 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3376, 3229, 1672, 1646, 1507, 1381, and 1249.

PMR (500 MHz,$CDCl_3$) : δ 9.99 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.22-7.21 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.04 (t, *J* = 8.5 Hz, 1H, Ar-H), 6.86-6.85 (d, *J* = 8.0 Hz, 2H,Ar-*H*), 6.76-6.75 (m, 1H, Ar-*H*), 6.63-6.60 (m, 1H, Ar-*H*), 5.06 (s, 1H), 4.37 (d, *J* = 4.0 Hz, 2H, C*H*$_2$-NH), 3.81 (s, 3H, Ar-OCH_3), 3.70 (s, 3H, N-CH_3), 3.65 (q, *J* = 6.5 Hz, 2H, CH_2-C*H*$_2$-NH), 2.92 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH_2), 2.84 (s, 3H, O-C-C*H*$_3$).

HR-MS(ESI) *m/z* :499.1543 $[M+1]^+$, 500.1576 $[M+2]^+$

5.1.103 2-((3-Chloro-4-fluorophenylamino)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (266)

Following the method of preparation described for compound (**253)**, compound **(244**, 0.2 g, 0.50 mmol) and 2-(4-methyl)phenethylamine (0.41 g, 3.04 mmol) furnished light brown compound (**266**), (52 %); m.p. 168-170 °C.

Anal.:

TLC : R_f0.31 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3385, 3232, 1681, 1636, 1514, 1381, and 1232.

PMR (500 MHz,$CDCl_3$) : δ 10.00 (s, 1H, CON*H*), 7.20-7.19 (d, *J* = 7.75 Hz, 2H, Ar-*H*), 7.13-7.12 (d, *J* = 7.75 Hz, 2H, Ar-*H*), 7.04 (t, *J* = 9.0 Hz, 1H, Ar-H), 6.76-6.75 (m, 1H, Ar-*H*), 6.63-6.60 (m, 1H, Ar-*H*), 4.37 (s, 2H, C*H*$_2$-NH), 3.70 (s, 3H, N-C*H*$_3$), 3.68-3.64 (m, 2H, CH_2-C*H*$_2$-NH), 2.94 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$), 2.34 (s, 3H, Ar-C*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 162.05, 161.14, 160.24, 158.77, 154.12, 136.17, 135.73, 129.42, 129.14, 128.66, 117.09, 114.19, 112.81, 112.46, 102.99, 46.54, 41.15, 35.44, 29.78, 21.05, 14.05.

MS (ESI) *m/z* : 483.3 $[M+H]^+$.

5.1.104 2-((4-Cyanophenylamino)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethylfuro[2,3-d]pyrimidine-5-carboxamide (267)

Following the method of preparation described for compound (**253)**, compound **(245**, 0.2 g, 0.54 mmol) and β-phenethylamine (0.39 g, 3.27 mmol) furnished yellow compound (**267**), (45 %); m.p. 188-190 °C.

Anal.:

TLC : R_f0.25 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3037, 2223, 1668, 1645, 1604, 1550, and 1242.

PMR (500 MHz,$CDCl_3$) : δ 9.96 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.53-7.52 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 7.19-7.11 (m, 5H, Ar-*H*), 6.76-6.74 (m, 2H, Ar-*H*), 5.76 (t, *J* = 4.5 Hz, 1H), 4.45 (d, 2H, *J* = 4.0 Hz, CH_2-NH), 3.70 (s, 3H, N-CH_3) 3.66-3.62 (m, 2H, -CH_2-CH_2-NH), 2.93 (t, *J* = 7.5 Hz, 2H, CH_2-CH_2), 2.84 (s, 3H, O-C-CH_3).

^{13}C-NMR(100 MHz, $CDCl_3$) : δ 161.96, 160.96, 160.12, 158.87, 153.25, 149.59, 136.10, 135.76, 133.93, 129.14, 128.64, 119.96, 112.81, 112.45, 103.67, 100.46, 45.15, 41.16, 35.39, 29.77, 29.71, 21.05, 14.06.

5.1.105 2-((4-Cyanophenylamino)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (268)

Following the method of preparation described for compound (**253)**, compound **(245**, 0.2 g, 0.54 mmol) and 2-(4-methyl)phenethylamine (0.44 g, 3.27 mmol) furnished brown compound

(**268**), (48 %); m.p. 172-175 °C.

Anal.:

TLC : R_f0.32 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3370, 2923, 2212, 1675, 1605, and 1521.

PMR (500 MHz,$CDCl_3$) : δ 7.55-7.42 (m, 4H, Ar-*H*), 6.86-6.66 (m, 4H, Ar-*H*),5.74 (s, 1H), 4.42-4.41 (d, *J* = 5.5 Hz, 2H, C*H*$_2$-NH), 3.84-3.78 (m, 2H, CH_2-C*H*$_2$-NH) 3.67 (s, 3H, N-CH_3), 2.86-2.80 (m, *J* =7.5 Hz,2H, C*H*$_2$-CH_2), 2.70 (s, 3H, O-C-C*H*$_3$), 2.06 (s, 3H, -C*H*$_3$).

MS (ESI) *m/z* : 456.3 $[M+H]^+$.

5.1.106 2-((4-Cyanophenylamino)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (269)

Following the method of preparation described for compound (**253)**, compound **(245**, 0.2 g, 0.54 mmol) and 2-(4-fluoro)phenethylamine (0.45 g, 3.27 mmol) furnished yellow compound (**269**), (44 %); m.p. 192-194 °C.

Anal.:

TLC : R_f0.30 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3274, 2923, 2212, 1666, 1603, and 1220.

PMR (500 MHz,$CDCl_3$) : δ 9.95 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.54-7.53 (d, *J* = 8.75 Hz, 2H, Ar-*H*), 7.25-7.23 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.99-6.97 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.77-6.75 (d, *J* = 8.75 Hz, 2H, Ar-*H*), 5.72 (t, *J* = 4.5 Hz,1H, CH_2-N*H*), 4.46-4.45 (d, *J* = 4.0 Hz, 2H, C*H*$_2$-NH), 3.69 (s, 3H, N-C*H*$_3$), 3.67-3.65 (m, 2H, CH_2-C*H*$_2$-NH), 2.95 (t, *J* = 7.5 Hz, 2H,C*H*$_2$-CH_2), 2.84 (s, 3H, O-C-C*H*$_3$).

MS(ESI) *m/z* : 459.5 $[M]^+$.

5.1.107 2-((4-Cyanophenylamino)methyl)-*N*-(4-chlorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (270)

Following the method of preparation described for compound (**253)**, compound **(245**, 0.2 g, 0.54 mmol) and 2-(4-chloro)phenethylamine (0.50 g, 3.27 mmol) furnished yellow compound (**270**), (42 %); m.p. 202-205 °C.

Anal.:

TLC : R_f0.28 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3078, 2924, 2216, 1676, 1649, 1608, 1550, and 1240.

PMR (500 MHz,$CDCl_3$) : δ 9.95 (t, *J* =5.5 Hz, 1H, CON*H*), 7.55-7.53 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.24-7.22 (m, 2H, Ar-*H*), 6.99-6.97 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.77-6.75 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 4.92 (s, 1H, CH_2-N*H*), 4.44-4.43 (d, *J* = 7.0 Hz, 2H, C*H*$_2$-NH), 3.68-3.65 (m, 5H,-CH_2-C*H*$_2$-NH & -N-C*H*$_3$), 2.95 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$).

HR-MS (ESI) *m/z* : 476.1484 $[M+H]^+$.

5.1.108 2-((4-Cyanophenylamino)methyl)-*N*-(4-methoxyphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (271)

Following the method of preparation described for compound (**253)**, compound **(245**, 0.2 g, 0.54 mmol) and 2-(4-methoxy)phenethylamine (0.49 g, 3.27 mmol) furnished yellow compound (**271**), (52 %); m.p. 198-200 °C.

Anal.:

TLC : R_f0.22 (*n*-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3391, 3247, 2214, 1677, 1649, 1607, and 1243.

PMR (500 MHz,$CDCl_3$) : δ 9.95 (t,*J* = 5.5 Hz, 1H, CON*H*), 7.54-7.53 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.23-7.21 (d, *J* = 8.25 Hz, 2H, Ar-*H*), 6.86-6.85 (d, *J* = 8.25 Hz, 2H, Ar-*H*), 6.77-6.75 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 5.72 (t, *J* = 4.5 Hz, 1H, Ar-*H*), 4.46-4.45 (d, *J* = 4.5 Hz, 2H, C*H*$_2$-NH), 3.81 (s, 3H, OC*H*$_3$) 3.70 (s, 3H, -N-C*H*$_3$), 3.65 (q, *J* = 7.0 Hz, 2H, CH_2-C*H*$_2$-NH), 2.92 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$).

HR-MS (ESI) *m/z* : 472.1979 $[M+H]^+$

5.1.109 2-((4-Cyanophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethyl-furo[2,3-d]pyrimidine-5-carboxamide (272)

Following the method of preparation described for compound (**253)**,compound **(251**, 0.2 g, 0.54 mmol) and β-phenethylamine (0.39 g, 3.26 mmol) furnished white compound (**272**), (60 %); m.p. 201-203 °C.

Anal.:

TLC : R_f0.25 (n-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3060, 2222, 1672, 1606, 1522, and 1244.

PMR (500 MHz,$CDCl_3$) : δ 10.01 (s, 1H, CON*H*), 7.66-7.65 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.32-7.29 (m, 4H, Ar-*H*), 7.24-7.21 (m, 1H, Ar-*H*), 7.16-7.14 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 5.28 (s, 2H, C*H*$_2$-NH), 3.78 (s, 3H, -N-CH_3) 3.71-3.66 (m, 2H, CH_2-C*H*$_2$-NH), 2.97 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-CH_2), 2.86 (s, 3H, O-C-C*H*$_3$).

^{13}C-NMR(100 MHz, $CDCl_3$) :δ161.54, 160.81, 160.39, 159.68, 151.44, 139.25, 134.34, 128.80, 128.44, 126.27, 115.67, 112.62, 106.03, 104.52, 69.24, 40.99, 35.87, 31.57, 14.15.

MS(ESI) *m/z* : 443.3 $[M+H]^+$

5.1.110 2-((4-Cyanophenoxy)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (273)

Following the method of preparation described for compound (**253)**, compound **(251,** 0.2 g, 0.54 mmol) and 2-(4-fluoro)phenethylamine (0.45 g, 3.26 mmol) furnished white compound (**273**), (62 %); m.p. 174-176 °C.

Anal.:

TLC	: R_f0.27 (n-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3230, 3044, 2225, 1676, 1642, and 1240
PMR (400 MHz, $CDCl_3$)	: δ 9.96 (s, 1H, CON*H*), 7.64-7.62 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.24-7.21 (m, 2H, Ar-*H*), 7.14-7.12 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.98-6.96 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 5.25 (s, 2H, -CH_2-O-), 3.75 (s, 3H, -N-CH_3) 3.66-3.64 (q, *J* = 7.4 Hz, 2H, CH_2-CH_2-NH), 2.91 (t, *J* = 8.0 Hz, 2H, CH_2-CH_2), 2.83 (s, 3H, O-C-CH_3).
HR-MS(ESI) *m/z*	:461.1620 $[M+H]^+$.

5.1.111 2-((4-Cyanophenoxy)methyl)-*N*-(4-chlorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (274)

Following the method of preparation described for compound (**253)**, compound **(251**, 0.2 g, 0.54 mmol) and 2-(4-chloro)phenethylamine (0.50 g, 3.26 mmol) furnished white compound (**274**), (63 %); m.p. 183-185 °C.

Anal.:

TLC	: R_f0.24 (n-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3480, 2226, 1677, 1642, 1551, and 1241.
PMR (400 MHz,$CDCl_3$)	: δ 9.99 (bs, 1H, -CON*H*), 7.25-7.22 (m, 2H, Ar-*H*), 7.20-7.18 (m, 2H, Ar-*H*), 6.96-6.92 (m, 2H, Ar-*H*), 6.70-6.66 (m, 2H, Ar-*H*), 4.36 (s, 2H,-CH_2-O-), 3.66 (s, 3H, -N-CH_3) 3.65-3.63 (q, *J* = 7.3 Hz, 2H, CH_2-

C*H*$_2$-NH), 2.91 (t, *J* = 7.8 Hz, 2H, C*H*$_2$-CH$_2$), 2.80 (s, 3H, O-C-C*H*$_3$).

5.1.112 2-((4-Cyanophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-N-(2-(pyridin-2-yl)ethyl)furo[2,3-d]pyrimidine-5-carboxamide (275)

Following the method of preparation described for compound (**253)**, compound **(251**, 0.2 g, 0.54 mmol) and 2-(2-pyridyl)ethylamine (0.40 g, 3.26 mmol) furnished white compound (**275**), (57 %); m.p. 200-202 °C.

Anal.:

TLC	: R$_f$0.12 (n-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3237, 3059, 2221, 1669, 1605, and 1241.
PMR (400 MHz, CDCl$_3$)	: δ 10.01 (t, *J* = 5.2 Hz, 1H, CON*H*), 8.56-8.54 (m, 1H, Ar-H), 7.64-7.60 (m, 3H, Ar-*H*), 7.25-7.23 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.14-7.11 (m, 3H, Ar-*H*), 5.25 (s, 2H, C*H*$_2$-O-), 3.84-3.81 (q, *J* = 7.0 Hz, 2H, CH$_2$-C*H*$_2$-NH), 3.73 (s, 3H, -N-C*H*$_3$), 3.13 (t, *J* = 7.5 Hz, 2H, C*H*$_2$-CH$_2$), 2.81 (s, 3H, O-C-C*H*$_3$).
^{13}C-NMR (100 MHz, CDCl$_3$)	: δ 161.99, 160.75, 160.38, 160.24, 159.57, 159.27, 151.45, 149.39, 136.33, 134.32, 123.27, 121.36, 118.57, 115.67, 112.61, 105.98, 104.47, 69.22, 39.19, 38.01, 31.41, 29.70, 14.13.
MS (ESI) *m/z*	: 444.3 [M+H]$^+$

5.1.113 2-((4-Cyanophenoxy)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (276)

Following the method of preparation described for compound (**253)**, compound **(251**, 0.2 g, 0.54 mmol) and 2-(4-methyl)phenethylamine (0.44g, 3.26 mmol) furnished off white compound (**276),** (56 %); m.p. 204-206°C.

Anal.:

TLC : R_f0.30 (n-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3053, 2224, 1672, 1606, and 1243.

PMR (500 MHz,$CDCl_3$) : δ 9.96 (t, *J* = 5.2 Hz, 1H, CON*H*), 7.65-7.64 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.18-7.08 (m, 6H, Ar-*H*), 5.25 (s, 2H, C*H*$_2$-O-), 3.75 (s, 3H, N-C*H*$_3$) 3.66-3.63 (m, 2H, -CH_2-C*H*$_2$-NH), 2.91 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-CH_2), 2.83 (s, 3H, O-C-C*H*$_3$), 2.31(s, 3H, Ar-CH_3).

5.1.114 2-((4-Chlorophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethyl-furo[2,3-d]pyrimidine-5-carboxamide (277)

Following the method of preparation described for compound (**253)**, compound **(249**, 0.2 g, 0.53 mmol) and β-phenethylamine (0.38g, 3.18 mmol) furnished white compound (**277**), (55 %); m.p. 171-173 °C.

Anal.:

TLC : R_f0.24 (n-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3233, 3059, 1673, 1649, 1600, and 1242.

PMR (500 MHz, $CDCl_3$) : δ 10.06 (t, *J* = 5.5 Hz, 1H, CON*H*), 7.31-7.28 (m, 6H, Ar-*H*), 7.25-7.21 (m, 1H, Ar-*H*), 7.00-6.98 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 5.19 (s, 2H,C*H*$_2$-O-), 3.78 (s, 3H, N-C*H*$_3$) 3.70-3.66 (m, 2H, CH_2-C*H*$_2$-NH), 2.98 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-CH_2), 2.85 (s, 3H, O-C-C*H*$_3$).

^{13}C-NMR (100 MHz, $CDCl_3$) : δ 162.04, 160.96, 160.50, 159.46, 155.82, 152.27, 139.29, 129.77, 128.81, 128.44, 127.49, 126.25, 116.23, 112.57, 104.31, 69.53, 41.00, 35.90, 31.54, 14.13.

HR-MS(ESI) *m/z* : 452.1372 $[M+1]^+$

5.1.115 2-((4-Chlorophenoxy)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (278)

Following the method of preparation described for compound (**253)**, compound **(249**, 0.2 g, 0.53 mmol) and 2-(4-fluoro)phenethylamine (0.44 g, 3.18 mmol) furnished off white compound (**278**), (53 %); m.p. 158-160 °C.

Anal.:

TLC	: R_f0.27 (n-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3229, 3038, 1680, 1640, 1551, 1328, and 1227.
PMR (500 MHz, $CDCl_3$)	: δ 10.04 (t, *J* = 4.8 Hz, 1H, CON*H*), 7.31-7.29 (m, 2H, Ar-*H*), 7.26-7.23 (m, 2H, Ar-*H*), 7.01-6.97 (m, 4H, Ar-*H*), 5.19 (s, 2H,CH_2-O-), 3.78 (s, 3H, N-CH_3) 3.68-3.64 (m, 2H, CH_2-CH_2-NH), 2.94 (t, *J* = 6.0 Hz, 2H, CH_2-CH_2), 2.85 (s, 3H, O-C-CH_3).
^{13}C-NMR ($CDCl_3$)	: δ 162.06, 160.97, 160.50, 159.51, 155.82, 152.29, 139.29, 130.23, 130.17, 129.78, 127.51, 116.23, 115.27, 115.11, 104.28, 69.53, 40.97, 35.01, 31.54, 14.12.
MS (ESI) m/z	: 470.3 $[M+H]^+$

5.1.116 2-((4-Fluorophenoxy)methyl)-3,4-dihydro-3,6-dimethyl-4-oxo-*N*-phenethyl-furo[2,3-d]pyrimidine-5-carboxamide (279)

Following the method of preparation described for compound (**253)**, compound **(250**, 0.2 g, 0.55 mmol) and β-phenethylamine (0.40 g, 3.33 mmol) furnished white compound (**279**), (58 %); m.p. 160-162 °C.

Anal.:

TLC	: R_f0.25 (n-Hexane: ethyl acetate; 3:2)
IR (KBr, cm^{-1})	: 3228, 3046, 1677, 1640, 1331, and 1218.

PMR (400 MHz, $CDCl_3$) : δ 10.04 (s, 1H, CON*H*), 7.31-7.26 (m, 4H, Ar-*H*), 7.23-7.18 (m, 1H, Ar-*H*), 7.03-6.95 (m, 4H, Ar-*H*), 5.15 (s, 2H,-C*H*$_2$-O-), 3.77 (s, 3H, -N-C*H*$_3$) 3.69-3.63 (m, 2H, -CH_2-C*H*$_2$-NH), 2.96 (t, *J* = 8.0 Hz, 2H, C*H*$_2$-CH_2), 2.82 (s, 3H, O-C-C*H*$_3$).

5.1.117 2-((4-Fluorophenoxy)methyl)-*N*-(4-chlorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (280)

Following the method of preparation described for compound (**253)**, compound **(250**, 0.2 g, 0.55 mmol) and 2-(4-chloro)phenethylamine (0.51g, 3.33 mmol) furnished compound **(280**) as a white solid (56 %); m.p. 164-166°C.

Anal.:

TLC : R_f0.24 (n-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3457, 3253, 1678, 1640, 1331, and 1216.

PMR (400 MHz, $CDCl_3$) : δ 10.02 (s, 1H, CON*H*), 7.24-7.19 (m, 4H, Ar-*H*), 7.03-6.95 (m, 4H, Ar-*H*), 5.15 (s, 2H, C*H*$_2$-O-), 3.76 (s, 3H, N-C*H*$_3$) 3.66-3.64 (q, *J* = 7.2 Hz, 2H, CH_2-C*H*$_2$-NH), 2.92 (t, *J* = 7.4 Hz, 2H, C*H*$_2$-CH_2), 2.82 (s, 3H, O-C-C*H*$_3$).

HR-MS (ESI) *m/z* : 470.1277 $[M+1]^+$.

5.1.118 2-((4-Methoxyphenylamino)methyl)-*N*-(4-fluorophenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (281)

Following the method of preparation described for compound (**253)**, compound **(247**, 0.2 g, 0.53 mmol) and 2-(4-fluoro)phenethylamine (0.44 g, 3.23 mmol) furnished yellow compound (**281**), (55 %); m.p. 174-176 °C.

Anal.:

TLC : R_f0.28 (n-Hexane: ethyl acetate; 3:2)

IR (KBr, cm^{-1}) : 3391, 3259, 1669, 1513, and 1233.

PMR (400 MHz, $CDCl_3$) : δ 10.05 (t, *J* = 4.8Hz, 1H, CON*H*), 7.26-7.23 (m, 2H, Ar-*H*), 7.01-6.97 (m, 2H, Ar-*H*), 6.87-6.84 (m, 2H, Ar-*H*), 6.77-6.74 (m, 2H, Ar-*H*), 4.41 (s, 2H, C*H*$_2$-NH), 3.78 (s, 3H, -OCH_3), 3.70 (s, 3H, N-C*H*$_3$), 3.68-3.64 (m, 2H, CH_2-C*H*$_2$-NH), 2.95 (t, *J* = 6.4 Hz, 2H, C*H*$_2$-CH_2), 2.84 (s, 3H, Ar-C*H*$_3$).

5.1.119 2-((5-Chloropyridin-2-ylamino)methyl)-*N*-(4-methylphenethyl)-3,4-dihydro-3,6-dimethyl-4-oxofuro[2,3-d]pyrimidine-5-carboxamide (282)

Following the method of preparation described for compound (**253)**, compound **(248**, 0.2 g, 0.53 mmol) and 2-(4-methyl)phenethylamine (0.43 g, 3.18 mmol) furnished white compound (**282**), (42 %); m.p. 148-150 °C.

Anal.:

TLC : R_f0.20 (n-Hexane: ethyl acetate; 1:1)

IR (KBr, cm^{-1}) : 3417, 3263, 1667, 1598, and 1483.

PMR (500 MHz, $CDCl_3$) : δ 10.06 (t, *J* = 5.5 Hz, 1H, CON*H*), 8.08-8.07 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 7.44-7.43 (dd, *J* = 2.5 & 7.5 Hz, 1H, Ar-*H*), 7.22-7.19 (m 2H, Ar-*H*), 7.14-7.11 (m, 2H, Ar-*H*), 6.63-6.61 (d, *J* = 9.0 Hz, 1H,Ar-*H*), 4.72 (d, *J* = 4.5 Hz, 2H, C*H*$_2$-NH), 3.72 (s, 3H, N-C*H*$_3$), 3.68-3.64 (m, 2H, CH_2-C*H*$_2$-NH), 2.94 (m, 2H, C*H*$_2$-CH_2), 2.82 (s, 3H, Ar-C-C*H*$_3$), 2.34 (s, 3H, Ar-C*H*$_3$).

MS (ESI) *m/z* : 466.3 $[M+H]^+$

5.2 Biological Evaluation

Direct FXa and thrombin enzyme chromogenic assay kits containing their substrates and buffers were obtained from Hyphen Biomed, France. The enzyme inhibitory activity was measured on Versa Max microplate reader. Healthy male Wistar rats (250-300 g) were used for

biological studies and the protocol for this study was approved by Institutional Animal Ethics Committee (IAEC) of Faculty of Pharmacy, The Maharaja Sayajirao University of Baroda, Vadodara and experiments were performed accordjng to the Committee for the Purpose of Supervision of Experiments on Animals (CPCSEA) guidelines (ApprovalNo. MSU/IAEC/2018-19/1829).

5.2.1 *In vitro* FXa and thrombin inhibition activity[11, 12]

In vitro enzyme inhibitory activities of the test compounds were measured for FXa and thrombin enzymes using a chromogenic substrate assay performed in 96 well-plates on a microplate reader at room temperature. A commercially available assay kit (Hyphen Biomed, France) containing human FXa enzyme, the substrate and buffer (*p*H 7.4) was used for this porpose. All the test compounds and the reference drugs, rivroxaban and dabigatran were dissolved in DMSO at a concentration of 10 mM and then serially diluted with Tris buffer to varying range of concentrations. An enzyme assay was performed as per the manufacturer's instructions. The test compund dilutions with enzyme and buffer were mixed, centrifuged and incubated at 37 °C. After incubation, enzyme specific substrate was added to initiate the reaction and then incubated at 37 °C. The enzyme reaction was stopped by addition of 20% acetic acid stop solution. The enzyme activity was measured at 405 nM on Versa max microplate reader. The positive control consisted of the above mixed solutions with standard drug in place of the test compound. After preliminary screening at a concentration of 20 μM, compounds that exhibited > 60 % inhibition were selected for their IC_{50} values determination using test compounds dilutions with final concentration in the range of 0.2 μM–200 μM. IC_{50} values were calculated from GraphPad Prism 5.

A procedure described as above for FXa was followed for *in vitro* evaluation of thrombin inhibition activity by the test compounds using commercially available chromogenic assay kit (Hyphen Biomed, France) including human thrombin enzyme, thrombin substrate and Tris buffer.

5.2.2 Evaluation of test compounds for *ex vivo* prothrombin time (PT) and activated partial thromboplastin time (aPTT) prolongation in rats [13]

Male Wistar rats weighing 230-280 g were used for this study. The test compounds and standard drug were suspended in sodium carboxymethylcellulose (0.5%) and administered to rats orally at 30 mg/kg dose. After 2 hr of oral administration blood was collected from retro-orbital plexus in a tube containing citrated salt. Platelet-poor plasma was separated by centrifugation to measure prothrombin time (PT) and activated partial thromboplastin time (aPTT) which were expressed in seconds.

5.2.3 *In vivo* rat tail-bleeding model [14, 15]

The test compounds, standard drug or vehicle were administered orally to healthy male wistar rats fasted overnight before 90 min. of their tail transection. The animals were anesthetized via intraperitoneal injection of pentobarbital sodium at a dose of 60 mg/kg and their tails were transected 4 mm from the tip and vertically immersed in saline solution at 37 ^{o}C. The time until continuous blood flow ceased from the tail incision beyond 10 sec. was measured.

5.3. Molecular Docking and Simulation studies

Crystal structuresfor FXa and thrombin enzymes were selected from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB-PDB). FXa (PDB ID: 2W26) and thrombin (PDB ID: 1KTS) were selected as these crystal structures hasa known active sites with rivaroxaban and dabigatran respectively in bound form. The crystal structure was prepared for docking studies by repairing the breaks in the crystal structure, energy minimization was performed to remove any strain due to crystallization process and protonation was performed with the MOE 2019.01.[16] A dataset consisting of rivaroxaban and the most potent compounds (**187, 201, 203, 208, 224**) from scheme 1 and dabigatran and potent compounds (**254, 255, 258, 259, 262, 263, 264, 275**) from scheme 2 were used to generate possible conformations with Omega module of OpenEye software.[17] A grid was generated by 'make_receptor' module with the bound standard drug as reference active site and molecular docking was performed with FRED.[18] The results and top poses with high dock scores were retained and further analyzed.

5.3.1 Molecular Dynamics (MD) Studies

System preparation: MD simulations were performed using the AMBER18 software package.[19] The Factor Xa (PDB: 2W26) in complexation with rivaroxaban and compounds **187, 201, 203, 208, 224** were studied. FXa-Rivaroxaban complex was immersed in truncated octahedron of TIP3P water[20] giving a total of 8473 water molecules. Complex of FXa-187, FXa-201, FXa-203, FXa-208, and FXa-224 were immersed in truncated octahedron of 8621, 8717, 8728, 8520 and 8764 TIP3P water molecules respectively. Na^+ and Cl^- counter ions were added to neutralize the respective systems and achieve an ionic strength of 0.1 M. The *ff14SB* force field was used to model the peptide.[21]

5.3.2 Unbiased MD simulation: Simulations were performed using the *pmemd.cuda* module.[22] Simulations were run at 300 K using the Langevin thermostat [23] with a collision frequency of 2 ps^{-1}; and 1 atm using a Monte Carlo barostat with volume exchange attempts every 100 fs. A 2 fs integration step was employed. Covalent bonds involving hydrogens were constrained using SHAKE.[24] A cutoff of 8 Å was used for short range nonbonded interactions whilst long range electrostatics were treated using the particle mesh Ewald method.[25] Equilibration consisted of rounds of NVT and NPT equilibration for 10 ns in total. Production MD run was performed for 100 ns for each complex. Interactions were analyzed using *cpptraj*[26] over complete 100 ns, taking the conformation every 4 ps.

5.4 References

1. Nakhai, A., Stensland, B., Svensson P. H., Bergman, J. Synthesis of Benzotriazine and Aryltriazene Derivatives starting from 2-Azidobenzonitrile Derivatives. *Eur. J. Org. Chem.* **2010**, 6588–6599.
2. Pavlidis, V. H., Perry, P. J. The Synthesis of a Novel Seriesof Substituted 2-Phenyl-4H-3,1-benzoxazin-4-ones. *Synthetic Comm.,* **1994**, *24*, 533-548.
3. Mason, J. J., Janosik, T., Bergman, J. A New Approach to Methoxyisatins Leading to the Total Synthesis of Ophiuroidine and Other Hydroxytryptanthrins. *Synthesis,* **2009**, *21*, 3642–3648.
4. Sun, Y. T., Wang, G. F., Yang, Y. Q., Jin, F., Wang, Y., Xie, X. Y., Mach, R. H., Huang, Y.S. Synthesis and pharmacological evaluation of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as sigma-2 receptor ligands. *Eur. J. Med. Chem.*, **2018**, *147*, 227-237.
5. Yadav, M. R., Shirude, S. T., Parmar, A., Balaraman, R. Giridhar, R. Synthesis and anti-inflammatory activity of 2,3-diaryl-4(3H)-quinazolinones *Chem. Heterocyc. Comp.* **2006**, *42*, 1038-1044.
6. Yu, J., Zhang-Negrerie, D., Du, Y. TBHP/$CoCl_2$-Mediated Intramolecular Oxidative Cyclization of *N*-(2-Formylphenyl)amides: An Approach to the Construction of 4*H*-3,1-Benzoxazin-4-ones. *Eur. J. Org. Chem*. **2016**, *3*, 562-568.
7. Prakash, R., Gogoi, S. Copper-Catalyzed C-N, C-O Coupling Reaction of Aryl Glyoxalic Acids with Isatins. *Adv. Synth. Catalysis*. **2016**, *358*, 3046-3049.
8. Lee, H. S., Lee, W., Bae, J-S., Ma, E. Synthesis and in vitro and in vivo anticoagulant and antiplatelet activities of amidino- and non-amidinobenzamides. *Molecules* **2016**, 21, 676.
9. Hu, Y-G.; Li, G-H.; Ding, M-W. Efficient Synthesis of furo[2,3-*d*]pyrimidin-4(3*H*)-ones. *ARKIVOC*, **2008**, (xiii), 151-158.
10. Basha, A.; Lipton M.; Weinreb, S. M. A mild, general method for conversion of esters to amides. *Tetrahedron Lett.,* **1977**, *48*, 4171-4174.

11. Wang, W., Yuan, J., Fu, X., Meng, F., Zhang, S., Xu, W., Xu, Y. Novel Anthranilamide-Based FXa Inhibitors: Drug Design, Synthesis and Biological Evaluation *Molecules*, **2016**, *21*, 491.
12. Lagos, C. F., Segovia, G. F., Nuñez-Navarro, N., Faúndez, M. A., Zacconi., F. C. Novel FXa Inhibitor Identification through Integration of Ligand- and Structure-Based Approaches *Molecules*, **2017**, 22, 1588.
13. Pandya, V., Jain, M., Chakrabarti, G., Soni, H., Parmar, B., Chaugule, B., Patel, J., T. Jarag, T., J. Joshi, J., Joshi, N., Sharma, B., Ajani, H., Kumar, J., Sairam, K. V.M., Patel, H., Patel, P. Synthesis and structure-activity relationship of potent, selective and orally active anthranilamide-based factor Xa inhibitors: application of weakly basic sulfoximine group as novel S4 binding element. *Eur. J. Med. Chem*. **2012**, *58*, 136-152.
14. Perzborn, E., Strassburger, J., Wilmen, A., Pohlmann, J., Roehrig, S., Schlemmer, K. H. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor *J Thromb. Haemost.* **2005**, 3, 514–521.
15. Dejana, E., Callioni, A. Quintana, G. de Gaetano, Bleeding time in laboratory animals. II - A comparison of different assay conditions in rats. *Thromb. Research*. **1979**, *15*, 191-197.
16. https://www.chemcomp.com (Acssessed, October, 2019)
17. Hawkins, P. C. D., Skillman, A. G., Warren, G. L., Ellingson, B. A., Stahl, M. T. *J. Chem. Inf. Model*.**2010**, 50, 572-584.
18. McGann, M. FRED Pose Prediction and Virtual Screening Accuracy *J. Chem. Inf. Model*. **2011**, 51, 578-596.
19. Case, D.A., Ben-Shalom, I. Y, Brozell, S. R., D.S. Cerutti, T.E. Cheatham, III, V.W.D. Cruzeiro, T.A. Darden, R.E. Duke, D. Ghoreishi, M. K. Gilson, H. Gohlke, A.W. Goetz, D. Greene, R Harris, N. Homeyer, S. Izadi, A. Kovalenko, T. Kurtzman, T.S. Lee, S. LeGrand, D. M. York and P. A. Kollman. AMBER Reference Manual **2018**, University of California, San Francisco.
20. Mark, P., Nilsson, L. Structure and Dynamics of the TIP3P, SPC, and SPC/E Water Models at 298 K. *J. Phys. Chem. A* **2001**, 105, 9954–9960.

21. Maier, J. A., Martinez, C., Kasavajhala, K., Wickstrom, L., Simmerling C. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J. Chem. Theory Comput.* 2015, 11, 3696–3713.
22. Salomon-Ferrer, R., Gotz, A. W., Poole, D., Grand, S., R., Walker, R. C. Routine Microsecond Molecular Dynamics Simulations with AMBER on GPUs. 2. Explicit Solvent Particle Mesh Ewald. *J. Chem. Theory Comput.* **2013**, 9, 3878–3888.
23. Cerutti, D. S., Duke, R., Freddolino, P. L., Fan, H., Lybrand, T. P. A Vulnerability in Popular Molecular Dynamics Packages Concerning Langevin and Andersen Dynamics. *J. Chem. Theory Comput.* **2008**, 4, 1669–1680.
24. Ryckaert, J. P., Ciccotti, G., Berendsen, H. J. Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of *n*-alkanes *J. Comput. Phys.* **1977**, 23, 327–341.
25. Nam, K., Gao, J., York, D. M. Quantum Mechanical/Molecular Mechanical Simulation Study of the Mechanism of Hairpin Ribozyme Catalysis *J. Am. Chem. Soc.* **2008**, 130, 14, 4680-4691.
26. Roe, D. R., Cheatham III, T. E. PTRAJ and CPPTRAJ: Software for Processing and Analysis of Molecular Dynamics Trajectory Data. *J. Chem. Theory Comput.* **2013**, 9, 3084–3095.