Experimental

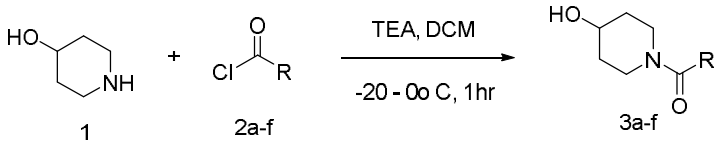
5 Experimental

5.1 Chemistry

5.1.1 Materials and Methods

Reagents were obtained from commercial suppliers and were used without further purification. Solvents were procured from commercial source and used after distilling or drying according to the known methods. All the air and/or moisture sensitive reactions were carried out in dry solvents under nitrogen atmosphere. Melting points were recorded in open glass capillaries, using a scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR 8300 spectrophotometer (ν_{max} in cm^{-1}, as film / in $CHCl_3$ for liquids and as KBr pellets for solid compounds). The ^1H NMR spectra were recorded on a Bruker Avance-300 (300 MHz) or Bruker Avance-400 (400 MHz) spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, either in $CDCl_3$ or DMSO-d_6. Signal multiplicities are represented as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). D_2O exchange experiments were carried out to confirm the exchangeable protons when present. ^{13}C NMR spectra were recorded on Bruker Avance-400 at 100 MHz either in $CDCl_3$ or in DMSO-d_6. Mass spectra (ESI-MS) were obtained on Shimadzu LCMS 2010-A spectrometer. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN analyzer. UPLC analyses were carried out at λ_{max} 220 nm using column ODS C-18, 150nm * 4.6 nm * 4 μ on AGILENT 1100. Progress of the reaction was monitored by TLC using precoated TLC plates (E. Merck Silica gel 60 F254) and the spots were visualized using UV and/or iodine vapours. The chromatographic purification was performed on silica gel (100-200 mesh or 230–400 mesh).

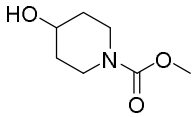
5.1.2 Synthesis of Compounds 3a-f



General procedure:

To the solution of 4-hydroxy piperidine (1 mole equivalent) in dichloromethane (6-fold), triethylamine (1.3 mole equivalent) was added at -20 °C followed by dropwise addition of chloroformates (methyl, ethyl, *t*-butyl, *i*-butyl and benzyl) or acetyl chloride (1.1 mole equivalent). After stirring for 30 min at 0 °C, the reaction mixture was poured into water (100 ml) and extracted with DCM (2 x 50 ml). The organic extracts were washed with water (50 ml), brine (50 ml) and were dried over calcium chloride or sodium sulphate. The organic extracts were concentrated on rotavapor to obtain oily products in excellent yields of the compounds **3a-f**.

5.1.2.1 Methyl 4-hydroxypiperidine-1-carboxylate (3a)

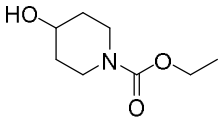


3a (5.8 gm, 73%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a colourless oil. Purity by UPLC: 99.50%.

^{1}H NMR ($CDCl_3$) : δ 1.45-1.54 (m, 2H), 1.86-1.91 (m. 3H), 3.28-3.39 (m, 2H), 3.79-3.84 (m, 2H), 4.63 (s, 3H), 4.85 (d, *J* = 8.0 Hz, 1H)

ESI/MS (m/z) : 160.12 $(M+H)^+$

5.1.2.2 Ethyl 4-hydroxypiperidine-1-carboxylate (3b)

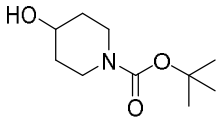


3b (7.2 gm, 84%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a pale-yellow oil. Purity by UPLC: 97.80%.

^{1}H NMR ($CDCl_3$) : δ 1.13 (t, *J* = 11.2 Hz, 3H), 1.43-1.52 (m, 2H), 1.84-1.89 (m. 3H), 3.07-3.13 (m, 2H), 3.26-3.36 (m, 2H), 3.85-3.90 (q, *J* =11.2 Hz 2H), 4.84-4.88 (m, 1H)

ESI/MS (m/z) **:** 173.80 $(M+H)^+$

5.1.2.3 *t*-Butyl 4-hydroxypiperidine-1-carboxylate (3c)



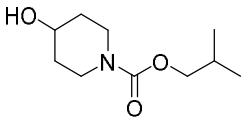
3c (8.2 gm, 82%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as an off-white solid. MP: 61-65 °C; Purity by UPLC: 98.90%.

IR (KBr) **:** 3427, 3016, 2981, 2933, 2866, 1672, 1475, 1429, 1367, 1168 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.45 (m, 11H), 1.81-1.87 (m, 3H), 2.99-3.05 (m, 2H), 3.80-3.86 (m, 3H).

ESI/MS (m/z) **:** 223.89 $(M+Na)^+$

5.1.2.4 *i*-Butyl 4-hydroxypiperidine-1-carboxylate (3d)

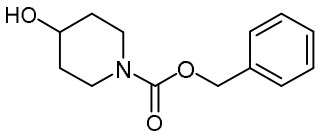


3d (8.0 gm, 80%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a pale-yellow liquid. Purity by UPLC: 97.01%.

^{1}H NMR ($CDCl_3$) **:** δ 0.97 (d, J = 8.0 Hz, 6H), 1.44-1.53 (m, 2H), 1.59-1.64 (m, 2H), 1.85-1.98 (m. 3H), 3.08-3.14 (m, 2H), 3.84-3.92 (m, 3H).

ESI/MS (m/z) **:** 201.91 $(M+H)^+$

5.1.2.5 Benzyl 4-hydroxypiperidine-1-carboxylate (3e)

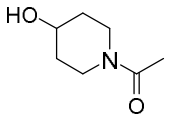


3e (7.56 gm, 65%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a colourless oil. Purity by UPLC: 96.99%.

^{1}H NMR ($CDCl_3$) **:** δ 1.47-1.49 (m, 2H), 1.55-1.62 (m, 2H), 3.11-3.17 (m, 2H), 3.83-3.92 (m, 3H), 5.12 (s, 2H), 7.30-7.38 (m, 5H)

ESI/MS (m/z) **:** 258.17 $(M+Na)^+$

5.1.2.6 1-(4-Hydroxypiperidin-1-yl) ethan-1-one (3f)

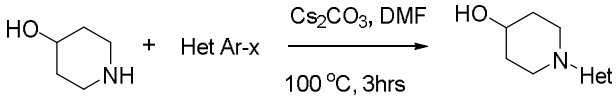


3f (4.11 gm, 58%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as colourless oil. Purity by UPLC: 98.70%.

^{1}H NMR ($CDCl_3$) : δ 1.45 (m, 2H), 1.81-1.87 (m, 3H), 2.52 (s, 3H), 2.99-3.05 (m, 2H), 3.80-3.86 (m, 3H)

ESI/MS (m/z) : 144.15 $(M+H)^+$

5.1.3 Synthesis of Compounds 3g-k

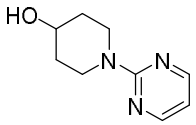


1 4 g-k 3 g-k

General procedure:

To a solution of **1** (1 mole equivalent) in DMF (5 fold), Cs_2CO_3 (2 mole equivalent) and hetero aryl halides such as pyrimidine, chloro pyrimidine, ethyl pyrimidine, bromo pyridine or benzyl bromide (1.2 mole equivalent) were added and the reaction mixture was stirred at 100 °C for 3 hours. The reaction mixture was poured in ice-cold water and extracted with ethyl acetate. The organic extracts were washed with water, followed by brine and were dried over Na_2SO_4 and were evaporated under reduced pressure to yield the compounds **3g-k**.

5.1.3.1 1-(Pyrimidin-2-yl) piperidin-4-ol (3g)

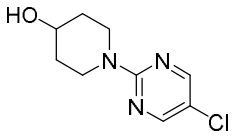


3g (7.95 gm, 90%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 95.20%.

^{1}H NMR ($CDCl_3$) : δ 1.49 (m, 2H), 1.93-1.99 (m, 2H), 3.28-3.34 (m, 2H), 3.92-3.98 (m, 1H), 4.38-4.44 (m, 2H), 6.46 (t, *J* = 4.8 Hz, 1H), 8.30 (d, *J* = 4.4 Hz, 2H).

ESI/MS (m/z) : 180.00 $(M+H)^+$

5.1.3.2 1-(5-Chloropyrimidin-2-yl) piperidin-4-ol (3h)



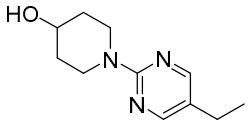
3h (10.12 gm, 95%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 97.51%.

IR (Neat) **:** 3016, 2974, 2928, 2908, 1898, 1583, 1506, 1437, 1359, 1325, 1301, 1242, 1166, 1066, 1026, 976, 935, 914 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.48-1.54 (m, 2H), 1.91-1.97 (m, 2H), 3.29-3.36 (m, 2H), 3.92-3.99 (m, 1H), 4.31-4.36 (m, 2H), 8.21 (s, 2H).

ESI/MS (m/z) **:** 213.90 $(M+H)^+$

5.1.3.3 1-(5-Ethylpyrimidin-2-yl) piperidin-4-ol (3i)

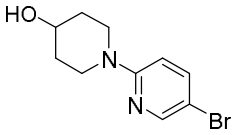


3i (7.0 gm, 68%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as viscous oil. Purity by UPLC: 98.01%.

^{1}H NMR ($CDCl_3$) **:** δ 1.18 (t, *J* = 7.6 Hz, 3H), 1.48-1.52 (m, 2H), 1.69 (br s, 1H), 1.92-1.98 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 3.90-3.96 (m, 1H), 4.36-4.41 (m, 2H), 8.16 (s, 2H).

ESI/MS (m/z) **:** 208.24 $(M+H)^+$

5.1.3.4 1-(5-Bromopyridin-2-yl) piperidin-4-ol (3J)



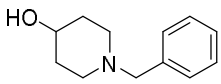
3J (4.66 gm, 36%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a viscous liquid. Purity by UPLC: 95.84%.

IR (Neat) **:** 3155, 3001, 2947, 2924, 2848, 1583, 1483, 1396, 1363, 1303, 1220, 1186, 1080, 1041, 985 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.52-1.61 (m, 2H), 1.93-1.99 (m, 2H), 3.12-3.19 (m, 2H), 3.89-4.02 (m, 3H), 6.57 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 8.17 (s, 1H).

ESI/MS (m/z) **:** 256.7 $(M+H)^+$

5.1.3.5 1-Benzylpiperidin-4-ol (3k)

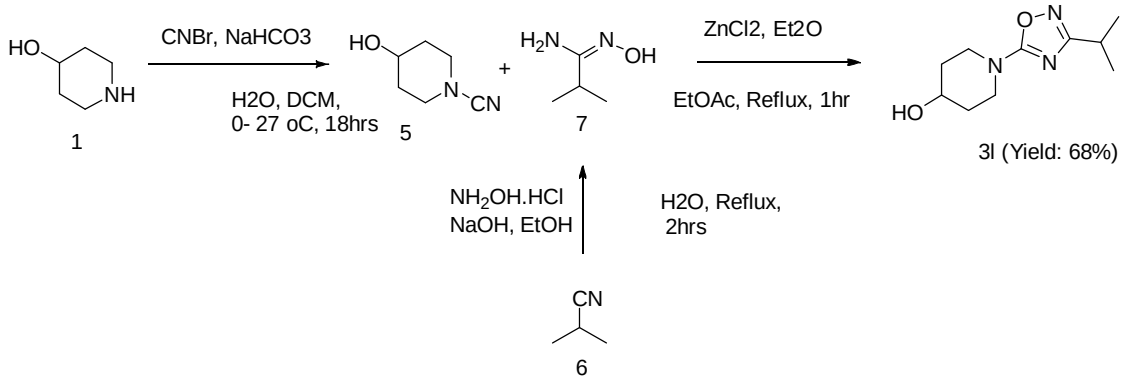


3k (3.31 gm, 35%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 91.98%.

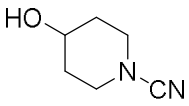
^{1}H NMR ($CDCl_3$) **:** δ 1.57-1.63 (m, 2H), 1.84-1.90 (m, 2H), 2.11-2.17 (m, 2H), 2.72-2.77 (m, 2H), 3.49 (s, 3H), 3.66-3.72 (m, 1H), 7.27-7.33 (m, 5H).

ESI/MS (m/z) **:** 191.90 $(M+H)^+$

5.1.4 Synthesis of Compound 3l

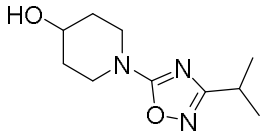


Step 1: Synthesis of 4-hydroxypiperidine-1-carbonitrile (5)



To a solution of **1** (1 mole equivalent) in dichloromethane (DCM)(8 fold), a solution of sodium bicarbonate (2 mole equivalent) in water (2 fold) was added and the reaction mixture was stirred for 30 min at 0 °C. Then was added CuBr (1.1 mole equivalent) portion wise at 0 °C and stirred for 1hr at 27 °C. The rection mixture was diluted with DCM (20 fold) and dried over sodium sulphate. The solvent was evaporated on rotavapor to yield compound **5** as an oil and directly used in next step.

Step 2: Synthesis of 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-ol (3l)

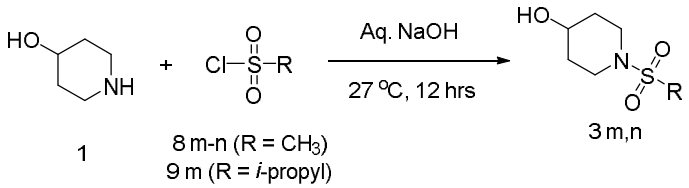


To a solution of compound **5** (4.0 gm, 1 mole equivalent) and N-hydroxy isobutyrimidamide **7** (3.25 gm, 1 mole equivalent) in a mixed solvents i.e diethyl ether and EtOAc (1:3 ratio), 1N $ZnCl_2$ in ether (1 mole equivalent) was added and the reaction mixture was stirred for 15 min at 27 °C. Then the solvent was removed and the residue was washed with diethyl ether (3 times). The washed residue was dissolved in a mixture of 1N HCl and ethanol and the mixture was refluxed for 1hr. The reaction mixture was cooled, solvent was removed using rotavapor and was basified with Na_2CO_3 solution and was extracted with DCM (3 times). The organic extracted were dried over sodium sulphate and the solvent was evaporated to yield the compound **3l** as a viscous oil. Purity by UPLC: 98.30%.

^{1}H NMR ($CDCl_3$) **:** δ 1.28 (d, *J* = 7.2 Hz, 6H), 1.59-1.68 (m, 2H), 1.92-1.98 (m, 2H), 2.27 (1H), 2.84-2.91 (m, 1H), 3.34-3.40 (m, 2H), 3.89-3.98 (m, 3H).

ESI/MS (m/z) **:** 212.0 $(M+H)^+$

5.1.5 Synthesis of compounds 3m & 3n

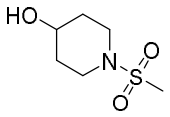


General procedure:

To solution of 4-hydroxypiperidine **1** (1 mole equivalent) in 2M aqueous sodium hydroxide (10 ml) was added sulphonyl chlorides (methyl, *i*-propyl) **8 & 9** (1.2 mole equivalent) over 10 minutes. The solution was stirred at ambient temperature for a further 1 hour. The reaction mixture was poured into EtOAc (30ml) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 x 300ml). The

combined organic phases were dried over Na_2SO_4 and evaporated on rotavapor under reduced pressure to yield the compounds **3m & 3n**.

5.1.5.1 1-(Methyl sulfonyl) piperidin-4-ol (3m)

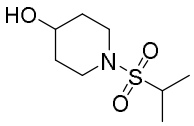


3m (1.15 gm, 13%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 91.80%.

^{1}H NMR ($CDCl_3$) : δ 1.45 (m, 2H), 1.81-1.87 (m, 3H), 3.52 (s, 3H), 2.99-3.05 (m, 2H), 3.80-3.86 (m, 3H).

ESI/MS (m/z) : 180.18 $(M+H)^+$

5.1.5.2 1-(*i*-Propyl sulfonyl) piperidin-4-ol (3n)

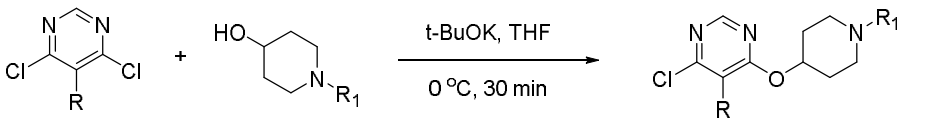


3n (1.01 gm, 10%) was prepared from **1** (5.0 gm, 1 mole equivalent) following the general procedure described above as a colourless oil. Purity by UPLC: 92.45%.

^{1}H NMR ($CDCl_3$) : δ 1.28 (d, J = 7.2 Hz, 6H), 1.59-1.68 (m, 2H), 1.92-1.98 (m, 2H), 2.84-2.91 (m, 1H), 3.34-3.40 (m, 2H), 3.89-3.98 (m, 3H), 4.18-4.24 (m, 1H).

ESI/MS (m/z) : 208.29 $(M+H)^+$

5.1.6 Synthesis of compounds 11 a-e, g, k, l, 12 a-l, 18 a-n, 19 a-m.



10 a (R = CH3)
10 b (R = H)

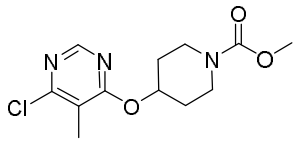
3 a-n

11 a-e, g, k, l & 18 a-n (R = CH_3)
12 a-l & 19 a-m (R = H)

General procedure:

Potassium *t*-butoxide (0.9 mole equivalent) was added to a solution of **3 a-n** (1 mole equivalent) and 4, 6-dichloro pyrimidine **10 a-b** (1 mole equivalent) in dry THF at 0 °C and the reaction mixture was stirred for 15-20 hours at 30 °C. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (2 x 50 ml). The organic extracts were washed with water and brine, were dried over sodium sulphate and the solvent was evaporated under reduced pressure to obtain the compounds **(11 a-e, g, k, l, 12 a-l, 18 a-n, 19 a-m)** in good yields and in high purity**.**

5.1.6.1 Methyl-4-((6-chloro-5-methylpyrimidin-4-yl)oxy)piperidine-1 carboxylate (11a):



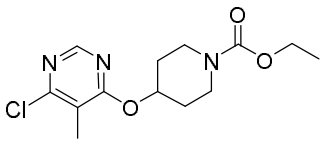
11a (1.40 gm, 75%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3a** (980 mg, 1 mole equivalent) following the general procedure described above as an off-white solid. Purity by UPLC: 99.29%.

IR (KBr) **:** 2993, 2864, 1716, 1556, 1442, 1359, 1313, 1228, 1049, 1022, 823, 765 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.76-1.82 (m, 2H), 1.97-2.02 (m, 2H), 2.29 (s, 3H), 3.40-3.46 (m, 2H), 3.71 (s, 3H), 3.73-3.77 (m, 2H), 5.33-5.37 (m, 1H), 8.38 (s, 1H).

ESI/MS (m/z) **:** 285.8 $(M)^+$

5.1.6.2 Ethyl 4-((6-chloro-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (11b):



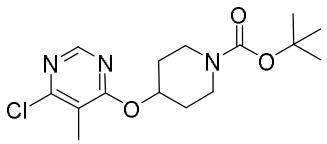
11b (950 mg, 52%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3b** (1.08 gm, 1 mole equivalent) following the general procedure described above as a yellow oil. Purity by UPLC: 98.57%.

IR ($CHCl_3$) **:** 3018, 2933, 2872, 1739, 1685, 1554, 1435, 1274, 1136 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.77-1.80 (m, 2H), 1.96-2.04 (m, 2H), 2.22 (s, 3H), 3.39-3.45 (m, 2H), 3.73-3.75 (m, 2H), 4.14 (q, 7.2 Hz, 2H), 5.30-5.36 (m, 1H), 8.40 (s, 1H).

ESI/MS (m/z) : 322.00 $(M+Na)^+$

5.1.6.3 *t*-Butyl4-((6-chloro-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (11c):



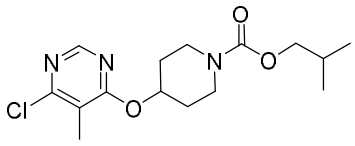
11c (1.5 gm, 73%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3c** (1.23 gm, 1 mole equivalent) following the general procedure described above as an off-white solid. m.p: 84-85 °C; Purity by UPLC: 99.79%.

IR (KBr) : 3433, 3416, 2997, 1691, 1560, 1421, 1253, 771 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.47 (s, 9H), 1.73-1.80 (m, 2H), 1.94-2.0 (m, 2H), 2.22 (s, 3H), 3.32-3.39 (m, 2H), 3.68-3.74 (m, 2H), 5.31-5.35 (m, 1H), 8.38 (s, 1H).

ESI/MS (m/z) : 328.0 $(M+H)^+$

5.1.6.4 *i*-Butyl4-((6-chloro-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (11d):



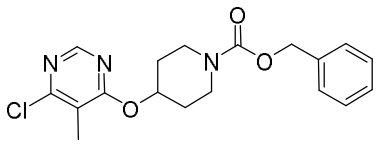
11d (1.23 gm, 61%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3d** (1.23 gm, 1 mole equivalent) following the general procedure described above as a pale-yellow oil. Purity by UPLC: 96.21%.

IR ($CHCl_3$) : 3247, 3074, 2929, 1768, 1608, 1506, 1215, 1174, 956, 806 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.74-1.80 (m, 2H), 1.93-2.00 (m, 2H), 2.23 (s, 3H), 2.48-2.52 (m, 1H), 3.40-3.46 (m, 2H), 3.73-3.79 (m, 2H), 3.88 (d, *J* = 6.4 Hz, 2H), 5.32-5.37 (m, 1H), 8.38 (s, 1H).

ESI/MS (m/z) : 327.8 $(M)^+$

5.1.6.5 Benzyl4-((6-chloro-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (11e):



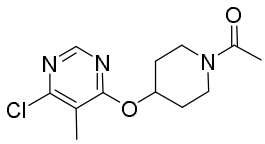
11e (880 mg, 40%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3e** (1.44 gm, 1 mole equivalent) following the general procedure described above as a yellow oil. Purity by UPLC: 90.84%.

IR ($CHCl_3$) **:** 3433, 3416, 3018, 2958, 1691, 1554, 1433, 1205, 1141, 1114, 954, 680 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.99 (s, 2H), 2.04 (d, *J* = 3.6 Hz, 2H), 2.22 (s, 3H), 3.75-3.81 (m, 2H), 4.09-4.15 (m, 2H), 5.15 (s, 2H), 5.32-5.38 (m, 1H), 7.26-7.39 (m, 5H), 8.38 (s, 1H).

ESI/MS (m/z) **:** 384.00 $(M+Na)^+$

5.1.6.6 4-chloro-5-methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy) pyrimidine (11f)

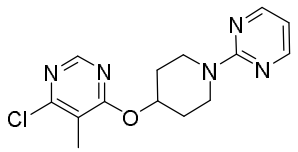


11f (1.50 mg, 90%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3f** (1.49 gm, 1 mole equivalent) following the general procedure described above as a yellow oil. Purity by UPLC: 91.29%.

^{1}H NMR ($CDCl_3$) **:** δ 1.72-1.78 (m, 2H), 1.88-1.98 (m, 2H), 2.15 (s, 3H), 2.34 (s, 3H), 3.32-3.38 (m, 2H), 4.02-4.08 (m, 2H), 5.13-5.19 (m, 1H), 8.36 (s, 1H).

ESI/MS (m/z) **:** 270.18 $(M+H)^+$

5.1.6.7 4-chloro-5-methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy) pyrimidine (11g)



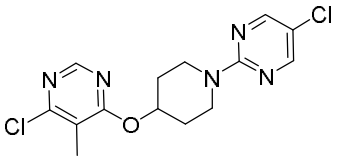
11g (1.2 gm, 65%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3g** (1.1 gm, 1 mole equivalent) following the general procedure described above, as an off-white solid. m.p: 119-121 °C; Purity by UPLC: 92.84%.

IR (KBr) **:** 3436, 3354, 3163, 1627, 1429, 1322, 1169, 1120, 1064, 1014, 896, 845 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.62-1.70 (m, 2H), 1.98-2.03 (m, 2H), 2.25 (s, 3H), 3.10-3.17 (m, 2H), 3.69-3.74 (m, 2H), 3.94-3.97 (m, 1H), 8.37 (s, 1H), 7.25 (s, 3H).

ESI/MS (m/z) **:** 306.05 $(M+H)^+$

5.1.6.8 4-chloro-6-((1-(5-chloropyrimidin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidine (11h)



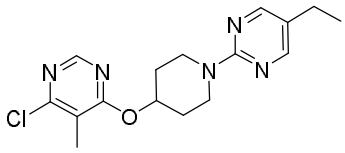
11h (1.65 gm, 79%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3h** (1.31 gm, 1 mole equivalent) following the general procedure described above as a colourless oil. Purity by UPLC: 97.48%.

IR ($CHCl_3$) **:** 3437, 2947, 2839, 1583, 1556, 1529, 1496, 1438, 1433, 1356, 1313, 1298, 1246, 1138, 1114, 1043, 1026, 995 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.79-1.87 (m, 2H), 2.03-2.09 (m, 2H), 2.23 (s, 3H), 3.3.69-3.75 (m, 2H), 4.10-4.16 (m, 2H), 5.40-5.46 (m, 1H), 8.23 (s, 2H), 8.40 (s, 1H).

ESI/MS (m/z) **:** 340.2 $(M+H)^+$

5.1.6.9 4-Chloro-6-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)oxy)-5-methyl-pyrimidine (11i)



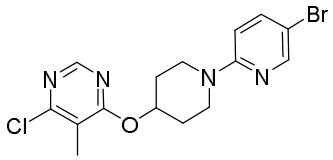
11i (1.25 gm, 61%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3i** (1.25 gm, 1 mole equivalent) following the general procedure described above as an off-white solid. m.p: 143-145 °C; Purity by UPLC: 98.62%.

IR (KBr) **:** 3012, 2958, 2926, 2858, 1604, 1556, 1427, 1309, 1224, 1043 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.18 (t, *J* = 3.8 Hz, 3H), 1.78-1.86 (m, 2H), 2.03-2.10 (m, 2H), 2.23 (s, 3H), 2.44 (q, *J* = 7.6 Hz, 2H), 3.65-3.74 (m, 2H), 4.14-4.20 (m, 2H), 5.39-5.45 (m, 1H), 8.19 (s, 2H), 8.40 (s, 1H).

ESI/MS (m/z) **:** 334.2 $(M+H)^+$

5.1.6.10 4-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)-6-chloro-5-methyl-pyrimidine (11J)



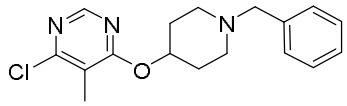
11J (1.62 gm, 69%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3J** (1.62 gm, 1 mole equivalent) following the general procedure described above, as a white solid. MP is 123.9 °C; Purity by UPLC: 98.27%.

IR (KBr) **:** 3433, 2962, 2941, 2833, 1566, 1554, 1444, 1388, 1357, 1313, 1238, 1188, 1118, 1043, 1026 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.82-1.90 (m, 2H), 2.05-2.12 (m, 2H), 2.22 (s, 3H), 3.44-3.51 (m, 2H), 3.83-3.89 (m, 2H), 5.37-5.43 (m, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 8.20 (s, 1H), 8.40 (s, 1H).

ESI/MS (m/z) **:** 384.70 $(M+H)^+$

5.1.6.11 4-((1-Benzylpiperidin-4-yl)oxy)-6-chloro-5-methylpyrimidine (11k)



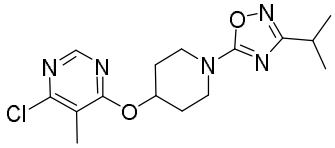
11k (936 mg, 48%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3k** (1.17 gm, 1 mole equivalent) following the general procedure described above, as an off-white solid. m.p: 74-75 °C; Purity by UPLC: 99.06%.

IR (KBr) **:** 2956, 28.4, 1560, 1550, 1450, 1383, 1315, 1251, 1041, 1010, 956, 860 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.79-1.88 (m, 2H), 1.99-2.06 (m, 2H), 2.21 (s, 3H), 2.34-2.38 (m, 2H), 2.70 (brs, 2H), 3.53 (s, 2H), 5.16-5.22 (m, 1H), 7.23-7.25 (m, 1H), 7.29-7.33 (m, 4H), 8.36 (s, 1H).

ESI/MS (m/z) **:** 318.13 $(M+H)^+$

5.1.6.12 5-(4-((6-Chloro-5-methylpyrimidin-4-yl)oxy)piperidin-1-yl)-3-isopropyl-1, 2, 4-oxadiazole (11l)



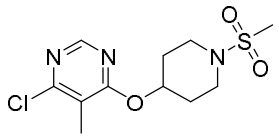
11l (1.96 gm, 90%) was prepared from **10a** (1.0 gm, 1 mole equivalent) and **3l** (1.30 gm, 1 mole equivalent) following the general procedure described above as an off-white solid. Purity by UPLC: 90.52%.

IR (KBr) **:** 2974, 2937, 2879, 1411, 1381, 1265, 1228, 1141, 1114, 978, 865 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.29 (d, J = 4.4 Hz, 6H), 1.89-1.97 (m, 2H), 2.07-2.14 (m, 2H), 2.24 (s, 3H), 2.86-2.93 (m, 1H), 3.60-3.66 (m, 2H), 3.81-3.87 (m, 2H), 5.40-5.45 (m, 1H), 8.40 (m, 1H).

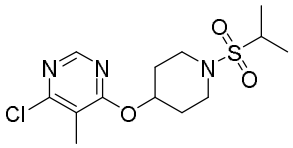
ESI/MS (m/z) **:** 338.1 $(M+H)^+$

5.1.6.13 4-Chloro-5-methyl-6-((1-(methylsulfonyl)piperidin-4-yl)oxy)pyrimidine (18m)



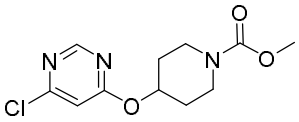
11m (960 mg, 50%) was prepared from **10a** (1. 0 gm, 1 mole equivalent) and **3m** (1.10 gm, 1 mole equivalent) following the general procedure described above as pale brown viscous oil and directly used in next step.

5.1.6.14 4-Chloro-6-((1-(isopropylsulfonyl)piperidin-4-yl)oxy)-5-methylpyrimidine (18n)



11n (881 mg, 42%) was prepared from **10a** (1. 0 gm, 1 mole equivalent) and **3n** (1.27 gm, 1 mole equivalent) following the general procedure described above as a viscous oil and directly used in the next step.

5.1.6.15 Methyl-4-((6-chloropyrimidin-4-yl)oxy)piperidine-1-carboxylate (12a)



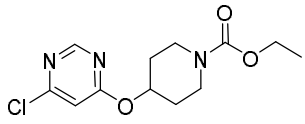
12a (1.33 gm, 73%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3a** (1.10 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 97.37%.

IR ($CHCl_3$) **:** 3016, 2958, 2870, 1745, 1697, 1568, 1452, 1276, 1238, 1141, 1085, 985, 756 cm^{-1}

^1H NMR ($CDCl_3$) **:** δ 1.75-1.79 (m, 2H), 1.97-2.01 (m, 2H), 3.29-3.39 (m, 2H), 3.71 (s, 3H), 3.73-3.77 (m, 2H), 5.30-5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H).

ESI/MS (m/z) **:** 271.8 $(M+H)^+$

5.1.6.16 Ethyl-4-((6-chloropyrimidin-4-yl)oxy)piperidine-1-carboxylate (12b)



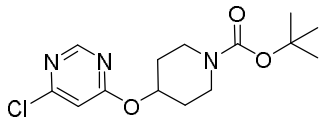
12b (1.28 gm, 67%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3b** (1.16 gm, 1 mole equivalent) following the general procedure described above as a white solid. Purity by UPLC: 99.54%.

IR (KBr) **:** 3014, 2978, 2868, 1685, 1568, 1460, 1425, 1352, 1234, 1130, 1085, 1028, 981, 775 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.71-1.79 (m, 2H), 1.96-2.01 (m, 2H), 3.32-3.39 (m, 2H), 3.78-3.81 (m, 2H), 4.16 (q, *J* = 14.2 Hz, 2H), 5.30-5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H).

ESI/MS (m/z) **:** 285.9 $(M+H)^+$

5.1.6.17 *t*-Butyl-4-((6-chloropyrimidin-4-yl)oxy)piperidine-1-carboxylate (12c)



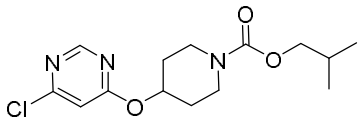
12c (630 mg, 30%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3c** (1.35 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 99.74%.

IR ($CHCl_3$) **:** 3392, 3019, 2979, 2935, 1680, 1569, 1216, 758 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.47 (s, 9H), 1.70-1.76 (m, 2H), 1.95-2.00 (m, 2H), 3.25-3.31(m, 2H), 3.75 (t, *J* = 12.4Hz, 2H), 5.28-5.32 (m, 1H), 6.75 (s, 1H), 8.54 (s, 1H).

ESI/MS (m/z) **:** 313.0 $(M)^+$

5.1.6.18 *i*-Butyl-4-((6-chloropyrimidin-4-yl)oxy)piperidine-1-carboxylate (12d)

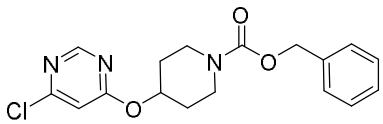


12d (1.30 gm, 65%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3d** (1.35 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 97.38%.

IR ($CHCl_3$) : 3012, 2962, 2874, 1691, 1568, 1454, 1350, 1230, 1085, 1030, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.96 (d, *J* = 7.6 Hz, 6H), 1.71-1.80 (m, 2H), 1.89-2.03 (m, 3H), 3.33-3.40 (m, 2H), 3.77-3.83 (m, 2H), 3.88 (d, *J* = 6.8 Hz, 2H), 5.30-5.36 (m, 1H), 6.76 (s, 1H), 8.55 (s, 1H).

5.1.6.19 Benzyl-4-((6-chloropyrimidin-4-yl)oxy)piperidine-1-carboxylate (12e)



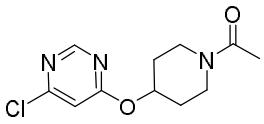
12e (1.26 gm, 54%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3e** (1.57 gm, 1 mole equivalent) following the general procedure described above as a viscous oil. Purity by UPLC: 98.57%.

IR ($CHCl_3$) : 3016, 2960, 2872, 1685, 1570, 1541, 1452, 1350, 1226, 1217, 1087, 1030, 985, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.75-1.77 (m, 2H), 1.98-2.04 (m, 2H), 3.37-3.43 (m, 2H), 3.79-3.85 (m, 2H), 5.14 (s, 2H), 5.30-5.36 (m, 1H), 6.75 (s, 1H), 7.30-7.37 (m, 5H), 8.54 (s, 1H).

ESI/MS (m/z) : 347.9 $(M+H)^+$

5.1.6.20 1-(4-((6-Chloropyrimidin-4-yl)oxy)piperidin-1-yl)ethan-1-one (12f)

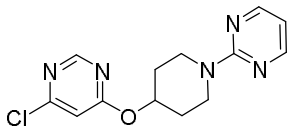


12f (840 mg, 49%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3f** (960 mg, 1 mole equivalent) following the general procedure described above as a pale-yellow oil. Purity by UPLC: 95.17%.

^{1}H NMR ($CDCl_3$) : δ 1.68-1.72 (m, 2H), 1.88-1.89 (m, 2H), 2.35 (s, 3H), 3.33-3.38 (m, 2H), 4.01-4.08 (m, 2H), 5.38-5.42 (m, 1H), 6.65 (s, 1H), 8.26 (s, 1H).

ESI/MS (m/z) : 256.17 $(M+H)^+$

5.1.6.21 4-Chloro-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidine (12g)



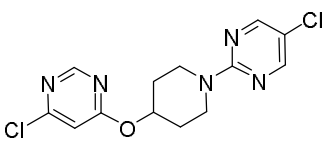
12g (1.10 gm, 49%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3g** (1.25 gm, 1 mole equivalent) following the general procedure described above as a colourless oil. Purity by UPLC: 97.45%.

IR ($CHCl_3$) : 3437, 3095, 2951, 2856, 1728, 1589, 1566, 1508, 1452, 1342, 1311, 1263, 1247, 1085, 1020, 977, 844 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.76-1.85 (m, 2H), 2.04-2.11 (m, 2H), 3.59-3.66 (m, 2H), 4.24-4.30 (m, 2H), 5.39-5.45 (m, 1H), 6.49 (t, *J* = 9.6 Hz, 1H), 6.76 (s, 1H), 8.31 (d, *J* = 4.8 Hz, 2H), 8.57 (s, 1H).

ESI/MS (m/z) : 292.0 $(M+H)^+$

5.1.6.22 5-Chloro-2-(4-((6-chloropyrimidin-4-yl)oxy)piperidin-1-yl) pyrimidine (12h)



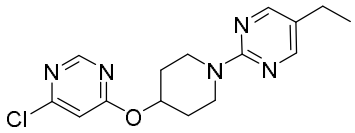
12h (1.10 gm, 49%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3h** (1.25 gm, 1 mole equivalent) following the general procedure described above as an off-white solid. Purity by UPLC: 93.18%.

IR (KBr) **:** 3218, 3095, 2951, 2856, 1727, 1589, 1566, 1508, 1452, 1342, 1311, 1236, 1085, 1020, 977, 854 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.74-1.82 (m, 2H), 2.02-2.10 (m, 2H), 3.59-3.66 (m, 2H), 4.24-4.30 (m, 2H), 5.41-5.45 (m, 1H), 6.76 (s, 1H), 8.31 (d, *J* = 4.8 Hz, 2H), 8.57 (s, 1H).

ESI/MS (m/z) **:** 327.18 $(M+H)^+$

5.1.6.23 2-(4-((6-Chloropyrimidin-4-yl)oxy)piperidin-1-yl)-5-ethylpyrimidine (12i)



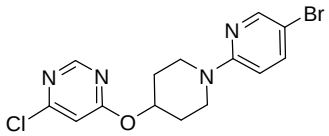
12i (1.21 gm, 56%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3i** (1.4 gm, 1 mole equivalent) following the general procedure described above as white solid. Purity by UPLC: 98.97%.

IR (KBr) **:** 3443, 3076, 2966, 2833, 1604, 1572, 1541, 1452, 1348, 1249, 1213, 1091, 991 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.19 (t, *J* = 7.6 Hz, 3H), 1.75-1.83 (m, 2H), 2.04-2.10 (m, 2H), 2.47 (q, *J* = 7.6 Hz, 2H), 3.54-3.61 (m, 2H), 4.22-4.28 (m, 2H), 5.37-5.43 (m, 1H), 6.76 (s, 1H), 8.18 (s, 2H), 8.56 (s, 1H).

ESI/MS (m/z) **:** 320.1 $(M+H)^+$

5.1.6.24 2-(4-((6-Chloropyrimidin-4-yl)oxy)piperidin-1-yl)-5-ethylpyrimidine (12J)

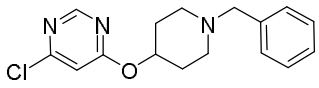


12J (893 mg, 36%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3J** (1.7 gm, 1 mole equivalent) following the general procedure described above as white solid. Purity by UPLC: 91.76%.

^{1}H NMR ($CDCl_3$) **:** δ 1.79-1.87 (m, 2H), 2.05-2.12 (m, 2H), 3.37-3.44 (m, 2H), 3.88-3.94 (m, 2H), 5.35-5.41 (m, 1H), 6.59 (t, *J* = 4.4 Hz, 1H), 6.76 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 8.19 (s, 1H), 8.56 (s, 1H).

ESI/MS (m/z) **:** 370.9 $(M+H)^+$

5.1.6.25 4-((1-Benzylpiperidin-4-yl) oxy)-6-chloropyrimidine (12k)



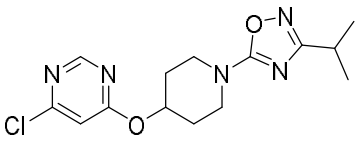
12k (1.12 gm, 54%) was prepared from **10b** (1.0 gm, 1 mole equivalent) and **3k** (1.28 gm, 1 mole equivalent) following the general procedure described above as colourless oil. Purity by UPLC: 97.91%.

IR ($CHCl_3$) **:** 3468, 3010, 2955, 2810, 1570, 1541, 1454, 1352, 1265, 1215, 1085, 1033, 1016, 985 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.77-1.86 (m, 2H), 2.00-2.04 (m, 2H), 2.30-2.34 (m, 2H), 2.72-2.75 (m, 2H), 3.53 (s, 2H), 5.13-5.19 (m, 1H), 6.73 (s, 1H), 7.23-7.33 (m, 5H), 8.53 (s, 1H).

ESI/MS (m/z) **:** 303.9 $(M+H)^+$

5.1.6.26 5-(4-((6-Chloropyrimidin-4-yl)oxy)piperidin-1-yl)-3-isopropyl-1,2, 4-oxadiazole (12l)



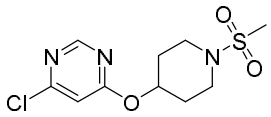
12l (1.45 gm, 35%) was prepared from **10b** (2.0 gm, 1 mole equivalent) and **3l** (2.84 gm, 1 mole equivalent) following the general procedure described above as white solid. m.p: 78.3 °C; Purity by UPLC: 98.11%.

IR (KBr) **:** 3443, 3078, 3057, 2985, 2974, 2949, 2852, 1595, 1568, 1465, 1402, 1354, 1321, 1276, 1261, 1093, 1035, 977 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.29 (d, J = 3.2 Hz, 6H), 1.86-1.95 (m, 2H), 2.06-2.13 (m, 2H), 2.89 (m, 1H), 3.55-3.62 (m, 2H), 3.83-3.89 (m, 2H), 5.38-5.43 (m, 1H), 6.78 (s, 1H), 8.56 (s, 1H).

ESI/MS (m/z) **:** 324.1 $(M+H)^+$

5.1.6.27 4-Chloro-6-((1-(methyl sulfonyl)piperidin-4-yl)oxy)pyrimidine (19m)

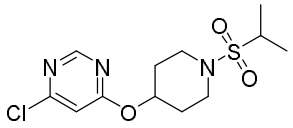


19m (1.21 gm, 61%) was prepared from **10b** (2.0 gm, 1 mole equivalent) and **3m** (2.41 gm, 1 mole equivalent) following the general procedure described above as pale-yellow viscous oil. Purity by UPLC: 91.37%.

^{1}H NMR ($CDCl_3$) : δ 1.68-1.75 (m, 2H), 1.84-1.91 (m, 2H), 3.01 (s, 3H), 3.32-3.38 (m, 2H), 4.12-4.18 (m, 2H), 5.31-5.35 (m, 1H), 6.65 (s, 1H), 8.26 (s, 1H).

ESI/MS (m/z) : 292.24 $(M+H)^+$

5.1.6.28 4-Chloro-6-((1-(isopropyl sulfonyl) piperidin-4-yl) oxy) pyrimidine (19n)

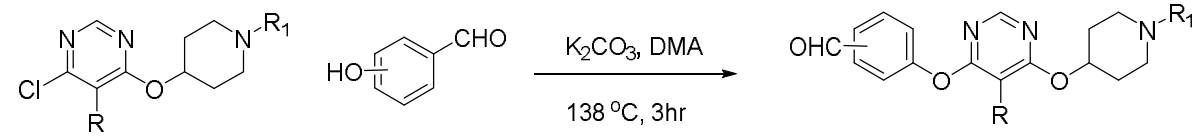


19n (830 mg, 40%) was prepared from **10b** (2.0 gm, 1 mole equivalent) and **3n** (2.78 gm, 1 mole equivalent) following the general procedure described above as off-white solid. Purity by UPLC: 93.56%.

^{1}H NMR ($CDCl_3$) : δ 1.18 (d, J = 6.8 Hz, 6H), 1.68-1.73 (m, 2H), 2.01-2.08 (m, 2H), 2.56-2.61 (m, 1H), 3.35-3.41 (m, 2H), 4.25 (br,s, 2H), 5.31 (br,s, 1H), 6.61 (s, 1H), 8.26 (s, 1H).

ESI/MS (m/z) : 320.18 $(M+H)^+$

5.1.7 Synthesis of Compounds 14 a-e, g, k, l, 15 a-l, 21 a-n & 22 a-m



11 a-l & 18 m-n (R = CH_3)
12 a-l & 19 m (R = H)

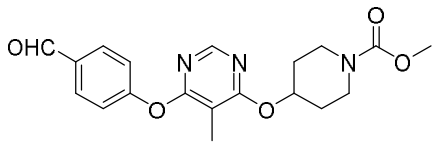
13 (para)
20 (meta)

14 a-e, g, k, l & 21 a-n (R = CH_3)
15 a-l & 22 a-m (R = H)

General procedure:

To a solution of intermediate **11a-e, g, k, l, 12a-l, 18m-n or 19m** (1 mole equivalent) and the hydroxybenzaldehyde **13 or 20** (1 mole equivalent) in N,N-dimethyl formamide (50 mL) was added potassium carbonate (2 eq) at 27 °C and the reaction mixture was stirred for 24 hours at 70 °C. Then, the reaction mixture was cooled and poured into ice-cold water (250 ml) and was extracted with ethyl acetate (2 x 50 ml). The organic extract was washed with water (2 x 100 ml), brine (100 ml) and was dried over sodium sulphate and was evaporated under reduced pressure to obtained the crude product. The crude product was purified through column chromatography using 15-20% ethyl acetate in hexane to give the desired respective intermediates **14a-e, g, k, l, 15a-l, 21 a-n or 22 a-m**.

5.1.7.1 Methyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (14a)



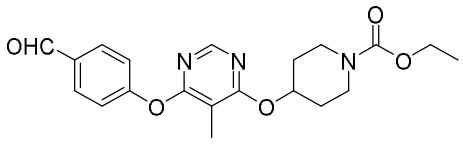
14a (1.72 gm, 92%) was prepared from **11a** (1.5 gm, 5.14 mmol) and **13** (1.29 gm, 5.14 mmol) following the general procedure described above as a colourless viscous gum. Purity by UPLC: 96.55%.

IR ($CHCl_3$) **:** 3375, 2955, 2862, 1701, 1685, 1566, 1411, 1259, 1215, 1109, 1026, 844, 763 cm^{-1}

^1H NMR ($CDCl_3$) **:** δ 1.77-1.85 (m, 2H), 1.98-2.04 (m, 2H), 2.18 (s, 3H), 3.42-3.48 (m, 2H), 3.71 (s, 3H), 3.75-3.77 (m, 2H), 5.33-5.39 (m, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 371.9 $(M+H)^+$

5.1.7.2 Ethyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (14b):



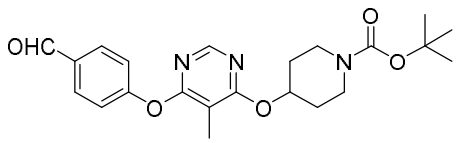
14b (1.22 gm, 36%) was prepared from **11b** (1.0 gm, 3.43 mmol) and **13** (0.81 gm, 3.43 mmol) following the general procedure described above as a colourless oil. Purity by UPLC: 96.51%.

IR ($CHCl_3$) **:** 3387, 2937, 2854, 1728, 1612, 1514, 1406, 1323, 1236, 1172, 1111, 1068, 1001, 898, 829 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.27 (t, *J* = 7.2 Hz, 3H), 1.63-1.69 (m, 2H), 1.92-1.97 (m, 2H), 2.11 (s, 3H), 3.32-3.38 (m, 2H), 3.61-3.67 (m, 2H), 4.05 (q, *J* = 10.0 Hz & 2.8 Hz, 2H), 5.30-5.32 (m, 1H), 7.38 (d, *J* = 6.8 Hz, 2H), 7.95 (d, *J* = 4.4 Hz, 2H), 8.29 (s, 1H), 9.98 (s, 1H).

ESI/MS (m/z) **:** 385.9 $(M+H)^+$

5.1.7.3 *t*-Butyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (14c):



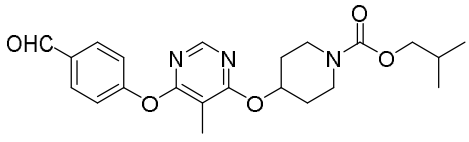
14c (0.88 gm, 66%) was prepared from **11c** (1.0 gm, 3.05 mmol) and **13** (0.37 gm, 3.05 mmol) following the general procedure described above as a viscous oil. Purity by UPLC: 98.27%.

IR ($CHCl_3$) **:** 3018, 2980, 2870, 1685, 1570, 1425, 1261, 1217, 1112, 1026, 758 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.48 (s, 9H), 1.75-1.81 (m, 2H), 1.96-2.01 (m, 2H), 2.18 (s, 3H), 3.34-3.41 (m, 2H), 3.70-3.76 (m, 2H), 5.32-5.36 (m, 1H), 7.28 (d, *J* = 6.4 Hz, 2H), 7.94 (d, *J* = 6.8 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 414.0 $(M+H)^+$

5.1.7.4 *i*-Butyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (14d):



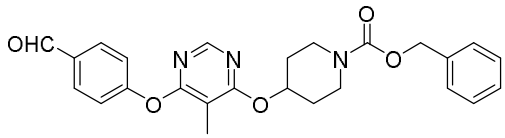
14d (1.15 gm, 63%) was prepared from **11d** (1.0 gm, 3.05 mmol) and **13** (0.373 gm, 3.05 mmol) following the general procedure described above as a pale-yellow viscous oil. Purity by UPLC: 92.56%.

IR ($CHCl_3$) **:** 2985, 2966, 2937, 1741, 1612, 1569, 1542, 1512, 1467, 1454, 1406, 1380, 1350, 1321, 1271, 1240, 1211, 1174, 1120, 1066, 1033, 997, 964, 950, 891, 858, 840, 675 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.77-1.85 (m, 2H), 1.92-2.04 (m, 3H), 2.18 (s, 3H), 3.42-3.48 (m, 2H), 3.75-3.81 (m, 2H), 3.89 (d, *J* = 6.8 Hz, 2H), 5.30-5.38 (m, 1H), 7.28 (d, *J* = 6.8 Hz, 2H), 7.94 (d, *J* = 9.2 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H)

ESI/MS (m/z) **:** 413.9 $(M+H)^+$

5.1.7.5 Benzyl 4-((6-(4-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (14e):



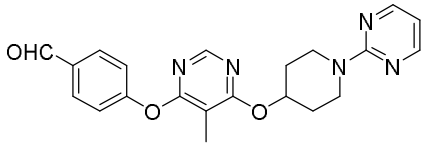
14e (0.556 gm, 46%) was prepared from **11e** (1.0 gm, 2.76 mmol) and **13** (0.338 gm, 2.76 mmol) following the general procedure described above as a colourless oil. Purity by UPLC: 93.54%.

IR ($CHCl_3$) **:** 2968, 2872, 1774, 1726, 1616, 1508, 1438, 1327, 1199, 1166, 1122, 1068, 1014, 964, 842 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.77-1.83 (m, 2H), 2.01-2.04 (m, 2H), 2.17 (s, 3H), 3.45-3.52 (m, 2H), 3.77-3.83 (m, 2H), 5.15 (s, 2H), 5.35-5.38 (m, 1H), 7.27-7.38 (m, 7H), 7.94 (d, *J* = 9.2 Hz, 2H), 8.25 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 447.9 $(M+H)^+$

5.1.7.6 4-((5-Methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)-oxy)benzaldehyde (14g)



14g (0.66 gm, 53%) was prepared from **11g** (1.0 gm, 3.27 mmol) and **13** (0.4 gm, 3.27 mmol) following the general procedure described above as a colourless oil. Purity by UPLC: 97.76%.

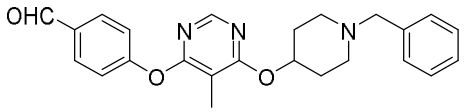
IR ($CHCl_3$) **:** 3412, 2989, 2926, 2854, 1703, 1585, 1550, 1506, 1415, 1356, 1298, 1267, 1217, 1161, 1118, 1028 cm^{-1}

^{1}H NMR **:** δ 1.85-188 (m, 2H), 2.07-2.12 (m, 2H), 2.19 (s, 3H), 3.72-3.78 (m,

($CDCl_3$) 2H), 4.18-4.24 (m, 2H), 5.42-4.57 (m, 1H), 6.49 (t, *J* = 4.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 6.2 Hz, 2H), 8.28 (s, 1H), 8.33 (d, *J* = 4.8 Hz, 2H), 10.00 (s, 1H).

ESI/MS (m/z) **:** 391.9 $(M+H)^+$

5.1.7.7 4-((6-((1-Benzylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)-benzaldehyde (14k)



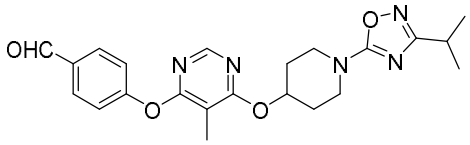
14k (0.43 gm, 35%) was prepared from **11k** (1.0 gm, 3.15 mmol) and **13** (0.384 gm, 3.15 mmol) following the general procedure described above as a colourless oil. Purity by UPLC: 95.73%.

IR ($CHCl_3$) **:** 3468, 3010, 2955, 2810, 1735, 1570, 1541, 1454, 1352, 1265, 1215, 1085, 1033, 1016, 985 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.77-1.86 (m, 2H), 2.00-2.04 (m, 2H), 2.15 (s, 3H), 2.30-2.34 (m, 2H), 2.72-2.75 (m, 2H), 3.53 (s, 2H), 5.13-5.19 (m, 1H), 6.73 (s, 1H), 7.23-7.33 (m, 4H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 8.53 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 404.4 $(M+H)^+$

5.1.7.8 4-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl) oxy) benzaldehyde (14l)



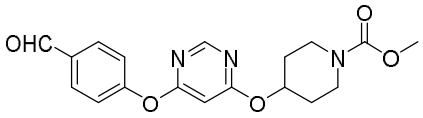
14l (0.75 gm, 62%) was prepared from **11l** (1.0 gm, 2.96 mmol) and **13** (0.362 gm, 2.96 mmol) following the general procedure described in the beginning as a colourless oil. Purity by UPLC: 98.01%.

IR ($CHCl_3$) **:** 3412, 3018, 2974, 2933, 2874, 1701, 1622, 1570, 1502, 1429, 1411, 1383, 1261, 1217, 1157, 1112, 1030, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.29 (d, *J* = 6.8 Hz, 6H), 1.94-1.97 (m, 2H), 2.08-2.11 (m, 2H), 2.19 (s, 3H), 2.88-2.92 (m, 1H), 3.62-3.68 (m, 2H), 3.83-3.88 (m, 2H), 5.41-5.44 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 6.4 Hz, 2H), 8.26 (s, 1H), 10.00 (s, 1H).

ESI/MS (m/z) **:** 423.9 $(M+H)^+$

5.1.7.9 Methyl 4-((6-(4-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (15a)



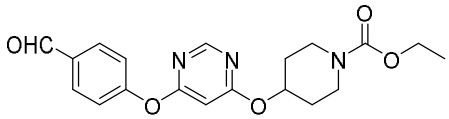
15a (1.72 gm, 81%) was prepared from **12a** (1.5 gm, 5.52 mmol) and **13** (0.674 gm, 5.52 mmol) following the general procedure described in the beginning as a viscous gum. Purity by UPLC: 97.23%.

IR ($CHCl_3$) **:** 3375, 2955, 2862, 1701, 1685, 1566, 1411, 1259, 1215, 1109, 1026, 844, 763 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.72-1.80 (m, 2H), 1.98-2.02 (m, 2H), 3.33-3.40 (m, 2H), 3.71 (s, 3H), 3.78-3.81 (m, 2H), 5.30-5.35 (m, 1H), 6.24 (s, 1H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 2H), 8.42 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 380.0 $(M+Na)^+$

5.1.7.10 Ethyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (15b)



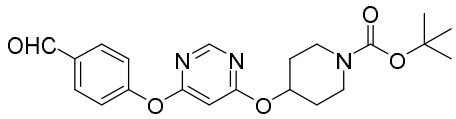
15b (1.41 gm, 70%) was prepared from **12b** (1.5 gm, 5.25 mmol) and **13** (0.641 gm, 5.25 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 96.89%.

IR (KBr) **:** 3429, 2989, 2864, 1687, 1581, 1438, 1246, 1211, 1134, 1028, 854, 767 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.27 (t, *J* = 7.4 Hz, 3H), 1.71-1.80 (m, 2H), 1.97-2.04 (m, 2H), 3.32-3.38 (m, 2H), 3.78-3.83 (m, 2H), 4.15 (q, *J* = 14.2 and 6.8 Hz, 2H), 5.30-5.35 (m, 1H), 6.24 (s, 1H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 8.43 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 372.1 $(M+H)^+$

5.1.7.11 *t*-Butyl 4-((6-(4-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (15c)



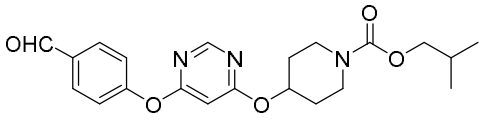
15c (0.72 gm, 57%) was prepared from **12c** (1.0 gm, 3.19 mmol) and **13** (0.389 gm, 3.19 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 98.84 %.

IR (KBr) **:** 3383, 2970, 2868, 1687, 1581, 1469, 1421, 1253, 1215, 1161, 1024, 846, 765 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.47 (s, 9H), 1.71-1.77 (m, 2H), 1.96-2.01 (m, 2H), 3.25-3.31(m, 2H), 3.76-3.79 (m, 2H), 5.28-5.32 (m, 1H), 6.24 (s, 1H), 7.30 (d, *J* = 6.4 Hz, 2H), 7.95 (d, *J* = 6.8 Hz, 2H), 8.42 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 400.0 $(M+H)^+$

5.1.7.12 *i*-Butyl 4-((6-(4-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (15d)



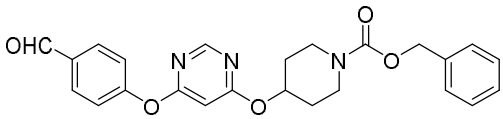
15d (0.96 gm, 78%) was prepared from **12d** (1.0 gm, 3.19 mmol) and **13** (0.386 gm, 5.14 mmol) following the general procedure described in the beginning as colourless viscous oil. Purity by UPLC: 97.71%.

IR ($CHCl_3$) **:** 3464, 3018, 2964, 1687, 1581, 1460, 1251, 1217, 1161, 1035, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.72-1.80 (m, 2H), 1.91-1.96 (m, 1H), 1.98-2.04 (m, 2H), 3.33-3.39 (m, 2H), 3.79-3.85 (m, 2H), 3.88 (d, *J* = 6.4 Hz, 2H), 5.30-5.36 (m, 1H), 6.24 (s, 1H), 7.30 (d, *J* = 9.2 Hz, 2H), 7.95 (d, *J* = 9.2 Hz, 2H), 8.42 (s, 1H), 10.01 (s, 1H).

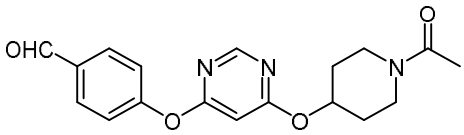
ESI/MS (m/z) **:** 400.1 $(M+H)^+$

5.1.7.13 Benzyl 4-((6-(4-formylphenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (15e)



15e (1.03 gm, 57%) was prepared from **12e** (1.5 gm, 4.31 mmol) and **13** (0.527 gm, 4.31 mmol) following the general procedure described in the beginning as pale brown viscous oil product and directly used in the next step.

5.1.7.14 4-((6-((1-Acetylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (15f)



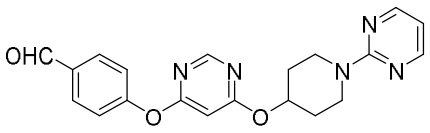
15f (1.50 gm, 78%) was prepared from **12f** (1.5 gm, 5.87 mmol) and **13** (0.716 gm, 5.87 mmol) following the general procedure described in the beginning as colourless viscous oil. Purity by UPLC: 91.64%.

IR ($CHCl_3$) **:** 3015, 2956, 2935, 2708, 1701, 1577, 1601, 1502, 1435, 1251, 1176, 1050, 855 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.65-1.68 (m, 2H), 1.94-1.97 (m, 2H), 2.02 (s, 3H), 3.17-3.35 (m, 2H), 3.68-3.74 (m, 2H), 5.27-5.31 (m, 1H), 6.46 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 8.46 (a, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 342.17 $(M+H)^+$

5.1.7.15 4-((6-((1-(Pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzaldehyde (15g)



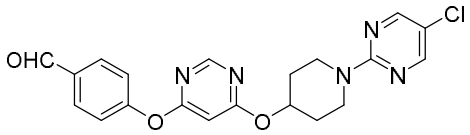
15g (0.57 gm, 46%) was prepared from **12g** (1.0 gm, 3.43 mmol) and **13** (0.420 gm, 3.43 mmol) following the general procedure described in the beginning as a colourless viscous oil. Purity by UPLC: 95.83%.

IR ($CHCl_3$) **:** 3412, 2989, 2926, 2854, 1703, 1585, 1550, 1506, 1415, 1356, 1298, 1267, 1217, 1161, 1118, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.85-188 (m, 2H), 2.07-2.12 (m, 2H), 3.72-3.78 (m, 2H), 4.18-4.24 (m, 2H), 5.42-4.57 (m, 1H), 6.22 (s, 1H), 6.49 (t, *J* = 4.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 6.2 Hz, 2H), 8.28 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 2H), 10.00 (s, 1H).

ESI/MS (m/z) : 378.4 $(M+H)^+$

5.1.7.16 4-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzaldehyde (15h)



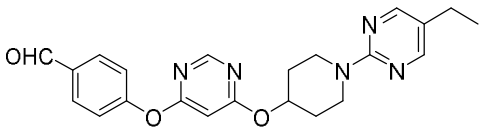
15h (1.01 gm, 66%) was prepared from **12h** (1.0 gm, 3.07 mmol) and **13** (0.37 gm, 3.07 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 93.86%.

IR ($CHCl_3$) : 3425, 3017, 2989, 2926, 2854, 1703, 1585, 1550, 1506, 1415, 1356, 1298, 1267, 1217, 1161, 1118, 1028 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.87-191 (m, 2H), 2.07-2.12 (m, 2H), 3.72-3.78 (m, 2H), 4.18-4.24 (m, 2H), 5.42-4.57 (m, 1H), 6.22 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 6.2 Hz, 2H), 8.28 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 2H), 10.00 (s, 1H).

ESI/MS (m/z) : 412.5 $(M+H)^+$

5.1.7.17 4-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy)benzaldehyde (15i)



15h (0.78 gm, 64%) was prepared from **12h** (1.0 gm, 3.13 mmol) and **13** (0.38 gm, 3.13 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 93.86%.

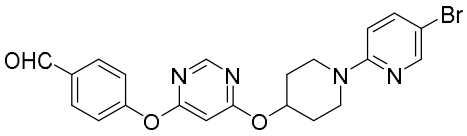
IR ($CHCl_3$) : 3115, 3015, 2989, 2926, 2854, 1703, 1585, 1550, 1506, 1415, 1356, 1298, 1267, 1217, 1161, 1118, 1028, 953, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.16 (t, *J* = 8.0 Hz, 3H), 1.81-1.89 (m, 2H), 2.04-2.12 (m, 2H), 2.47 (q, *J* = 15.2 Hz, 2H), 3.67-3.73 (m, 2H), 4.16-4.22 (m, 2H),

5.42-5.46 (m, 1H), 6.22 (s, 1H), 7.27 (d, *J* = 9.6 Hz, 2H), 7.94 (d, *J* = 6.4 Hz, 2H), 8.19 (s, 2H), 8.28 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 406.5 $(M+H)^+$

5.1.7.18 4-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)--oxy) benzaldehyde (15J)



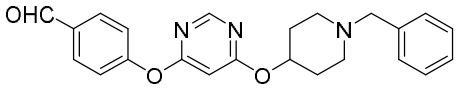
15J (0.7 gm, 59%) was prepared from **12J** (1.0 gm, 2.71 mmol) and **13** (0.33 gm, 2.71 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 93.86%.

IR ($CHCl_3$) **:** 3115, 3015, 2989, 2926, 2854, 1703, 1585, 1550, 1506, 1415, 1356, 1298, 1267, 1217, 1161, 1118, 1028, 953, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.81-1.89 (m, 2H), 2.04-2.12 (m, 2H), 3.67-3.73 (m, 2H), 4.16-4.22 (m, 2H), 5.42-5.46 (m, 1H), 6.22 (s, 1H), 7.27 (d, *J* = 9.6 Hz, 2H),7.42 (s, 1H), 7.94 (d, *J* = 6.4 Hz, 2H), 8.19 (s, 2H), 8.28 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 406.5 $(M+H)^+$

5.1.7.19 4-((6-((1-Benzylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzalde-hyde (15k)



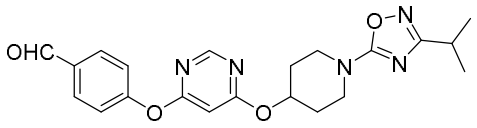
15k (0.50 gm, 41%) was prepared from **12k** (1.0 gm, 3.29 mmol) and **13** (0.402 gm, 3.29 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 93.88%.

IR (KBr) **:** 3437, 3018, 2956, 2814, 1701, 1581, 1502, 1460, 1411, 1251, 1161, 1037, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.79-1.87 (m, 2H), 2.02-2.07 (m, 2H), 2.30-2.35 (m, 2H), 2.74-2.77 (m, 2H), 3.57 (s, 2H), 5.13-5.29 (m, 1H), 6.22 (s, 1H), 7.23-7.33 (m, 7H), 7.95 (d, *J* = 9.2 Hz, 2H), 8.41 (s, 1H), 10.00 (s, 1H).

ESI/MS (m/z) **:** 390.2 $(M+H)^+$

5.1.7.20 4-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzaldehyde (15l)



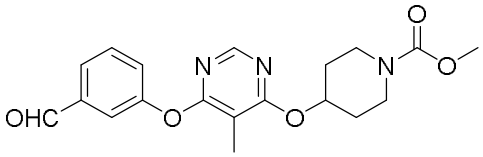
14l (0.7 gm, 56%) was prepared from **11l** (1.0 gm, 3.09 mmol) and **13** (0.377 gm, 3.09 mmol) following the general procedure described in the beginning as a colourless oil. Purity by UPLC: 98.01%.

IR ($CHCl_3$) **:** 3285, 3018, 2974, 2933, 2874, 1701, 1622, 1570, 1502, 1429, 1411, 1383, 1261, 1217, 1157, 1112, 1030, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.30 (d, *J* = 6.8 Hz, 6H), 1.94-1.97 (m, 2H), 2.08-2.11 (m, 2H), 2.88-2.92 (m, 1H), 3.62-3.68 (m, 2H), 3.83-3.88 (m, 2H), 5.41-5.44 (m, 1H), 6.23 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 6.4 Hz, 2H), 8.26 (s, 1H), 9.90 (s, 1H).

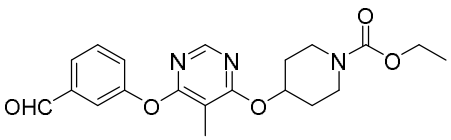
ESI/MS (m/z) **:** 410.2 $(M+H)^+$

5.1.7.21 Methyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (21a)



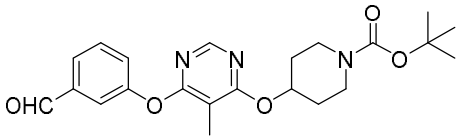
21a (0.9 gm, 71%) was prepared from **11a** (1.0 gm, 3.50 mmol) and **20** (0.427 gm, 3.50 mmol) following the general procedure described in the beginning as a colourless oil and directly used in the next step.

5.1.7.22 Ethyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (21b)



21b (1.01 gm, 46%) was prepared from **11b** (1.0 gm, 3.34 mmol) and **20** (0.407 gm, 3.34 mmol) following the general procedure described in the beginning as a colourless oil and directly used in the next step.

5.1.7.23 4-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (21c)



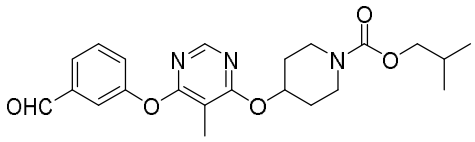
21c (1.01 gm, 81%) was prepared from **11c** (1.0 gm, 3.05 mmol) and **20** (0.373 gm, 3.05 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 98.57%.

IR ($CHCl_3$) **:** 3010, 2978, 2866, 1701, 1585, 1570, 1425, 1365, 1261, 1232, 1143, 1026, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.48 (s, 9H), 1.76-1.81 (m, 2H), 1.97-2.01 (m, 2H), 2.18 (s, 3H), 3.35-3.41 (m, 2H), 3.70-3.76 (m, 2H), 5.32-5.36 (m, 1H), 7.39-7.42 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 8.23 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 414.0 $(M+H)^+$

5.1.7.24 *i*-Butyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (21d)



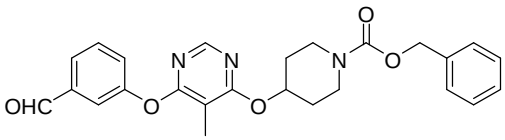
21d (0.55 gm, 45%) was prepared from **11d** (1.0 gm, 3.05 mmol) and **20** (0.373 gm, 3.05 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 95.57%.

IR ($CHCl_3$) **:** 3126, 3051, 2895, 2756, 1753, 1705, 1684, 1582, 1564, 1426, 1396, 1325, 1275, 1234, 1169, 1124, 1064, 1023 985 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.92 (d, *J* = 6.8 Hz, 6H), 1.66-1.71 (m, 2H), 1.88-1.92 (m, 1H), 1.96-2.01 (m, 2H), 2.15 (s, 3H), 3.36 (brs, 2H), 3.68 (brs, 2H), 3.82 (d, *J* = 7.2 Hz, 2H), 5.32-5.35 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 9.99 (s, 1H).

ESI/MS (m/z) **:** 414.12 $(M+H)^+$

5.1.7.25 Benzyl 4-((6-(3-formylphenoxy)-5-methylpyrimidin-4-yl)oxy) piperidine-1-carboxylate (21e)



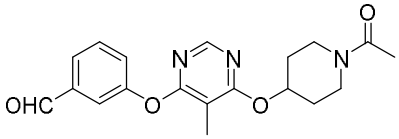
21e (1.01 gm, 81%) was prepared from **11e** (1.0 gm, 2.76 mmol) and **20** (0.338 gm, 2.76 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 89.76%.

IR ($CHCl_3$) **:** 3216, 3152, 3056, 2945, 2856, 1745, 1689, 1579, 1554, 1465, 1409, 1352,1255, 1235, 1172, 1134, 1055, 1008 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.68-1.72 (m, 2H), 1.81-1.95 (m, 2H), 2.14 (s, 3H), 3.30 (brs, 2H), 3.75-3.78 (m, 2H), 5.10 (s, 2H), 5.35 (brs, 1H), 7.10 (d, *J* = 6.8 Hz, 1H), 7.15-7.38 (m, 6H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 8.27 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 448.21 $(M+H)^+$

5.1.7.26 3-((6-((1-Acetylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy) benzaldehyde (21f)



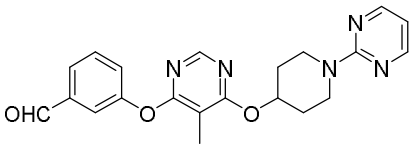
21f (0.98 gm, 77%) was prepared from **11f** (1.0 gm, 3.71 mmol) and **20** (0.45 gm, 3.71 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 94.21%.

IR ($CHCl_3$) **:** 3326, 3010, 2925, 2751, 1750, 1710, 1618, 1595, 1561, 1428, 1301, 1268, 1245, 1156, 1115, 1056, 985, 856 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.80-1.88 (m, 2H), 2.02-2.12 (m, 2H), 2.15 (s, 3H), 2.35 (s, 3H), 3.66-3.72 (m, 2H), 3.98-4.05 (m, 2H), 5.41-5.45 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 8.28 (s, 1H), 10.05 (s, 1H).

ESI/MS (m/z) **:** 356.12 $(M+H)^+$

5.1.7.27 3-((5-Methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (21g)



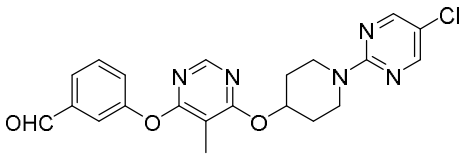
21g (0.9 gm, 72%) was prepared from **11g** (1.0 gm, 3.27 mmol) and **20** (0.4 gm, 3.27 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 96.75%.

IR ($CHCl_3$) **:** 3135, 2964, 3015, 2859, 2755, 1741, 1569, 1556, 1490, 1426, 1363, 1309, 1284, 1269, 1167, 1028, 1005, 854 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.68-1.73 (m, 2H), 1.98-2.03 (m, 2H), 2.15 (s, 3H), 3.65-3.71 (m, 2H), 4.11-4.16 (m, 2H), 5.40-5.42 (m, 1H), 6.62 (t, *J* = 5.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 8.37 (d, *J* = 4.8 Hz, 2H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 392.10 $(M+H)^+$

5.1.7.28 3-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl) oxy) benzaldehyde (21h)

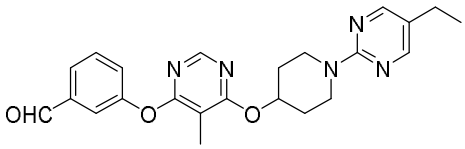


21h (0.76 gm, 63%) was prepared from **11h** (1.0 gm, 2.94 mmol) and **20** (0.36 gm, 2.94 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 99.24%.

^{1}H NMR ($CDCl_3$) **:** δ 1.82-1.90 (m, 2H), 2.04-2.11 (m, 2H), 2.19 (s, 3H), 3.72-3.78 (m, 2H), 4.12-4.18 (m, 2H), 5.41-5.47 (m,1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 3H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 425.8 $(M+H)^+$

5.1.7.29 3-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl) oxy) benzaldehyde (21i)



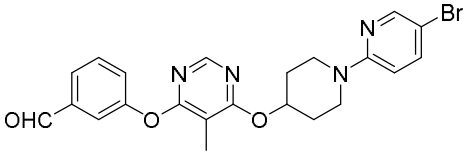
21i (0.85 gm, 70%) was prepared from **11i** (1.0 gm, 2.94 mmol) and **20** (0.36 gm, 2.94 mmol) following the general procedure described in the beginning as off-white solid. Purity by UPLC: 98.25%.

IR (KBr) **:** 3111, 3065, 2956, 2845, 2756, 1754, 1705, 1589, 1565, 1504, 1452, 1406, 1269, 1239, 1195, 1121, 1015, 958 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.09 (t, *J* = 6.8 Hz, 3H), 1.68-1.72 (m, 2H), 1.88-1.99 (m, 2H), 2.16 (s, 3H), 2.44 (brs, 2H), 3.66 (brs, 2H), 4.12 (brs, 2H), 5.41 (brs, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 8.27-8.36 (m, 3H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 420.20 $(M+H)^+$

5.1.7.30 3-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl) oxy) benzaldehyde (21J)



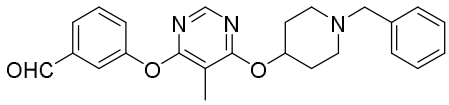
21J (0.6 gm, 51%) was prepared from **11J** (1.0 gm, 2.61 mmol) and **20** (0.32 gm, 2.61 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 99.13%.

IR (KBr) **:** 3433, 2962, 2833, 1583, 1566, 1554, 1447, 1388, 1357, 1313, 1238, 1188, 1155, 1118, 1043, 1026 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.86-1.93 (m, 2H), 2.07-2.12 (m, 2H), 2.18 (s, 3H), 3.47-3.53 (m, 2H), 3.85-3.91 (m, 2H), 5.39-5.42 (m, 1H), 6.61 (d, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.64 (s, 1H), 7.74 (d, 7.2 Hz, 1H), 8.20 (s, 1H), 8.24 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 384.7 $(M+H)^+$

5.1.7.31 3-((6-((1-Benzylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy) benzaldehyde (21k)



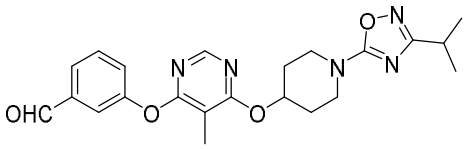
21k (0.45 gm, 37%) was prepared from **11k** (1.0 gm, 3.15 mmol) and **20** (0.38 gm, 3.15 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 95.21%.

IR (KBr) **:** 3155, 3025, 2924, 2765, 1703, 1564, 1485, 1421, 1389, 1284, 1215, 1155, 1106, 1035, 956, 877 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.68-1.79 (m, 2H), 1.90-1.98 (m, 2H), 2.14 (s, 3H), 2.56 (brs, 2H), 2.82 (brs, 2H), 3.75 (s, 2H), 5.28 (brs, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.33-7.39 (m, 5H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 8.25 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 404.6 $(M+H)^+$

5.1.7.32 3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl) oxy)benzaldehyde (21l)



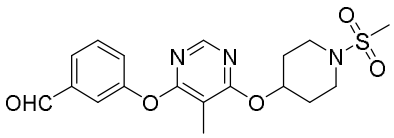
21l (0.9 gm, 74%) was prepared from **11l** (1.0 gm, 2.96 mmol) and **20** (0.36 gm, 2.96 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 95.21%.

IR (KBr) **:** 3410, 3018, 2974, 2931, 2874, 1703, 1626, 1570, 1437, 1411, 1383, 1261, 1217, 1107, 1030, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.30 (d, *J* = 6.8 Hz, 6H), 1.92-1.99 (m, 2H), 2.07-2.14 (m, 2H), 2.15 (s, 3H), 2.87 (m, 1H), 3.62-3.68 (m, 2H), 3.83-3.89 (m, 2H), 5.41-5.45 (m, 1H),7.42 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 424.1 $(M+H)^+$

5.1.7.33 3-((5-Methyl-6-((1-(methyl sulfonyl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy)benzaldehyde (21m)



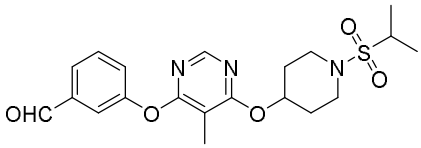
21m (0.45 gm, 36%) was prepared from **18m** (1.0 gm, 3.27 mmol) and **20** (0.4 gm, 3.27 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 92.35%.

IR (KBr) **:** 3354, 3068, 2935, 2860, 1762, 1705, 1583, 1535, 1426, 1356, 1215, 1158, 1050, 951 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.82-1.86 (m, 2H), 2.03-2.08 (m, 2H), 2.14 (s, 3H), 2.92 (s, 3H), 3.20-3.25 (m, 2H), 3.35 (brs, 2H), 5.31-5.36 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 8.28 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 392.12 $(M+H)^+$

5.1.7.34 3-((6-((1-(Isopropylsulfonyl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl)oxy)benzaldehyde (21n)



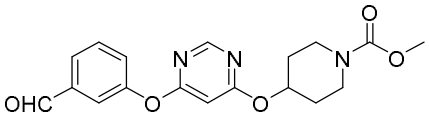
21n (0.72 gm, 59%) was prepared from **18n** (1.0 gm, 3.00 mmol) and **20** (0.366 gm, 3.00 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 92.35%.

IR (KBr) **:** 3422, 3156, 3056, 2935, 2812, 1735, 1710, 1584, 1452, 1415, 1358, 1271, 1150, 1115, 1056, 984, 850 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.25 (d, *J* = 6.8 Hz, 6H), 1.71-1.80 (m, 2H), 2.01-2.06 (m, 2H), 2.14 (s, 3H), 2.18-2.21 (m, 1H), 3.32-3.40 (m, 2H), 3.48-3.55 (m, 2H), 5.34 (brs, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 420.21 $(M+H)^+$

5.1.7.35 Methyl 4-((6-(3-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (22a)

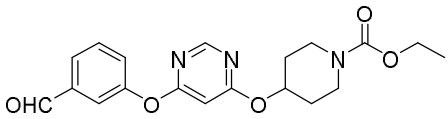


22a (1.12 gm, 77%) was prepared from **12a** (1.0 gm, 3.68 mmol) and **20** (0.45 gm, 3.68 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 98.25%.

^{1}H NMR ($CDCl_3$) : δ 1.74-1.78 (m, 2H), 1.97-2.01 (m, 2H), 3.33-3.42 (m, 2H), 3.71 (s, 3H), 3.78-3.80 (m, 2H), 5.30-5.33 (m, 1H), 6.21 (s, 1H), 7.40-7.43 (m, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 8.40 (s, 1H), 10.08 (s, 1H).

ESI/MS (m/z) : 357.9 $(M+H)^+$

5.1.7.36 Ethyl 4-((6-(3-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (22b)

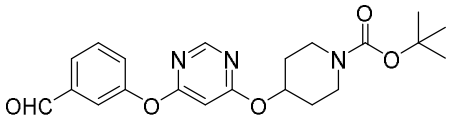


22b (0.84 gm, 67%) was prepared from **12b** (1.0 gm, 3.50 mmol) and **20** (0.427 gm, 3.50 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 97.29%.

^{1}H NMR ($CDCl_3$) : δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.71-1.79 (m, 2H), 1.97-2.01 (m, 2H), 3.32-3.38 (m, 2H), 3.80-3.83 (m, 2H), 4.16 (q, *J* = 14.2 & 6.8 Hz, 2H), 5.29-5.35 (m, 1H), 6.21 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.41 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) : 372.0 $(M+H)^+$

5.1.7.37 *t*-Butyl 4-((6-(3-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (22c)

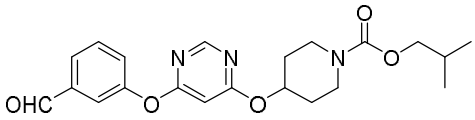


22c (0.716 gm, 58%) was prepared from **12c** (1.0 gm, 3.19 mmol) and **20** (0.389 gm, 3.19 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 92.54%.

^{1}H NMR ($CDCl_3$) : δ 1.47 (s, 9H), 1.71-1.76 (m, 2H), 1.96-2.01 (m, 2H), 3.24-3.31 (m, 2H), 3.76-3.79 (m, 2H), 5.28-5.32 (m, 1H), 6.20 (s, 1H), 7.40-7.43 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.78 (d, *J* = 6.4 Hz, 1H), 8.41 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) : 400.2 (M+H)+

5.1.7.38 *i*-Butyl 4-((6-(3-formylphenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (22d)



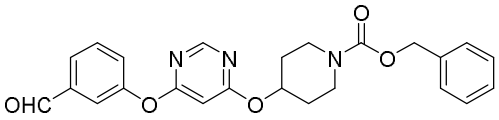
22d (1.02 gm, 83%) was prepared from **12d** (1.0 gm, 3.19 mmol) and **20** (0.39 gm, 3.19 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 98.96 %.

IR ($CHCl_3$) : 3016, 2962, 2874, 1701, 1581, 1460, 1450, 1251, 1230, 1170, 1035, 837, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.94 (d, *J* = 6.8 Hz, 6H), 1.73-1.79 (m, 2H), 1.98-2.04 (m, 3H), 3.33-3.39 (m, 2H), 3.79-3.85 (m, 2H), 3.88 (d, *J* = 6.4 Hz, 2H), 5.29-5.34 (m, 1H), 6.21 (s, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 8.40 (s, 1H), 10.02 (s, 1H).

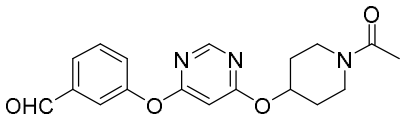
ESI/MS (m/z) : 401.2 $(M+H)^+$

5.1.7.39 Benzyl 4-((6-(3-formyl-phenoxy)pyrimidin-4-yl)oxy)piperidine-1-carboxylate (22e)



22e (0.68 gm, 56%) was prepared from **12e** (1.0 gm, 2.88 mmol) and **20** (0.35 gm, 2.88 mmol) following the general procedure described in the beginning as a viscous oil and directly used in next step.

5.1.7.40 3-((6-((1-Acetylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (22f)



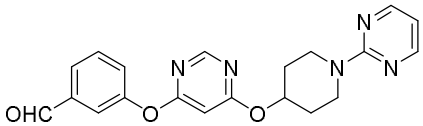
22f (0.63 gm, 49%) was prepared from **12f** (1.0 gm, 2.88 mmol) and **20** (0.35 gm, 2.88 mmol) following the general procedure described in the beginning as a viscous oil. Purity by UPLC: 98.96%.

IR ($CHCl_3$) **:** 3411, 3054, 2954, 2871, 1710, 1685, 1595, 1564, 1467, 1354, 1251, 1175, 1065, 975 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.68-1.79 (m, 2H), 1.93-1.99 (m, 2H), 2.16 (s, 3H), 3.33-3.37 (m, 2H), 3.70-3.92 (m, 2H), 5.27-5.32 (m, 1H), 6.45 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 342.14 $(M+H)^+$

5.1.7.41 3-((6-((1-(Pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzaldehyde (22g)



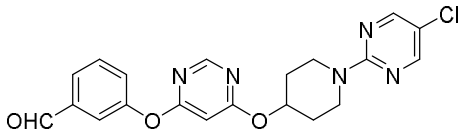
22g (1.04 gm, 83%) was prepared from **12g** (1.0 gm, 3.43 mmol) and **20** (0.42 gm, 3.43 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 96.72%.

IR (KBr) **:** 3411, 3052, 2961, 2746, 1710, 1585, 1493, 1254, 1139, 1115, 1061, 921 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.62-1.70 (m, 2H), 2.00-2.06 (m, 2H), 3.48 (brs, 2H), 4.26 (brs, 2H), 5.33-5.38 (m, 1H), 6.45 (s, 1H), 6.62 (t, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 5.2 Hz, 2H), 8.48 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) : 378.15 $(M+H)^+$

5.1.7.42 3-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (22h)



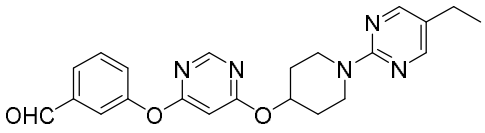
22h (0.78 gm, 64%) was prepared from **12h** (1.0 gm, 3.07 mmol) and **20** (0.37 gm, 3.07 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 95.21%.

IR (KBr) : 3435, 3138, 3051, 2826, 1710, 1685, 1572, 1255, 1115, 1075, 1012, 987 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 1.68-1.72 (m, 2H), 2.02-2.06 (m, 2H), 3.52-3.58 (m, 2H), 4.21-4.25 (m, 2H), 8.35-5.39 (m, 1H), 6.45 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.41 (s, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 8.42 (s, 2H), 8.48 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) : 412.12 $(M+H)^+$

5.1.7.43 3-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzaldehyde (22i)



22i (0.652 gm, 53%) was prepared from **12i** (1.0 gm, 3.13 mmol) and **20** (0.382 gm, 3.43 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 98.43%.

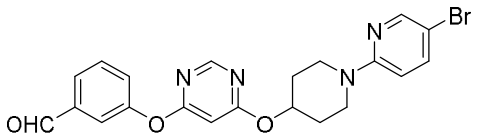
IR (KBr) : 3379, 3012, 2960, 2858, 2733, 1699, 1610, 1583, 1554, 1452,

1413, 1361, 1330, 1257, 1174, 1124, 1028, 985, 794 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.20 (t, *J* = 7.6 Hz, 3H), 1.76-1.84 (m, 2H), 2.05-2.011 (m, 2H), 2.46 (q, *J* = 15.2 Hz, 2H), 3.54-3.60 (m, 2H), 4.24-4.30 (m, 2H), 5.36-5.41 (m, 1H), 6.21 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.18 (s, 2H), 8.43 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 406.1 $(M+H)^+$

5.1.7.44 3-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy)benzaldehyde (22J)



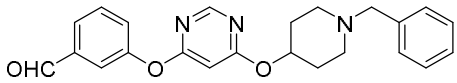
22J (0.85 gm, 71%) was prepared from **12J** (1.0 gm, 2.71 mmol) and **20** (0.33 gm, 2.71 mmol) following the general procedure described in the beginning as a colourless viscous oil. Purity by UPLC: 96.82%.

IR ($CHCl_3$) **:** 3415, 3356, 3114, 2945, 2856, 1710, 1691, 1585, 1485, 1365, 1256, 1181, 1025, 921 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.65-1.71 (m, 2H), 2.01-2.06 (m, 2H), 3.33-3.38 (m, 2H), 4.12-4.21 (m, 2H), 5.31-5.35 (m, 1H), 6.49 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.66-7.70 (m, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 8.42 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 456.13 $(M+H)^+$

5.1.7.45 3-((6-((1-Benzylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzal-dehyde (22k)



22k (0.6 06 gm, 52%) was prepared from **12k** (1.0 gm, 3.29 mmol) and **20** (0.402 gm, 3.29 mmol) following the general procedure described in the beginning as colourless viscous oil. Purity by UPLC: 89.35%.

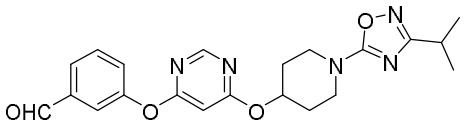
IR ($CHCl_3$) **:** 3433, 3025, 2953, 2808, 1701, 1581, 1460, 1411, 1327, 1253, 1170, 1037, 756 cm^{-1}

^{1}H NMR **:** δ 1.80-1.88 (m, 2H), 2.02-2.08 (m, 2H), 2.33-2.37 (m, 2H), 2.75-2.78 (m, 2H), 3.56 (s, 2H), 5.13-5.17 (m, 1H), 6.19 (s, 1H), 7.27-

($CDCl_3$) 7.33 (m, 5H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.65 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.39 (s, 1H), 10.01 (s, 1H).

ESI/MS (m/z) **:** 390.1 $(M+H)^+$

5.1.7.46 3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy) pyrimidin-4-yl) oxy) benzaldehyde (22l)



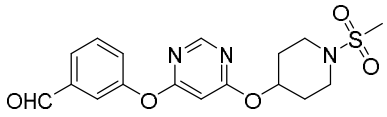
22l (0.77 gm, 66%) was prepared from **12l** (1.0 gm, 2.96 mmol) and **20** (0.36 gm, 2.96 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 98.77%.

IR (KBr) **:** 3410, 3018, 2974, 2931, 2874, 1703, 1626, 1570, 1437, 1411, 1383, 1261, 1217, 1107, 1030, 756 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.30 (d, *J* = 6.8 Hz, 6H), 1.92-1.99 (m, 2H), 2.07-2.14 (m, 2H), 2.87 (m, 1H), 3.62-3.68 (m, 2H), 3.83-3.89 (m, 2H), 5.41-5.45 (m, 1H),6.41 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.64 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 10.02 (s, 1H).

ESI/MS (m/z) **:** 410.1 $(M+H)^+$

5.1.7.47 3-((6-((1-(Methyl sulfonyl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzaldehyde (22m)



22m (0.55 gm, 41%) was prepared from **19m** (1.0 gm, 3.43 mmol) and **20** (0.419 gm, 3.43 mmol) following the general procedure described in the beginning as an off-white solid. Purity by UPLC: 87.69%.

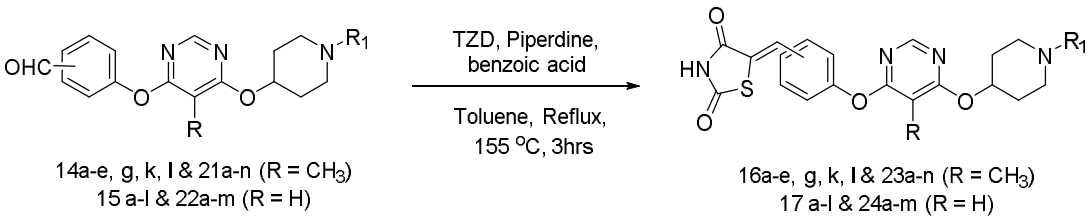
IR (KBr) **:** 3051, 2924, 2852, 1759, 1703, 1585, 1566, 1435, 1329, 1020, 937, 850 cm^{-1}

^{1}HNMR : δ 1.83-1.85 (m, 2H), 2.05-2.09 (m, 2H), 2.15 (s, 3H), 3.18-3.22 (m, 2H), 3.34 (brs, 2H), 5.28 (brs, 1H), 6.36 (s, 1H), 7.29 (d, *J* = 7.6 Hz,

($CDCl_3$) 1H), 7.40 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 8.28 (s, 1H), 10.03 (s, 1H).

ESI/MS (m/z) : 378.14 $(M+H)^+$

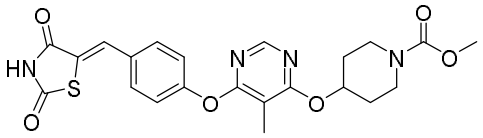
5.1.8 Synthesis of compounds 16 a-e, g, k, l, 17 a-l, 23 a-n & 24 a-m.



General procedure:

To a solution of the intermediate **14a-e, g, k, l, 15a-l, 21a-n or 22a-m** (1 eq) in toluene (30 ml), thiazolidine-2, 4-dione (0.9 eq) and benzoic acid (0.1 eq) were added followed by the addition of piperdine (1.5 eq) at 27 °C and the reaction mixture was refluxed for 7 hrs. Then, the reaction mixture was cooled to 30 °C and the solid product was filtered, washed with ice-cold toluene and was dried to give final desired product. In all the final compounds **16a-e, g, k, l, 17a-l, 23a-n & 24a-m**, the –CH= proton from the newly introduced benzylidene moiety appeared as a sharp singlet between 7.70–7.90 ppm. This value indicates that all final compounds **16 a-e, g, k, l, 17 a-l, 23 a-n & 24a-m** are having *Z* stereochemistry being more thermodynamically stable isomer.[200, 201]

5.1.8.1 Methyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (16a)



16a (1.01 gm, 67%) was prepared from **14a** (0.55 gm, 1.347 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 97.65%

IR (KBr) : 3194, 3072, 2862, 2748, 1755, 1703, 1687, 1572, 1413, 1220 cm^{-1}

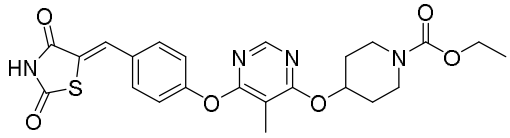
^{1}HNMR : δ 1.63-1.71 (m, 2H), 1.93-1.98 (m, 2H), 2.13 (s, 3H), 3.37-3.40 (m,

(DMSO-d_6) 2H), 3.61 (s, 3H), 3.63-3.68 (m, 2H), 5.29-5.34 (m, 1H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.82 (s, 1H), 8.28 (s, 1H), 12.64 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.92, 30.63, 66.72, 71.72, 102.76, 122.86, 123.44, 128.19, 128.90, 130.31, 131.78, 137.43, 154.59, 155.00, 167.48, 167.81, 168.24, 168.30

ESI/MS (m/z) : 471.12 $(M+H)^+$

5.1.8.2 Ethyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (16b)



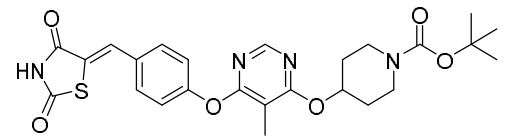
16b (0.26 gm, 38%) was prepared from **14b** (0.55 gm, 1.428 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 97.19%

IR (KBr) : 3109, 2953, 2933, 2852, 2750, 1743, 1701, 1589, 1572, 1222, 1111 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.81 (t, *J* = 7.0 Hz, 3H), 1.62-1.69 (m, 2H), 1.91-1.96 (m, 2H), 2.11 (s, 3H), 3.31-3.37 (m, 2H), 3.60-3.66 (m, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 5.27-5.33 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.80 (s, 1H), 8.26 (s, 1H), 12.60 (s, 1H).

ESI/MS (m/z) : 485.0 $(M+H)^+$

5.1.8.3 *t*-Butyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (16c)



16c (0.7 gm, 47%) was prepared from **14c** (0.97 gm, 2.298 mmol) following the general procedure described in the beginning as a white solid. m.p: 207-208 °C; Purity by UPLC: 99.48%

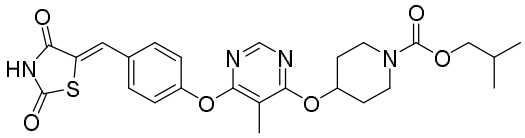
IR (KBr) : 3500, 3070, 2928, 2750, 1743, 1705, 1685, 1589, 1566, 1506, 1415, 1220, 1020, 900 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.41 (s, 9H), 1.62-1.64 (m, 2H), 1.93 (brs, 2H), 2.12 (s, 3H), 3.30 (brs, 2H), 3.60-3.63 (m, 2H), 5.30 (brs, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 8.27 (s, 1H), 12.62 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.91, 28.53, 30.74, 71.93, 79.25, 102.73, 121.86, 122.84, 123.50, 130.32, 130.82, 131.52, 131.96, 154.35, 154.99, 167.46, 167.88, 168.30

ESI/MS (m/z) : 513.17 $(M+H)^+$

5.1.8.4 *i*-Butyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy)piperidine-1-carboxylate (16d)



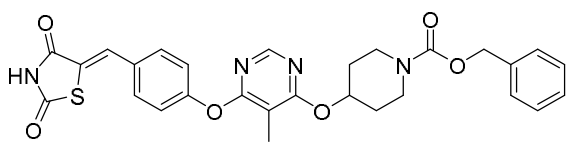
16d (0.24 gm, 40%) was prepared from **14d** (0.5 gm, 1.21 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 98.77%

IR (KBr) : 2962, 2750, 1745, 1705, 1589, 1570, 1417, 1219, 1112, 1022 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 0.89 (d, *J* = 6.8 Hz, 6H), 1.62-1.69 (m, 2H), 1.83-1.90 (m, 1H), 1.93-1.97 (m, 2H), 2.11 (s, 3H), 3.30-3.35 (m, 2H), 3.60-3.66 (m, 2H), 3.79 (d, *J* = 6.4 Hz, 2H), 5.30-5.33 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.81 (s, 1H), 8.27 (s, 1H), 12.61 (s, 1H).

ESI/MS (m/z) : 512.9 $(M+H)^+$

5.1.8.5 Benzyl (Z)-4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (16e)



16e (0.7 gm, 58%) was prepared from **14e** (1.0 gm, 1.428 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 97.59%

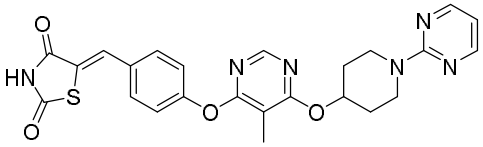
IR (KBr) : 3435, 2951, 2748, 1745, 1708, 1587, 1570, 1504, 1419, 1220, 1112 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.64-1.72 (m, 2H), 1.94-1.99 (m, 2H), 2.12 (s, 3H), 3.41 (brs, 2H), 3.68 (m, 2H), 5.10 (s, 2H), 5.30-5.34 (m, 1H), 7.30-7.40 (m, 7H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.82 (s, 1H), 8.28 (s, 1H), 12.63 (br,s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.92, 30.63, 41.12, 66.72, 71.72, 102.76, 122.86, 123.44, 128.19, 130.31, 131.58, 131.98, 137.43, 154.59, 155.00, 167.65, 168.24, 168.30.

ESI/MS (m/z) : 547.15 $(M+H)^+$

5.1.8.6 5-(4-((5-Methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy)benzylidene)thiazolidine-2,4-dione (16g)



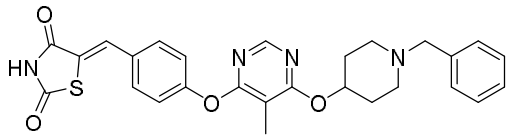
16g (0.14 gm, 26%) was prepared from **14g** (0.46 gm, 1.18 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 97.45%

IR (KBr) : 3128, 2958, 2941, 2856, 2752, 1741, 1707, 1587, 1504, 1438, 1359, 1317, 1220, 1172, 1114, 1028, 900, 783 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.68-1.74 (m, 2H), 1.97-2.03 (m, 2H), 2.49 (s, 3H), 3.64-3.70 (m, 2H), 4.08-4.14 (m, 2H), 5.37-5.42 (m, 1H), 6.61 (t, *J* = 4.6 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.81 (s, 1H), 8.28 (s, 1H), 8.35 (d, *J* = 4.4 Hz, 2H), 12.60 (s, 1H).

ESI/MS (m/z) : 491.0 $(M+H)^+$

5.1.8.7 5-(4-((6-((1-Benzylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy) benzylidene)thiazolidine-2,4-dione (16k)



16k (0.55 gm, 63%) was prepared from **14k** (0.66 gm, 1.64 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 212-214 °C; Purity by UPLC: 97.59%

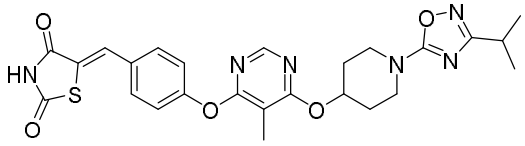
IR (KBr) : 3435, 2945, 2758, 1745, 1708, 1589, 1504, 1222.,1114 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.78-1.80 (m, 2H), 2.00-2.04 (m, 2H), 2.12 (m, 3H), 2.51 (brs, 2H), 2.77 (brs, 2H), 3.67 (s, 2H), 5.18-5.20 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 3H), 7.23-7.37 (m, 4H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.73 (s, 1H), 8.26 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.94, 30.36, 50.09, 61.89, 71.60, 102.65, 122.73, 125.90, 127.86, 128.67, 128.77, 129.36, 129.68, 129.76, 130.87, 131.71, 137.35, 154.61, 167.50, 168.32, 169.72, 170.70.

ESI/MS (m/z) : 503.17 $(M+H)^+$

5.1.8.8 5-(4-((6-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (16l)



16l (0.11 gm, 20%) was prepared from **14l** (0.45 gm, 1.059 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 97.59%

IR (KBr) : 2966, 2931, 2754, 1745, 1708, 1587, 1504, 1419, 1269, 1114 cm^{-1}

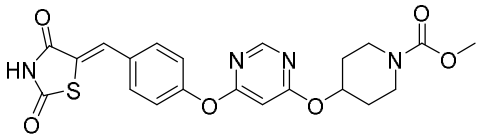
^{1}HNMR (DMSO-d_6) : δ 1.19 (d, *J* = 7.2 Hz, 6H), 1.80-1.85 (m, 2H), 2.04-2.09 (m, 2H), 2.14 (s, 3H), 2.80-2.84 (m, 1H), 3.55-3.61 (m, 2H), 3.73-3.79 (m, 2H), 5.365.38 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.8 Hz,

2H), 7.82 (s, 1H), 8.29 (s, 1H), 12.69 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.92, 20.75, 26.72, 29.90, 43.21, 70.94, 102.82, 122.86, 123.51, 130.35, 131.52, 131.97, 154.60, 154.98, 167.50, 167.89, 168.18, 168.34, 170.95, 175.35.

ESI/MS (m/z) : 523.16 $(M+H)^+$

5.1.8.9 Methyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl) oxy)piperidine-1-carboxylate (17a)



17a (0.32 gm, 70%) was prepared from **15a** (0.36 gm, 1.01 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 228-230 °C; Purity by UPLC: 95.31%

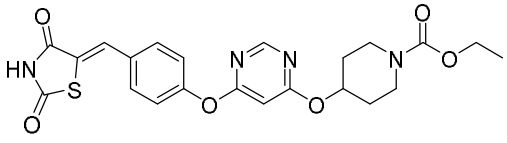
IR (KBr) : 3427, 3109, 3041, 2958, 2764, 1745, 1705, 1583, 1460, 1253,1174 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.68-1.80 (m, 2H), 1.98-2.03 (m, 2H), 3.34-3.40 (m, 2H), 3.71 (s, 3H), 3.73-3.79 (m, 2H), 5.30-5.36 (m, 1H), 6.25 (s, 1H), 7.23-7.26 (m, 2H), 7.53-7.56 (m, 2H), 7.81 (s, 1H), 8.42 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 30.54, 41.05, 52.75, 71.93, 93.00, 122.42, 122.63, 130.42, 131.96, 132.56, 137.43, 154.31, 157.75, 166.82, 167.25, 170.33, 170.96

ESI/MS (m/z) : 457.0 $(M+H)^+$

5.1.8.10 Ethyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy) piperidine-1-carboxylate (17b)



17b (0.3 gm, 63%) was prepared from **15b** (0.5 gm, 1.006 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 200-202 °C; Purity by UPLC: 99.62%

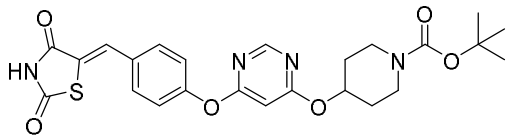
IR (KBr) : 3429, 3119, 2949, 2748, 1745, 1701, 1601, 1589, 1554, 1502, 1475, 1435, 1253, 1174, 1155, 1132 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.76-1.80 (m, 2H), 2.01-2.06 (m, 2H), 3.35-3.42 (m, 2H), 3.82-3.85 (m, 2H), 4.17 (q, *J* = 15.2 Hz, 2H), 5.32-5.38 (m, 1H), 6.46 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.79 (s, 1H), 8.44 (s, 1H), 9.74 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 14.70, 30.55, 40.97, 61.54, 72.09, 93.09, 122.45, 130.35, 132.03, 132.64, 154.37, 155.61, 157.68, 166.64, 167.05, 170.29, 171.02

ESI/MS (m/z) : 471.24 $(M+H)^+$

5.1.8.11 *t*-Butyl 4-((6-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (17c)



17c (0.28 gm, 43%) was prepared from **15c** (0.52 gm, 3.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 180-182 °C; Purity by UPLC: 97.52%

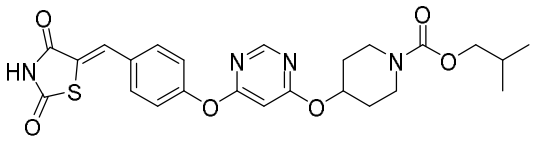
IR (KBr) : 2976, 2858, 2758, 1743, 1701, 1608, 1589, 1465, 1411, 1251, 1174, 1033 cm^{-1}

^{1}HNMR (DMSO-*d*$_6$) : δ 1.43 (s, 9H), 1.55-1.61 (m, 2H), 1.94-1.97 (m, 2H), 3.17 (brs, 2H), 3.66-3.71 (m, 2H), 5.22-5.27 (m, 1H), 6.46 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.83 (s, 1H), 8.46 (s, 1H), 12.65 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 28.51, 30.77, 72.48, 79.28, 92.78, 122.90, 123.71, 130.77, 131.44, 132.16, 154.30, 158.33, 167.81, 168.28, 170.54, 170.91

ESI/MS (m/z) : 499.16 $(M+H)^+$

5.1.8.12 *i*-Butyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (17d)



17d (0.4 gm, 45%) was prepared from **15d** (0.7 gm, 2.56 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 168-170 °C; Purity by UPLC: 97.56%

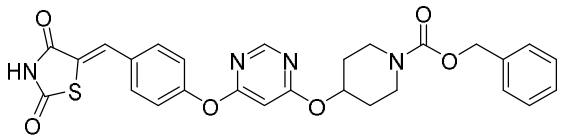
IR (KBr) : 3418, 2960, 2874, 2756, 1743, 1705, 1587, 1504, 1465, 1413, 1253, 1220, 1153, 1028 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 0.88 (d, *J* = 6.8 Hz, 6H), 1.83-1.89 (m, 1H), 1.96-1.99 (m, 2H), 2.50 (brs, 2H), 3.25 (brs, 2H), 3.71-3.75 (m, 2H), 3.79 (d, *J* = 6.8 Hz, 2H), 5.23-5.29 (m, 1H), 6.46 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.82 (s, 1H), 8.46 (s, 1H), 12.65 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 19.35, 28.02, 30.71, 41.24, 71.17, 72.33, 92.80, 122.89, 123.70, 130.77, 131.44, 132.16, 154.25, 155.11, 158.33, 167.80, 168.27, 170.55, 170.90.

ESI/MS (m/z) : 419.16 $(M+H)^+$

5.1.8.13 Benzyl 4-((6-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (17e)



17e (0.16 gm, 40%) was prepared from **15e** (0.33 gm, 0.923 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 190-192 °C; Purity by UPLC: 96.39%

IR (KBr) : 3435, 3064, 2931, 2748, 1745, 1693, 1504, 1255, 1220 cm^{-1}

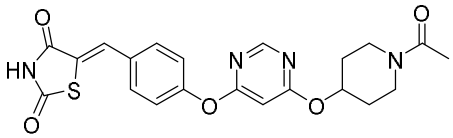
^{1}HNMR (DMSO-d_6) : δ 1.58-1.65 (m, 2H), 1.98-2.00 (m, 2H), 3.29 (brs, 2H), 3.74-3.78 (m, 2H), 5.09 (s, 2H), 5.25-5.30 (m, 1H), 6.48 (s, 1H), 7.32-7.40 (m, 7H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.83 (s, 1H), 8.47 (s, 1H), 12.65 (brs,

1H).

^{13}CNMR (DMSO-d_6) : δ 30.69, 41.34, 66.73, 72.28, 92.80, 122.90, 123.72, 128.20, 128.90, 130.77, 131.45, 132.17, 137.41, 154.25, 154.88, 158.33, 167.81, 168.29, 170.55, 170.90

ESI/MS (m/z) : 533.15 $(M+H)^+$

5.1.8.14 5-(4-((6-((1-Acetylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (17f)



17f (0.11 gm, 14%) was prepared from **15f** (1.0 gm, 1.96 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 266.5 °C; Purity by UPLC: 99.13%

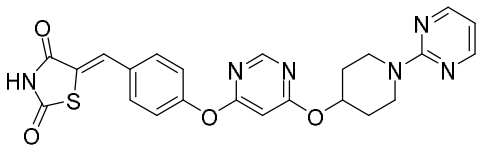
IR (KBr) : 3429, 2956, 2935, 2702, 1735, 1701, 1577, 1600, 1502, 1460, 1253, 1174 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.52-1.68 (m, 2H), 1.93-1.96 (m, 2H), 2.02 (s, 3H), 3.16-3.34 (m, 2H), 3.67-3.70 (m, 1H), 3.87-3.91 (m, 1H), 5.27-5.31 (m, 1H), 6.47 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.82 (s, 1H), 8.46 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 21.73, 30.63, 31.32, 38.57, 43.44, 72.48, 92.80, 122.90, 123.73, 130.77, 131.43, 132.17, 154.26, 158.34, 167.83, 168.30, 168.30, 168.60, 170.55, 170.93.

ESI/MS (m/z) : 441.12 $(M+H)^+$

5.1.8.15 5-(4-((6-((1-(Pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy) benzylidene)thiazolidine-2,4-dione (17g)



17g (0.44 gm, 65%) was prepared from **15g** (0.54 gm, 1.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 222-224 °C; Purity by UPLC: 97.07%

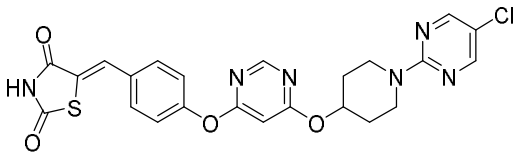
IR (KBr) : 3429, 2964, 2760, 1755, 1707, 1585, 1548, 1464, 1255, 1178 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.64-1.68 (m, 2H), 2.02-2.06 (m, 2H), 3.47-3.54 (m, 2H), 4.22-4.28 (m, 2H), 5.33-5.39 (m, 1H), 6.48 (s, 1H), 6.61-6.63 (dd, *J* = 4.4 Hz & 9.2 Hz, 1H), 7.35-7.37 (m, 2H), 7.66-7.68 (m, 2H), 7.79 (s, 1H), 8.36 (d, *J* = 4.8 Hz, 2H), 8.48 (s, 1H), 12.63 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 22.69, 30.58, 41.13, 44.22, 73.04, 92.74, 110.45, 122.83, 131.30, 131.94, 153.91, 158.37, 158.47, 161.55, 170.64, 171.00

ESI/MS (m/z) : 477.2 $(M+H)^+$

5.1.8.16 5-(4-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (17h)



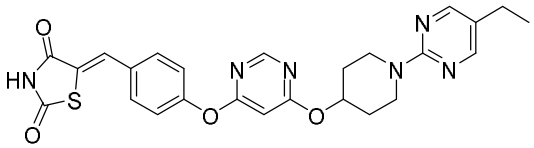
17h (0.3 gm, 56%) was prepared from **15h** (0.35 gm, 0.675 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 234.7 °C; Purity by UPLC: 94.85%

IR (KBr) : 3421, 3117, 2958, 2922, 2764, 1741, 1699, 1610, 1587, 1467, 1253 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.63-1.70 (m, 2H), 2.01-2.09 (m, 2H), 3.51-3.56 (m, 2H), 4.17-4.20 (m, 2H), 5.34-5.38 (m, 1H), 6.49 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.83 (s, 1H), 8.42 (s, 2H), 8.48 (s, 1H), 12.64 (s, 1H).

ESI/MS (m/z) : 511.0 $(M+H)^+$

5.1.8.17 5-(4-((6-((1-(5-Ethylpyrimidin-2-yl) piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (17i)



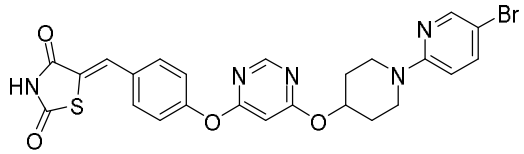
17i (0.8 gm, 72%) was prepared from **15i** (0.9 gm, 2.22 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 198-200 °C; Purity by UPLC: 97.65%

IR (KBr) : 3429, 3109, 2956, 2926, 2748, 1741, 1707, 1606, 1587, 1456,1263, 1155 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.13 (t, *J* = 7.6 Hz, 3H), 1.77-1.85 (m, 2H), 2.06-2.12 (m, 2H), 2.44-2.50 (m, 2H), 3.55-3.61 (m, 2H), 4.24-4.30 (m, 2H), 5.37-5.42 (m, 1H), 6.26 (s, 1H), 7.24-7.27 (m, 2H), 7.53-7.57 (m, 2H), 7.80 (s, 1H), 8.19 (s, 2H), 8.44 (s, 1H)

ESI/MS (m/z) : 505.16 $(M+H)^+$

5.1.8.18 5-(4-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy) benzylidenethiazolidine-2,4-dione (17j)



17j (0.2 gm, 53%) was prepared from **15j** (0.33 gm, 0.68 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 247.6 °C; Purity by UPLC: 93.77%

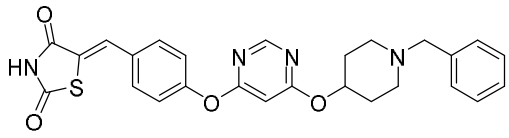
IR (KBr) : 3441, 3043, 2945, 2922, 1743, 1701, 1585, 1465, 1263, 1222, 1180, 1157 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.61-1.70 (m, 2H), 2.03-2.08 (m, 2H), 3.30-3.37 (m, 2H), 3.93-3.99 (m, 2H), 5.30-5.36 (m, 1H), 6.48 (s, 1H), 6.89 (d, *J* = 9.2 Hz,

1H), 7.36 (dd, *J* = 6.8 Hz & 2Hz, 2H), 7.66-7.69 (m, 3H), 7.82 (s, 1H), 8.16 (d, *J* = 2.4Hz, 1H), 8.48 (s, 1H), 12.64 (s, 1H).

ESI/MS (m/z) : 556.1 $(M+H)^+$

5.1.8.19 5-(4-((6-((1-Benzylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (17k)



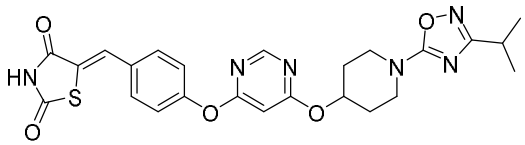
17k (0.22 gm, 20%) was prepared from **15k** (0.94 gm, 3.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 170-172 °C; Purity by UPLC: 99.13%

IR (KBr) : 3425, 3024, 2945, 2764, 1741, 1701, 1610, 1589, 1465, 1217, 1035 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.84-1.1.93 (m, 2H), 2.08-2.11 (m, 2H), 2.42-2.46 (m, 2H), 2.84-2.87 (m, 2H), 3.64 (s, 2H), 5.19-5.21 (m, 1H), 6.19 (s, 1H), 7.22-7.31 (m, 5H), 7.35 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.77 (s, 1H), 8.41 (s, 1H).

ESI/MS (m/z) : 489.16 $(M+H)^+$

5.1.8.20 5-(4-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (17l)



17l (0.36 gm, 42%) was prepared from **15l** (0.69 gm, 3.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 190-192 °C; Purity by UPLC: 98.14%

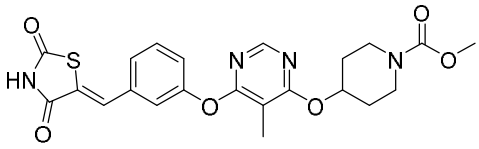
IR (KBr) : 3423, 2970, 2758, 1741, 1701, 1608, 1587, 1174, 1035 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.19 (d, *J* = 6.8 Hz, 6H), 1.75-1.78 (m, 2H), 2.06-2.10 (m, 2H), 2.80-2.84 (m, 1H), 3.47-3.53 (m, 2H), 3.77-3.82 (m, 2H), 5.33 (brs, 1H), 6.50 (s, 1H), 7.37 (d, *J* = 6.8 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.83 (s, 1H), 8.49 (s, 1H), 12.68 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 20.74, 26.71, 29.97, 43.44,71.51, 92.85, 122.90, 123.80, 130.81, 131.38, 132.17, 154.23, 158.36, 167.90, 168.33, 170.58, 170.85, 170.87, 175.34

ESI/MS (m/z) : 509.10 $(M+H)^+$

5.1.8.21 Methyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (23a)



23a (1.01 gm, 50%) was prepared from **21a** (1.67 gm, 4.501 mmol) following the general procedure described in the beginning as an off-white solid. m.p: 120-122 °C; Purity by UPLC: 97.43%

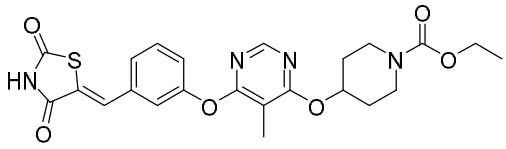
IR (KBr) : 3435, 3064, 2958, 2754, 1753, 1705, 1589, 1568, 1413, 1234, 1112 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.65-1.70 (m, 2H), 1.93-1.98 (m, 2H), 2.13 (s, 3H), 3.34-3.38 (m,2H), 3.59 (s, 3H), 3.61-3.68 (m, 2H), 5.30-5.32 (m, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.27 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.91, 22.68, 52.83, 71.71, 102.50, 123.48, 124.08, 125.12, 126.71, 129.72, 130.97, 135.08, 153.99, 154.54, 155.55, 167.61, 168.18

ESI/MS (m/z) : 471.13 $(M+H)^+$

5.1.8.22 Ethyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy)piperidine-1-carboxylate (23b)



23b (0.6 gm, 48%) was prepared from **21b** (1.0 gm, 2.59 mmol) following the general procedure described in the beginning as an off-white solid. m.p: 138-140 °C; Purity by UPLC: 99.34%

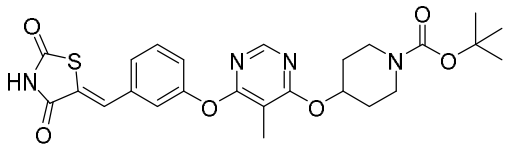
IR (KBr) : 3169, 3068, 2947, 2754, 1753, 1708, 1585, 1570, 1425, 1236, 1157 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.19 (t, *J* = 7.2 Hz, 3H), 1.65-1.70 (m, 2H), 1.93-1.99 (m, 2H), 2.14 (s, 3H), 3.39 (brs, 2H), 3.62-3.68 (m, 2H), 4.06 (q, *J* = 15.0 Hz, 2H), 5.31-5.33 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H), 8.27 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.90, 14.43, 15.07, 22.54, 30.64, 31.43, 61.21, 71.75, 102.50, 123.47, 124.08, 125.08, 126.71, 130.97, 131.33, 135.07, 153.99, 154.54, 155.11, 167.61, 167.67, 168.17.

ESI/MS (m/z) : 485.13 $(M+H)^+$

5.1.8.23 *t*-Butyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (23c)



23c (0.3 gm, 34%) was prepared from **21c** (0.7 gm, 3.43 mmol) following the general procedure described in the beginning as a white solid. m.p: 151-153 °C; Purity by UPLC: 97.44%

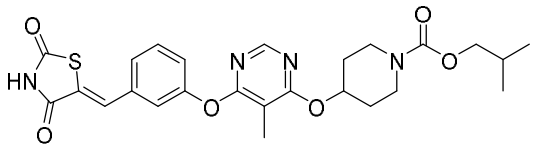
IR (KBr) : 3455, 3066, 2976, 2756, 1753, 1707, 1589, 1568, 1477, 1273, 1161 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.42 (s, 9H), 1.60-1.68 (m, 2H), 1.92-1.97 (m, 2H), 2.14 (s, 3H), 3.30 (brs, 2H), 3.59-3.65 (m, 2H), 5.29-5.33 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.27 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 7.91, 28.53, 30.75, 71.89, 79.25, 102.49, 123.47, 124.07, 125.13, 125.78, 126.71, 128.66, 129.36, 130.97, 131.29, 135.08, 153.99, 154.40, 167.65, 168.19.

ESI/MS (m/z) : 513.16 $(M+H)^+$

5.1.8.24 *i*-Butyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (23d)



23d (0.6 gm, 50%) was prepared from **21d** (1.0 gm, 2.42 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 112-113 °C; Purity by UPLC: 98.94%

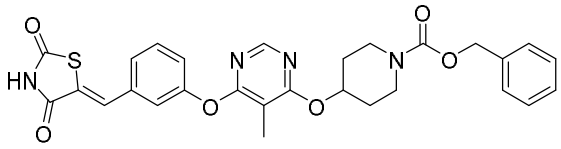
IR (KBr) : 3437, 3126, 2958, 2756, 1753, 1705, 1589, 1566, 1429, 1383, 1323, 1271, 1230, 1161, 1111, 1026 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 0.90 (d, *J* = 6.4 Hz, 6H), 1.65-1.70 (m, 2H), 1.84-1.89 (m, 1H), 1.94-1.99 (m, 2H), 2.14 (s, 3H), 3.35 (brs, 2H), 3.66 (brs, 2H), 3.80 (d, *J* = 6.8 Hz, 2H), 5.31-5.33 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.27 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 7.91, 19.36, 28.03, 30.67, 71.17, 71.74, 102.50, 123.48, 124.09, 125.07, 126.71, 130.97, 131.33, 135.07, 153.99, 154.54, 155.14, 167.61, 168.17.

ESI/MS (m/z) : 513.1 $(M+H)^+$

5.1.8.25 Benzyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (23e)



23e (0.1 gm, 20%) was prepared from **21e** (0.5 gm, 1.24 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 128-129 °C; Purity by UPLC: 98.48%

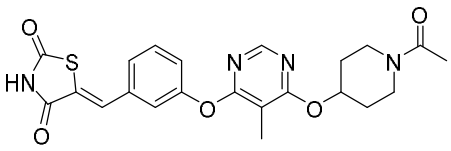
IR (KBr) : 3161, 3057, 2951, 1741, 1678, 1587, 1554, 1465, 1452, 1402, 1323, 1255, 1232, 1172, 1134, 1033, 1008 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.68-1.70 (m, 2H), 1.82-1.96 (m, 2H), 2.14 (s, 3H), 3.29 (brs, 2H), 3.74-3.77 (m, 2H), 5.10 (s, 2H), 5.33 (brs, 1H), 7.05 (d, *J* = 6.8 Hz, 1H), 7.12-7.38 (m, 6H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 8.27 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.92, 22.69, 30.63, 66.72, 71.67, 102.50, 123.43, 123.97, 125.68, 126.68, 128.02, 128.32, 128.90, 130.88, 130.94, 135.21, 137.43, 153.98, 154.54, 154.92, 167.61, 168.16, 168.40, 168.53.

ESI/MS (m/z) : 503.1 $(M+H)^+$

5.1.8.26 5-(3-((6-((1-Acetylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy) benzylidene)thiazolidine-2,4-dione (23f)



23f (0.3 gm, 67%) was prepared from **21f** (0.524 gm, 1.19 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 212.9 ^oC; Purity by UPLC: 98.86%

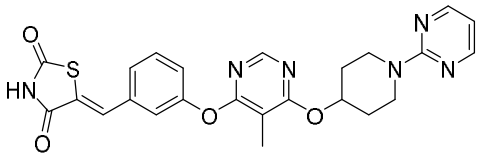
IR (KBr) : 3400, 3010, 2926, 2739, 1741, 1704, 1614, 1581, 1568, 1429, 1300, 1265, 1238, 1151, 1111, 779 cm^{-1}

^{1}HNMR : δ 1.80 (m, 2H), 2.02-2.07 (m, 2H), 2.14 (s, 3H), 3.65-3.71 (m, 2H),

($CDCl_3$) 3.97-4.03 (m, 2H), 5.40-5.44 (m, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 7.24 (dd, *J* = 7.6 & 1.6 Hz, 1H), 7.37 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.85 (dd, *J* = 9.2 & 2.4, 1H), 8.28 (s, 1H), 8.49 (d, *J* = 2.4 Hz, 1H).

ESI/MS (m/z) : 455.0 $(M+H)^+$

5.1.8.27 5-(3-((5-Methyl-6-((1-(pyrimidin-2-yl)piperidin-4-yl)oxy) pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23g)



23g (0.87 gm, 73%) was prepared from **21g** (1.0 gm, 2.55 mmol) following the general procedure described in the beginning as a yellow solid. m.p: >200 °C; Purity by UPLC: 96.72%

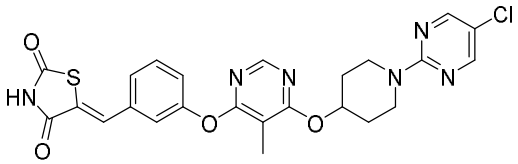
IR (KBr) : 3427, 3134, 2968, 2858, 2744, 1741, 1712, 1597, 1568, 1556, 1491, 1423, 1363, 1309, 1284, 1265, 1166, 1114, 1026 cm^{-1}

^{1}HNMR (DMSO-*d*$_6$) : δ 1.68-1.72 (m, 2H), 1.99-2.04 (m, 2H), 2.14 (s, 3H), 3.65-3.71 (m, 2H), 4.10-4.15 (m, 2H), 5.39-5.41 (m, 1H), 6.62 (t, *J* = 4.8 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.29 (s, 1H), 8.37 (d, *J* = 4.8 Hz, 2H), 12.68 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 7.94, 30.54, 72.46, 102.49, 110.44, 123.51, 124.11, 125.10, 126.70, 130.98, 131.32, 135.08, 154.00, 154.57, 158.46, 161.60, 167.61, 167.71, 168.20, 68.28.

ESI/MS (m/z) : 491.14 $(M+H)^+$

5.1.8.28 5-(3-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23h)



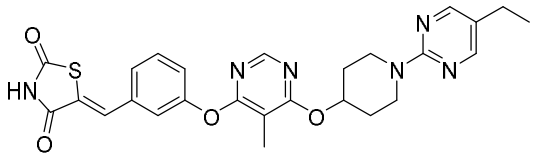
23h (0.37 gm, 63%) was prepared from **21h** (0.48 gm, 1.128 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 232.1 °C; Purity by UPLC: 98.82%

IR (KBr) : 3118, 3005, 2850, 2756, 1751, 1701, 1583, 1566, 1427, 1411, 1319, 1284, 1271, 1161, 1109, 1020 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.71-1.76 (m, 2H), 2.00-2.05 (m, 2H), 2.14 (s, 3H), 3.68-3.74 (m, 2H), 4.04-4.10 (m, 2H), 5.41 (brs, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.29 (s, 1H), 8.43 (s, 2H), 12.67 (brs, 1H).

ESI/MS (m/z) : 525.10 $(M+H)^+$

5.1.8.29 5-(3-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23i)



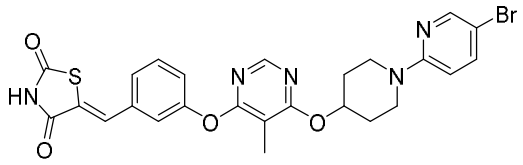
23i (0.15 gm, 21%) was prepared from **21i** (0.73 gm, 1.74 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 166-168 °C; Purity by UPLC: 99.11%

IR (KBr) : 3118, 3066, 2956, 2846, 2758, 1751, 1703, 1589, 1566, 1541, 1504, 1429, 1409, 1284, 1269, 1236, 1161, 1109, 1014 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.14 (t, *J* = 6.8 Hz, 3H), 1.68-1.70 (m, 2H), 1.88 (brs, 2H), 2.14 (s, 3H), 2.44 (brs, 2H), 3.63 (brs, 2H),4.10 (brs, 2H), 5.40 (brs, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.41 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.79 (s, 1H), 8.27-8.36 (m, 3H), 12.67 (brs, 1H).

ESI/MS (m/z) : 519.14 $(M+H)^+$

5.1.8.30 5-(3-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23j)



23j (0.17 gm, 28%) was prepared from **21j** (0.5 gm, 1.066 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 180.6 °C; Purity by UPLC: 98.71%

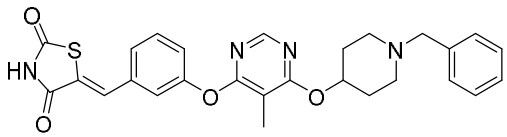
IR (KBr) : 3120, 3066, 2841, 2756, 1751, 1703, 1583, 1566, 1483, 1429, 1411, 1284, 1269, 1226, 1161, 1112 1031, 914 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.68-176 (m, 2H), 2.00-2.05 (m, 2H), 2.14 (s. 3H), 3.45-3.51 (m, 2H), 3.85-3.91 (m, 2H), 5.35-5.41 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.79 (s, 1H), 8.18 (s, 1H), 8.29 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.93, 22.09, 22.69, 30.17, 42.48, 44.23, 72.34, 102.50, 106.82, 109.66, 123.45, 124.06, 125.18, 126.69, 130.69, 131.26, 135.10, 140.20, 148.29, 154.01, 154.56, 157.79, 167.60, 167.78, 168.22, 168.28.

ESI/MS (m/z) : 470.14 $(M+H)^+$

5.1.8.31 5-(3-((6-((1-Benzylpiperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)-oxy)benzylidene)thiazolidine-2,4-dione (23k)



23k (0.21 gm, 41%) was prepared from **21k** (0.5 gm, 1.24 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 128-129 °C; Purity by UPLC: 98.48%

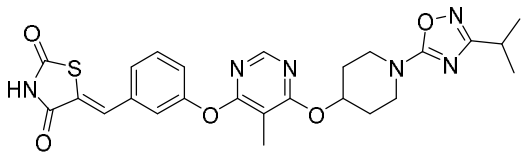
IR (KBr) : 3026, 2924, 2760, 1751, 1705, 1564, 1485, 1411, 1379, 1284, 1261, 1232, 1153, 1105, 1035, 873 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.80 (brs, 2H), 1.91-1.99 (m, 2H), 2.12 (s, 3H), 2.55 (brs, 2H), 2.81 (brs, 2H), 3.72 (s, 2H), 5.20 (brs, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 6.4 Hz, 1H), 7.32-7.37 (m, 5H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 8.25 (s, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 7.46, 22.11, 29.66, 49.48, 61.21, 70.82, 101.98, 122.60, 122.89, 126.11, 127.57, 127.91, 128.34, 128.53, 129.38, 130.31, 135.37, 136.28, 153.49, 154.08, 167.15, 167.74, 169.70, 171.25.

ESI/MS (m/z) : 503.14 $(M+H)^+$

5.1.8.32 5-(3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23l)



23l (0.45 gm, 34%) was prepared from **21l** (1.3 gm, 2.49 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 114-115 °C; Purity by UPLC: 98.28%

IR (KBr) : 3419, 3155, 3034, 2974, 2862, 2773, 1747, 1689, 1624, 1564, 1525, 1465, 1433, 1411, 1336, 1276, 1259, 1238, 1151, 1111, 1031 cm^{-1}

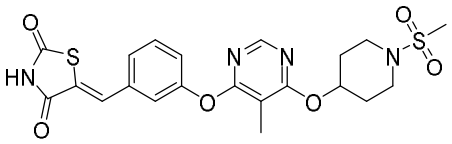
^{1}HNMR (CDCl$_3$) : δ 1.19 (d, *J* = 7.2 Hz, 6H), 1.80-1.84 (m, 2H), 2.04-2.09 (m, 2H), 2.15 (s, 3H), 2.80-2.84 (m, 1H), 3.55-3.61 (m, 2H), 3.73-3.79 (m,

2H), 5.35-5.38 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.28 (s, 1H), 12.67 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.92, 20.75, 26.72, 29.91, 43.21, 70.90, 102.58, 123.49, 124.10, 125.08, 126.73, 130.98, 131.32, 135.08, 153.98, 154.55, 167.64, 167.67, 168.10, 168.17, 170.95, 175.34.

ESI/MS (m/z) : 523.17 $(M+H)^+$

5.1.8.33 5-(3-((5-Methyl-6-((1-(methylsulfonyl)piperidin-4-yl)oxy) pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23m)



23m (0.3 gm, 51%) was prepared from **21m** (0.524 gm, 1.190 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 213 °C; Purity by UPLC: 96.77%

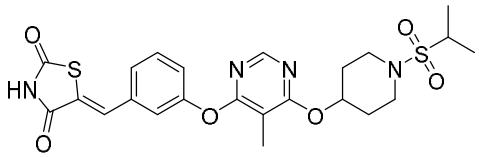
IR (KBr) : 3153, 3051, 2924, 2852, 1759, 1703, 1585, 1566, 1435, 1329, 1020, 937 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.83-1.85 (m, 2H), 2.05-2.09 (m, 2H), 2.15 (s, 3H), 2.92 (s, 3H), 3.18-3.22 (m, 2H), 3.34 (brs, 2H), 5.28 (brs, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 8.28 (s, 1H), 12.67 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.98, 30.27, 34.83, 43.00, 70.84, 102.58, 123.47, 124.08, 125.10, 126.73, 131.00, 131.32, 135.08, 153.98, 154.56, 167.64, 167.68, 168.11, 168.18

ESI/MS (m/z) : 491.1 $(M+H)^+$

5.1.8.34 5-(3-((6-((1-(isopropylsulfonyl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (23n)



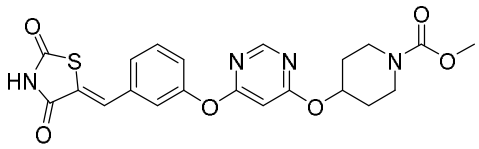
23n (0.16 gm, 31%) was prepared from **21n** (0.45 gm, 0.993 mmol) following the general procedure described in the beginning as a white solid. m.p: 213.2 °C; Purity by UPLC: 89.41%

IR (KBr) : 3450, 3151, 3066, 2935, 2754, 1735, 1707, 1589, 1568, 1429, 1413, 1429, 1323, 1269, 1163 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.23 (d, *J* = 6.8 Hz, 6H), 1.72-1.80 (m, 2H), 2.00-2.05 (m, 2H), 2.15 (s, 3H), 3.32-3.39 (m, 3H), 3.46-3.52 (m, 2H), 5.30-5.34 (m, 1H), 7.28 (dd, *J* = 8.0 & 1.6 Hz, 1H), 7.40 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.27 (s, 1H), 12.65 (s, 1H).

ESI/MS (m/z) : 519.0 $(M+H)^+$

5.1.8.35 Methyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (24a)



24a (0.15 gm, 35%) was prepared from **22a** (0.3 gm, 0.808 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 200-202 °C; Purity by UPLC: 92.97%

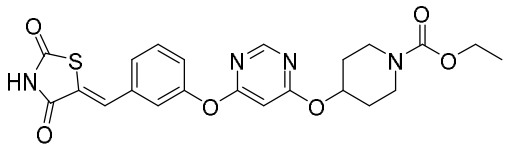
IR (KBr) : 3433, 3130, 3026, 2958, 1747, 1695, 1593, 1456, 1255, 1182 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.74-1.80 (m, 2H), 1.98-2.02 (m, 2H), 3.34-3.40 (m, 2H), 3.71 (s, 3H), 3.75-3.81 (m, 2H), 5.30-5.34 (m, 1H), 6.20 (s, 1H), 7.18-7.23

(m, 1H), 7.26-7.28 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.41 (s, 1H).

ESI/MS (m/z) : 457.0$(M+H)^+$

5.1.8.36 Ethyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (24b)



24b (0.4 gm, 66%) was prepared from **22b** (0.7 gm, 1.27 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 169-170 °C; Purity by UPLC: 96.27%

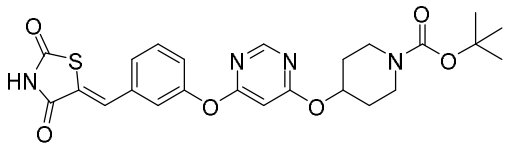
IR (KBr) : 3455, 3126, 2929, 2777, 1743, 1691, 1599, 1570, 1462, 1330, 1247, 1178, 1134, 1024, 846 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.55-1.63 (m, 2H), 1.96-1.99 (m, 2H), 3.24 (brs, 2H), 3.70-3.74 (m, 2H), 4.01-4.06 (m, 2H), 5.24-5.28 (m, 1H), 6.44 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.43 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 8.46 (s, 1H), 12.66 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 15.05, 30.68, 41.19, 61.23, 72.32, 92.55, 123.51, 123.98, 125.40, 127.03, 131.10, 131.22, 135.36, 153.32, 155.06, 158.31, 167.84, 168.23, 170.72.

ESI/MS (m/z) : 471.13 $(M+H)^+$

5.1.8.37 *t*-Butyl 4-((6-(3-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenoxy) pyrimidin-4-yl) oxy) piperidine-1-carboxylate (24c)



24c (0.7 gm, 55%) was prepared from **22c** (1.0 gm, 2.55 mmol) following the general procedure described in the beginning as a white solid. m.p: 170-171 °C; Purity by UPLC: 99.69%

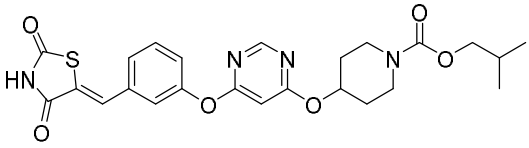
IR (KBr) : 3433, 3117, 3036, 2974, 2762, 1745, 1707, 1593, 1574, 1460, 1321, 1176, 1033 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.14 (s, 9H), 1.56-1.58 (m, 2H), 1.95 (brs, 2H), 3.01 (brs, 2H), 3.67-3.71 (m, 2H), 5.25 (brs, 1H), 6.45 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.46 (s, 1H), 12.69 (brs, 1H).

^{13}CNMR (DMSO-d_6) : δ 28.52, 30.52, 72.45, 79.29, 92.56, 123.50, 123.96, 125.57, 127.03, 130.99, 131.23, 135.41, 153.33, 154.36, 158.41, 168.16, 170.80.

ESI/MS (m/z) : 499.15 $(M+H)^+$

5.1.8.38 *i*-Butyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (24d)



24d (0.7 gm, 54%) was prepared from **22d** (1.0 gm, 2.56 mmol) following the general procedure described in the beginning as a white solid. m.p: 133-134 °C; Purity by UPLC: 97.43%

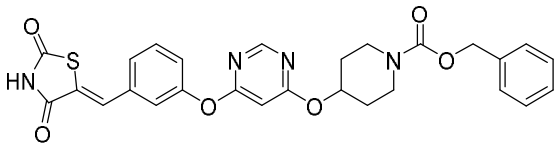
IR (KBr) : 3479, 3153, 3063, 2960, 2872, 1743, 1705, 1600, 1570, 1460, 1437, 1278, 1251, 1230, 1178, 1028, 835 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 0.87 (d, *J* = 9.6 Hz, 6H), 1.56-1.64 (m, 2H), 1.83-1.90 (m, 1H), 1.91-1.99 (m, 2H), 3.26-3.34 (m, 2H), 3.72-3.80 (m, 4H), 5.25-5.29 (m, 1H), 6.44 (s, 1H), 7.32 (d, *J* = 6.4 Hz, 1H), 7.43 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.46 (s, 1H), 12.68 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 19.35, 28.02, 30.73, 41.25, 71.17, 72.30, 92.57, 115.67, 123.52, 124.01, 125.28, 127.04, 129.82, 131.24, 131.24, 135.34, 153.33, 155.12, 158.32, 167.68, 168.15, 170.80.

ESI/MS (m/z) : 499.15 $(M+H)^+$

5.1.8.39 Benzyl 4-((6-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate (24e)



24e (0.2 gm, 41%) was prepared from **22e** (0.4 gm, 0.923 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 178-180 °C; Purity by UPLC: 97.08%

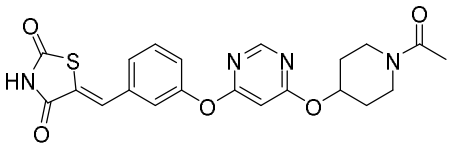
IR (KBr) : 3176, 3057, 2951, 2359, 1743, 1589, 1570, 1465, 1172 cm^{-1}

^{1}HNMR (DMSO-*d*$_6$) : δ 1.59-1.63 (m, 2H), 1.97-1.99 (m, 2H), 3.29-3.35 (m, 2H), 3.74-3.77 (m, 2H), 5.09 (s, 2H), 5.26-5.28 (m, 1H), 6.44 (s, 1H), 7.30-7.38 (m, 6H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.46 (s, 1H), 12.68 (brs, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 30.74, 66.72, 72.24, 92.57, 123.51, 123.99, 125.38, 127.04, 128.08, 128.90, 131.13, 131.23, 135.36, 137.41, 153.32, 154.88, 158.31, 167.80, 168.21, 170.75.

ESI/MS (m/z) : 533.21 $(M+H)^+$

5.1.8.40 5-(3-((6-((1-Acetylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy) benzylidene)thiazolidine-2,4-dione (24f)



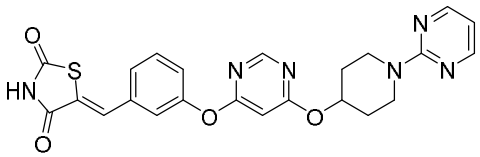
24f (0.11 gm, 21%) was prepared from **22f** (1.0 gm, 1.96 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 103.9 °C; Purity by UPLC: 97.36%

IR (KBr) : 3433, 2955, 2928, 2752, 1747, 1707, 1591, 1572, 1458, 1251, 1176 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.50-1.58 (m, 1H), 1.62-1.71 (m, 1H), 1.93-1.96 (m, 1H), 2.02-2.08 (m, 1H), 2.16 (s, 3H), 3.17-3.23 (m, 1H), 3.33-3.37 (m, 1H), 3.67-3.70 (m, 1H), 3.86-3.92 (m, 1H), 5.27-5.32 (m, 1H), 6.45 (s, 1H), 7.31-7.33 (m, 1H), 7.44 (s, 1H), 7.49 (d, *J* = 8.0 Hz,1H), 7.59-7.63 (dd, *J* = 7.8 & 8.0 Hz, 1H), 7.80 (s, 1H), 8.46 (s, 1H), 12.67 (s, 1H).

ESI/MS (m/z) : 441.12 $(M+H)^+$

5.1.8.41 5-(3-((6-((1-(Pyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy) benzylidene)thiazolidine-2,4-dione (24g)



24g (0.34 gm, 42%) was prepared from **22g** (0.64 gm, 1.697 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 230-232 °C; Purity by UPLC: 95.22%

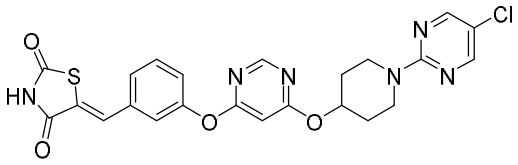
IR (KBr) : 3435, 2970, 2764, 1751, 1712, 1587, 1554, 1492, 1257, 1174 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.60-1.68 (m, 2H), 2.02-2.06 (m, 2H), 3.47-3.54 (m, 2H), 4.22-4.28 (m, 2H), 5.33-5.39 (m, 1H), 6.46 (s,1H), 6.61-6.63 (dd, *J* = 4.4 & 9.2 Hz, 1H), 7.32-7.34 (m, 1H), 7.44-7.45 (t, *J* = 3.6 Hz, 1H), 7.49 (d, *J* = 8Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.36 (d, *J* = 4.8 Hz, 2H), 8.48 (s, 1H), 12.66 (s, 1H)

^{13}CNMR (DMSO-d_6) : δ 30.59, 41.13, 73.02, 92.58, 110.45, 123.51, 123.97, 125.57, 127.02, 129.37, 131.00, 131.23, 135.40, 153.34, 158.34, 158.46, 161.54, 168.03, 168.33, 170.73, 170.98.

ESI/MS (m/z) : 477.10 $(M+H)^+$

5.1.8.42 5-(3-((6-((1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy) benzylidene)thiazolidine-2,4-dione (24h)



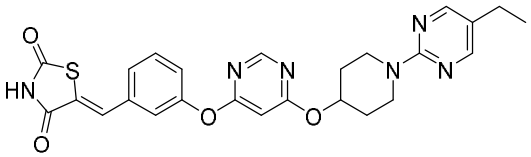
24h (0.15 gm, 20%) was prepared from **22h** (0.345 gm, 0.675 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 226.7 °C; Purity by UPLC: 96.97%

IR (KBr) : 3431, 3140, 3028, 2920, 2775, 1741, 1707, 1591, 1572, 1255, 1076 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.62-1.69 (m, 2H), 2.01-2.09 (m, 2H), 3.51-3.56 (m, 2H), 4.17-4.20 (m, 2H), 5.34-5.38 (m, 1H), 6.46 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.42 (s, 2H), 8.47 (s, 1H), 12.67 (s, 1H).

ESI/MS (m/z) : 511.0 $(M+H)^+$

5.1.8.43 5-(3-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (24i)



24i (0.6 gm, 54%) was prepared from **22i** (0.9 gm, 2.22 mmol) following the general procedure described in the beginning as a white solid. m.p: 219-220 °C; Purity by UPLC: 94.58%

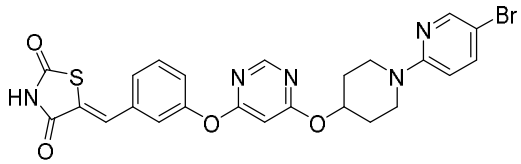
IR (KBr) : 3398, 3020, 2931, 2767, 1743, 1709, 1595, 1460, 1359, 1178, 1028, 840 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.14 (s, 3H), 1.61-1.63 (m, 2H), 2.01-2.03 (m, 2H), 2.40-2.45 (m, 2H), 3.45 (q, *J* = 10.0 Hz, 2H), 4.12 (brs, 2H), 5.33 (brs, 1H), 6.45 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.25 (s, 2H), 8.47 (s, 1H), 12.68 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 15.60, 21.93, 30.09, 35.83, 40.95, 72.67, 92.11, 123.07, 123.55, 124.37, 124.85, 126.57, 130.72, 130.77, 134.88, 152.89, 157.16, 157.88, 160.21, 167.28, 167.73, 170.26, 170.52

ESI/MS (m/z) : 505.16 $(M+H)^+$

5.1.8.44 5-(3-((6-((1-(5-Bromopyridin-2-yl)piperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzylidene) thiazolidine-2,4-dione (24j)



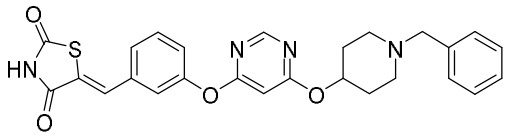
24j (0.09 gm, 37%) was prepared from **22j** (0.2 gm, 0.439 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 184.7 °C; Purity by UPLC: 94.39%

IR (KBr) : 3416, 3119, 2947, 2854, 1757, 1685, 1591, 1487, 1255, 1178 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.68-1.70 (m, 2H), 2.02-2.05 (m, 2H), 3.32-3.37 (m, 2H), 3.93-3.99 (m, 2H), 5.30-5.36 (m, 1H), 6.45 (s, 1H), 6.89 (d, *J* = 9.2 Hz, 1H), 7.30-7.32 (dd, *J* = 7.6 Hz & 1.6Hz, 1H), 7.43 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.58-7.62 (m, 1H), 7.66-7.69 (m, 1H), 7.77 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.47 (s, 1H), 12.64 (s, 1H).

ESI/MS (m/z) : 555.6 $(M+H)^+$

5.1.8.45 5-(3-((6-((1-Benzylpiperidin-4-yl)oxy)pyrimidin-4-yl)oxy)benzyl-idene)thiazolidine-2,4-dione (24k)



24k (0.66 gm, 51%) was prepared from **22k** (1.0 gm, 3.57 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 170-172 °C; Purity by UPLC: 92.96%

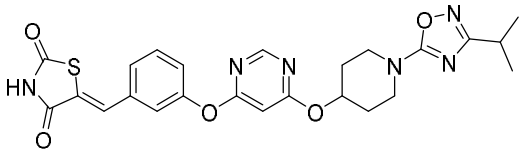
IR (KBr) : 3416, 3030 2929, 2760, 1743, 1707, 1591, 1570, 1458,1170, 1035 cm^{-1}

^{1}HNMR (DMSO-*d*$_6$) : δ 1.76-1.78 (m, 2H), 1.91-2.01 (m, 2H), 2.48-2.51 (m, 2H), 2.84-2.85 (m, 2H), 3.79 (s, 2H), 5.13-5.15 (m, 1H), 6.31 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 4.4 Hz, 1H), 7.31-7.39 (m, 5H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 8.48 (s, 1H).

^{13}CNMR (DMSO-*d*$_6$) : δ 29.63, 49.67, 61.07, 71.34, 91.96, 122.61, 122.78, 126.47, 127.62, 128.09, 128.37, 129.41, 130.60, 135.72, 136.15, 152.80, 157.88, 169.86, 170.32, 170.43, 171.57.

ESI/MS (m/z) : 489.12 $(M+H)^+$

5.1.8.46 5-(3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy) pyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (24l)



24l (0.5 gm, 50%) was prepared from **22l** (1.0 gm, 3.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 217.5 °C; Purity by UPLC: 94.79%

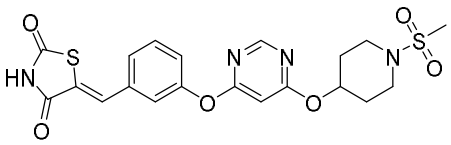
IR (KBr) : 3429, 3140, 2970, 2864, 2775, 1743, 1691, 1624, 1593, 1460, 1408, 1249 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.18 (d, *J* = 6.8 Hz, 6H), 1.71-1.80 (m, 2H), 2.0-2.29 (m, 2H), 2.78-2.85 (m, 1H), 3.46-3.52 (m, 2H), 3.78-3.81 (m, 2H), 5.30-5.34 (m, 1H), 6.46 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.48 (s, 1H), 12.61 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 20.74, 26.71, 29.98, 43.44, 71.47, 92.62, 123.51, 123.97, 125.44, 127.05, 128.66, 129.36, 131.08, 131.23, 135.38, 153.32, 158.33, 167.86, 168.24, 170.75, 170.81, 170.87, 175.34.

ESI/MS (m/z) : 509.16 $(M+H)^+$

5.1.8.47 5-(3-((6-((1-(Methyl sulfonyl)piperidin-4-yl)oxy)pyrimidin-4-yl) oxy)benzylidene)thiazolidine-2,4-dione (24m)



24l (1.01 gm, 41%) was prepared from **22l** (1.0 gm, 3.43 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 256.0 °C; Purity by UPLC: 95.00%

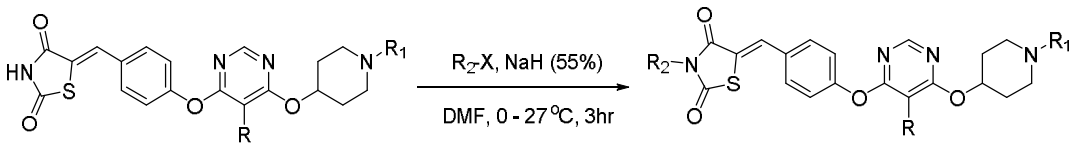
IR (KBr) : 3018, 2968, 2791, 1745, 1689, 1589, 2568, 1463, 1404, 1327, 1288, 1249, 1172, 1141, 1026, 972 cm^{-1}

^{1}HNMR (DMSO-d_6)) : δ 1.79-1.99 (m, 2H), 2.05-2.08 (m, 2H), 2.90 (s, 3H), 3.10-3.16 (m, 2H), 3.32-3.39 (m, 2H), 5.20-5.26 (m, 1H), 6.45 (s,1H), 7.31 (dd, *J* = 8.0 & 1.6 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 8.47 (s, 1H), 12.67 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 30.27, 34.91, 43.19, 43.60, 71.33, 79.64, 92.61, 123.50, 124.00, 125.28, 127.07, 131.21, 131.26, 135.35, 153.33, 158.34, 167.65, 168.13, 170.74, 170.82.

ESI/MS (m/z) : 477.09 $(M+H)^+$

5.1.9 Synthesis of compounds 25 a-k.

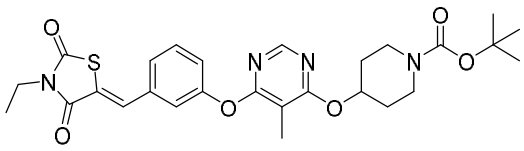


23c, 23i & 23l 25 a-k

General procedure:

To a suspension of NaH (55%, 1.5 eq) in DMF (10-fold), compound **23c, 23i or 23l** (1 eq) was added followed by the addition of an alkyl halide (R_2-X) (1.2 eq) at 0 °C and the reaction mixture was stirred at 27 °C for 7 hrs. Then, the reaction mixture was poured in ice-cold water (30 ml) and was extracted with ethyl acetate (3 x 15 ml). The organic extracts were combined, washed with water (3 x 20 ml), brine (20 ml) and were dried over Na_2SO_4. The organic layer was then concentrated on rotavapor and the residue was purified through column chromatography to yield the final desired products **25 a-k**.

5.1.9.1 *t*-Butyl-4-((6-(3-((3-ethyl-2,4-dioxothiazolidin-5-ylidene)methyl)-phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (25a)



25a (240 mg, 76%) was prepared from **23c** (300 mg, 0.585 mmol) and iodo ethane (110 mg, 0.702 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 90.9 °C; Purity by UPLC: 94.84%

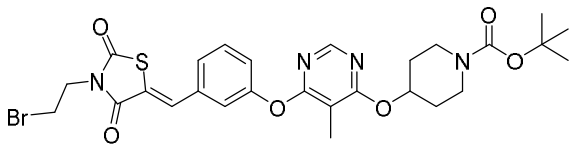
IR (KBr) : 3059, 2976, 2933, 2848, 1747, 1681, 1585, 1566, 1415, 1265 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.42 (s, 9H), 1.61-1.67 (m, 2H), 1.92-1.97 (m, 2H), 2.14 (s, 3H), 3.36-3.42 (m, 2H), 3.59-3.62 (m, 2H), 3.63-3.71 (m, 2H), 5.29-5.32 (m, 1H), 7.30 (d, *J* = 8.0 Hz. 1H), 7.44 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 8.27 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.91, 13.17, 14.42, 22.53, 28.54, 30.75, 31.43, 37.20, 71.90, 79.25, 102.53, 123.02, 123.55, 124.24, 126.75, 131.03, 132.32, 135.01, 154.03, 154.36, 154.53, 165.80, 167.43, 167.59, 168.21

ESI/MS (m/z) : 541.21 $(M+H)^+$

5.1.9.2 *t*-Butyl-4-((6-(3-((3-(2-bromoethyl)-2,4-dioxothiazolidin-5-ylidene)-methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (25b)



25b (260 mg, 72%) was prepared from **23c** (300 mg, 0.586 mmol) and 1,2-dibromo ethane (132 mg, 0.702 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 127.7 °C; Purity by UPLC: 99.43%

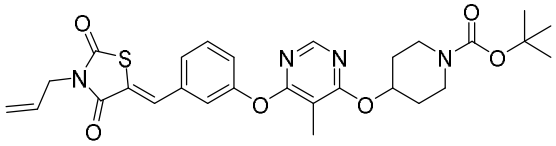
IR (KBr) : 3061, 2976, 2928, 2850, 1732, 1670, 1566, 1427, 1109, 1022 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.50 (s, 9H), 1.80-1.83 (m, 2H), 1.99-2.03 (m, 2H), 2.21 (s, 3H), 3.37-3.43 (m, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.73-3.77 (m, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 5.35-5.37 (m, 1H), 7.21-7.23 (m, 1H), 7.31 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 8.26 (s, 1H).

^{13}CNMR ($CDCl_3$) : δ 7.65, 26.80, 28.46, 30.70, 40.82, 42.72, 71.67, 79.66, 102.97, 121.93, 122.99, 123.85, 126.83, 130.36, 133.65, 134.58, 153.87, 154.07, 154.81, 165.72, 167.38, 168.34.

ESI/MS (m/z) : 619.0 $(M+H)^+$

5.1.9.3 *t*-Butyl-4-((6-(3-((3-allyl-2,4-dioxothiazolidin-5-ylidene)methyl)-phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (25c)



25c (269 mg, 83%) was prepared from **23c** (300 mg, 0.586 mmol) and allyl bromide (85 mg, 0.702 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 64-66 °C; Purity by UPLC: 98.25%

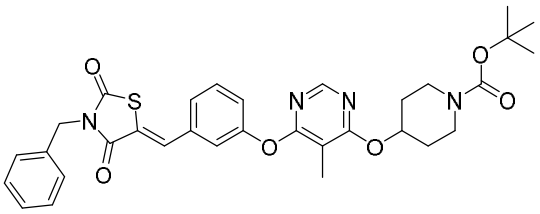
IR (KBr) : 3064, 2976, 2927, 2953, 1747, 1678, 1585, 1566, 1417, 1261, 1228, 1161, 1112, 1020 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.50 (s, 9H), 1.79-1.85 (m, 2H), 1.99-2.04 (m, 2H), 2.20 (s, 3H), 3.37-3.43 (m, 2H), 3.73-3.77 (m, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 5.26-5.29 (m, 2H), 5.34-5.38 (m, 1H), 5.83-5.88 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 10.0 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.90 (s, 1H), 8.26 (s, 1H).

^{13}CNMR ($CDCl_3$) : δ 7.65, 28.46, 29.69, 43.90, 71.65, 79.66, 102.96, 119.09, 122.48, 122.93, 123.66, 126.79, 130.10, 130.31, 133.05, 134.75, 153.84, 154.07, 154.81, 165.76, 167.25, 167.40, 168.33.

ESI/MS (m/z) : 553.28 $(M+H)^+$

5.1.9.4 *t*-Butyl-4-((6-(3-((3-benzyl-2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-5-methylpyrimidin-4-yl) oxy) piperidine-1-carboxylate (25d)



25d (270 mg, 77%) was prepared from **23c** (300 mg, 0.586 mmol) and benzyl bromide (120 mg, 0.702 mmol) following the general procedure described in the beginning as a yellow solid. m.p: 148.6 °C; Purity by UPLC: 97.47%

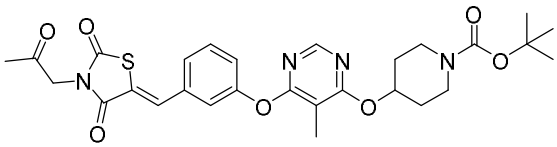
IR (KBr) : 3404, 3066, 2972, 2866, 1747, 1695, 1680, 1585, 1431, 1381, 1168 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.50 (s, 9H), 1.80-1.83 (m, 2H), 1.98-2.03 (m, 2H), 2.20 (s, 3H), 3.37-3.43 (m, 2H), 3.73-3.77 (m, 2H), 4.91 (s, 2H), 5.35-5.37 (m, 1H), 7.19-7.24 (m, 1H), 7.28-7.38 (m, 5H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 8.25 (s, 1H).

^{13}CNMR ($CDCl_3$) : δ 7.66, 28.47, 30.71, 45.34, 71.65, 79.68, 102.96, 122.51, 122.92, 123.66, 126.78, 128.32, 128.77, 128.88, 130.31, 133.14, 134.74, 135.05, 153.83, 154.07, 154.82, 166.00, 167.40, 167.56, 168.33.

ESI/MS (m/z) : 603.0 $(M+H)^+$

5.1.9.5 *t*-Butyl-4-((6-(3-((2,4-dioxo-3-(2-oxopropyl)thiazolidin-5-ylidene)-methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (25e)



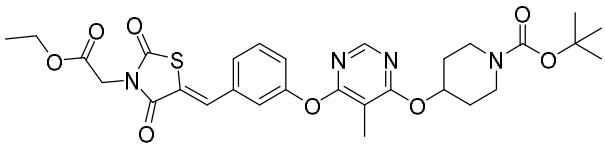
25e (60 mg, 27%) was prepared from **23c** (200 mg, 0.388 mmol) and chloroacetone (43.3 mg, 0.468 mmol) following the general procedure described in the beginning as an off-white solid. m.p: 120-121 °C; Purity by UPLC: 94.62%

IR (KBr) : 3437, 2978, 2928, 1734, 1695, 1683, 1585, 1568, 1423, 1176 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.48 (s, 9H), 1.76-1.83 (m, 2H), 1.97-2.02 (m, 2H), 2.19 (s, 3H), 2.27 (s, 3H), 3.35-3.41 (m, 2H), 3.70-3.75 (m, 2H), 4.54 (s, 2H), 5.32-5.36 (m, 1H), 7.19-7.29 (m, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 8.24 (s, 1H).

ESI/MS (m/z) : 591.2 $(M+Na)^+$

5.1.9.6 *t*-Butyl-4-((6-(3-((3-(2-ethoxy-2-oxoethyl)-2,4-dioxothiazolidin-5-lidene) methyl)phenoxy)-5-methylpyrimidin-4-yl)oxy)piperidine-1-carboxylate (25f)



25f (160 mg, 55%) was prepared from **23c** (250 mg, 0.488 mmol) and ethyl chloroacetate (71.1 mg, 0.585 mmol) following the general procedure described in the beginning as a white solid. m.p: 122-124 °C; Purity by UPLC: 98.06%

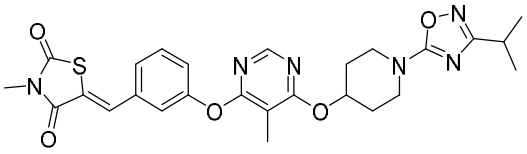
IR (KBr) : 2974, 2928, 2870, 1739, 1685, 1614, 1583, 1566, 1419, 1379, 1365, 1265, 1163 cm^{-1}

^{1}HNMR (CDCl$_3$) : δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.50 (s, 9H), 1.76-1.83 (m, 2H), 1.99-2.04 (m, 2H), 2.21 (s, 3H), 3.37-3.43 (m, 2H), 3.73-3.77 (m, 2H), 4.25 (q, *J* = 10.4 Hz, 2H), 4.49 (s, 2H), 5.35-5.37 (m, 1H), 7.19-7.29 (m, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.89 (s, 1H), 8.24 (s, 1H).

^{13}CNMR (CDCl$_3$) : δ 7.65, 14.08, 28.46, 30.70, 42.17, 62.18, 71.65, 79.66, 102.97, 122.10, 122.97, 123.84, 126.82, 130.36, 133.74, 134.58, 153.86, 154.07, 154.81, 165.42, 166.16, 167.22, 167.38, 168.34.

ESI/MS (m/z) : 599.21 $(M+H)^+$

5.1.9.7 5-(3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)-3-methylthiazolidine-2,4-dione (25g)



25g (260 mg, 84%) was prepared from **23l** (300 mg, 0.574 mmol) and iodomethane (98 mg, 0.689 mmol) following the general procedure described in the beginning as a white solid. m.p: 111.3 °C; Purity by UPLC: 99.39%

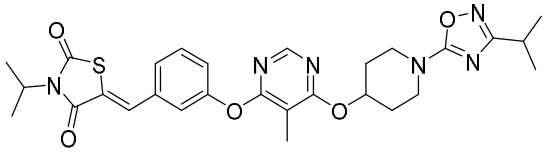
IR (KBr) : 2964, 2864, 1741, 1681, 1612, 1581, 1562, 1413, 1357, 1274, 1263, 1236, 1163, 1107 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.19 (d, *J* = 6.8 Hz, 6H), 1.79-1.85 (m, 2H), 2.05-2.10 (m, 2H), 2.16 (s, 3H), 2.79-2.86 (m, 1H), 3.11 (s, 3H), 3.55-3.62 (m, 2H), 3.73-3.79 (m, 2H), 5.36-5.39 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 8.29 (s, 1H).

^{13}CNMR ($CDCl_3$) : δ 0.56, 7.93, 20.76, 26.72, 28.35, 29.92, 43.22, 70.92, 102.63, 123.13, 123.58, 124.24, 126.77, 131.06, 132.10, 135.02, 154.03, 154.56, 166.16, 167.64, 167.67, 168.13, 170.96, 175.36.

ESI/MS (m/z) : 537.19 $(M+H)^+$

5.1.9.8 3-Isopropyl-5-(3-((6-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (25h)



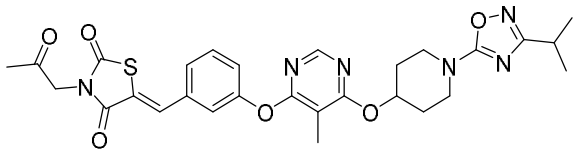
25h (60 mg, 27%) was prepared from **23l** (200 mg, 0.383 mmol) and 2-iodo propane (78 mg, 0.459 mmol) following the general procedure described in the beginning as colourless oil; Purity by UPLC: 94.67%

IR ($CHCl_3$) : 3020, 2978, 2881, 1738, 1686, 1616, 1568, 1414, 1340, 1263, 1159, 1111, 1033 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.30 (d, *J* = 6.8 Hz, 6H), 1.48 (d, *J* = 7.2 Hz, 6H), 1.93-2.00 (m, 2H), 2.07-2.14 (m, 2H), 2.20 (s, 3H), 2.87-2.94 (m, 1H), 3.62-3.68 (m, 2H), 3.84-3.89 (m, 2H), 4.63-4.70 (m, 2H), 5.30-5.45 (m, 1H), 7.17-7.20 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.49-7.53 (dd, *J* = 8.0 & 4.4 Hz, 1H), 7.82 (s, 1H), 8.25 (s, 1H).

ESI/MS (m/z) : 565.1 $(M+H)^+$

5.1.9.9 5-(3-((6-((1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)-3-(2-oxopropyl)thiazolidine-2,4-dione (25i)



25i (100 mg, 45%) was prepared from **23l** (200 mg, 0.383 mmol) and chloro acetone (42.5 mg, 0.459 mmol) following the general procedure described in the beginning as a brown solid; m.p: 164.2 °C; Purity by UPLC: 94.41%

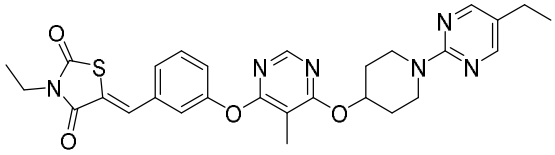
IR (KBr) : 2970, 2922, 2873, 2164, 1730, 1689, 1610, 1566, 1539, 1429, 1406, 1375, 1288, 1265, 1174, 1109, 1029 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.21 (d, *J* = 6.8 Hz, 6H), 1.79-1.99 (m, 2H), 2.05-2.11 (m, 2H), 2.14 (s, 3H), 2.23 (s, 3H), 2.79-2.86 (m, 1H), 3.56-3.62 (m, 2H), 3.74-3.80 (m, 2H), 4.68 (s, 2H), 5.37-5.40 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.98 (s, 1H), 8.30 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.94, 20.76, 26.72, 27.51, 29.92, 43.22, 50.83, 70.92, 102.65, 122.40, 123.73, 124.49, 126.83, 131.10, 133.29, 134.84, 154.04, 154.57, 165.40, 167.14, 167.63, 168.14, 170.96, 175.36.

ESI/MS (m/z) : 579.20 $(M+H)^+$

5.1.9.10 3-Ethyl-5-(3-((6-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)oxy)-5-methylpyrimidin-4-yl)oxy)benzylidene)thiazolidine-2,4-dione (25j)



25j (95 mg, 60%) was prepared from **23i** (150 mg, 0.289 mmol) and iodoethane (54.1 mg, 0.347 mmol) following the general procedure described in the beginning as a white solid; m.p: 144.2 °C; Purity by UPLC: 99.40%

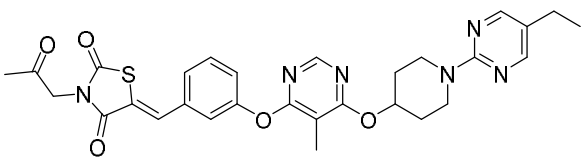
IR (KBr) : 2933, 2860, 1749, 1693, 1604, 1589, 1568, 1541, 1504, 1438, 1415, 1371, 1336, 1263, 1220, 1159, 1112 cm^{-1}

^{1}HNMR (DMSO-d_6) : δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.37 (t, *J* = 7.6 Hz, 3H), 1.83-1.91 (m, 2H),,2.05-2.12 (m, 2H), 2.21 (s, 3H), 2.48 (q, *J* = 15.2 Hz, 2H), 3.69-3.75 (m, 2H), 3.80-3.85 (m, 2H), 4.17-4.23 (m, 2H), 5.43-5.47 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), , 1H), 7.29 (s, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.89 (s, 1H), 8.20 (s, 2H), 8.28 (s, 1H).

^{13}CNMR (DMSO-d_6) : δ 7.67, 13.11, 15.62, 22.71, 30.62, 37.16, 41.28, 72.34, 102.98, 122.72, 122.93, 123.59, 124.44, 126.72, 130.28, 132.72, 134.83, 153.86, 154.10, 157.17, 160.78, 166.05, 167.39, 167.54, 168.47.

ESI/MS (m/z) : 547.28 $(M+H)^{+}$

5.1.9.11 5-(3-((6-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)-5-methyl-pyrimidin-4-yl)oxy)benzylidene)-3-(2-oxopropyl)thiazolidine-2,4-dione (25k)



25k (79 mg, 47.5%) was prepared from **23i** (150 mg, 0.289 mmol) and chloro acetone (32.1 mg, 0.347) following the general procedure described in the beginning as an off-white solid; m.p: 184.1 °C; Purity by UPLC: 97.77%

IR (KBr) : 2978, 2929, 2860, 1755, 1728, 1697, 1589, 1568, 1504, 1436, 1406, 1373, 1348, 1290, 1263, 1242, 1178, 1165, 1114, 1101, 1016, 783 cm^{-1}

^{1}HNMR ($CDCl_3$) : δ 1.22 (t, *J* = 7.6 Hz, 3H), 1.83-1.92 (m, 2H), 2.07-2.14 (m, 2H), 2.21 (s, 3H), 2.29 (s, 3H), 2.48 (q, *J* = 15.2 Hz, 2H), 3.69-3.76 (m, 2H), 4.18-4.24 (m, 2H), 4.56 (s, 2H), 5.43-5.49 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 8.21 (s, 2H), 8.29 (s, 1H).

^{13}CNMR ($CDCl_3$) : δ 7.67, 15.61, 22.71, 27.02, 30.62, 41.29, 50.19, 72.34, 103.00, 122.22, 122.98, 23.81, 124.44, 126.74, 130.33, 133.68, 134.62, 153.90, 154.10, 157.17, 160.78, 165.51, 167.29, 167.36, 168.48, 198.13.

ESI/MS (m/z) : 575.28 $(M+H)^+$

5.2 Biology

5.2.1 *in-vitro* hGPR119 Agonistic Activity

Cell Culture: Chinese Hamster Ovarian (CHO-K1) cells stably transfected with a human GPR119 (hGPR119) vector and cultured in Ham's F-12 medium (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS) and 0.8 mg/ml G418 at 37 °C in 5% CO_2.

cAMP ELISA Assay: Cyclic adenosine monophosphate (cAMP) secretion was measured using cAMP ELISA kit (R & D systems) according to manufacturer's instructions. Briefly, CHO-hGPR119 cells were seeded in culture medium (Ham's F-12 medium having 10% Fetal Bovine Serum) at a density of 40,000 cells/well in 96 well plate. Plates were incubated overnight at 37 °C. Next day, the cells were washed with PBS. Plates were incubated with assay medium (1mM IBMX in serum free Ham's F-12) for 20 min at 37 °C before adding the test compounds. Different concentrations (1-100 µM) of the test compounds were prepared in assay medium

and added to corresponding wells. After the treatment for 20 min at 37 °C, the reactions were stopped by addition of lysis buffer containing 0.1N HCl + 0.1% Triton X-100. Plates were then incubated for 45 min at room temperature on shaker and then the content was centrifuged. Supernatant was collected and cAMP was measured using commercially available kit. EC_{50} values of the test compounds were calculated using Graph Pad Prism.

5.2.2 *in-vivo* experiments

All the animals were bred at animal breeding facility of the Zydus Research Centre, registered under Rule 5(a) for the “Breeding and Experiments on Animals (control and supervision) rules 1998, [Registration no.77/1999 (CPCSEA)]. All the study protocols were approved by Institutional Animal Ethics Committee.

5.2.2.1 Pharmacokinetics experiments

Pharmacokinetic behaviour of the test compounds was studied via per-oral route of administration in male *Sprague Dawley* (SD) / Wistar rats / Beagle dogs. The animals were fasted for 18 hours and food was supplied after 4 hours of administration of the test compound. There was free access to water throughout the study. A homogenous suspension of the test substance was prepared in 0.5% w/v carbomethoxy cellulose (CMC) in normal saline and a per-oral dose of 30 mg/kg was administered. After the administration of the test compounds, blood samples were withdrawn at various time intervals through retro-orbital plexus and were collected into heparinized micro centrifuge tubes. Plasma was separated by centrifugation at 4000 rpm for 5 min at an ambient temperature and analysed immediately. Remaining samples were stored at -20 °C until analysed. The analysis was carried out by taking an aliquots of 180 µL plasma and 20 µL of internal standard (Atorvastatin) and was extracted with 2.5 mL of extracting solvent (ethyl acetate: acetonitrile 80:20, v/v) in a glass test-tube by vortexing with spinix vortex mixture for a minute. This was then centrifuged at 2000 rpm for 2.0 min. The supernatant was transferred to another glass test-tube and the solvent was evaporated under nitrogen using Zymark evaporator at 40 °C. Finally, the tubes were reconstituted with 0.1 mL diluent (acetonitrile: methanol: water 40:40:20, v/v/v).

The reconstituted samples were analysed on Agilent 1100 Series HPLC system with a mobile phase of 0.05% v/v trifluoroacetic acid in water: acetonitrile (32:68, v/v); flowing at a flow rate of 1.0 mL/min through a Kromasil 250 mm x 4.6 mm x 5 µ column maintained at 30 °C. Chromatographic separation was achieved within 15 min. Agilent software version Chemstation Rev.A.09.01. (1206) was used to acquire and process all chromatographic data. Quantification was based on a series of calibrators ranging from 0.031 to 32 µg/mL, prepared by adding a test compound to drug free rat plasma. Quality control samples were analyzed in parallel to verify that the system performs in control. Pharmacokinetic parameters namely; maximum plasma concentration (C_{max}), time point of maximum plasma concentration (t_{max}), area under the plasma concentration−time curve from 0 hour to infinity ($AUC_{0-\infty}$) and half-life of drug elimination during the terminal phase (t1/2) were calculated from plasma concentration versus time data, by standard non-compartmental methods, using the WinNonLin software version 4.0.1 procured from Pharsight Corporation, USA.

5.2.2.2 Oral Glucose Tolerance Tests (oGTT) in C57/BL6 mice:

C57/BL6 mice of 6–8-week age were used for this experiment. Animals were grouped based on non-fasting serum glucose levels and were kept on fasting overnight (day before OGTT). On the experiment day, each animal received a single dose of vehicle/test compounds (50 mg/kg) administered orally, 30 min post dosing animals were bled for basal glucose level estimation followed by oral glucose load (3gm/kg) administration. Blood was collected at the time points corresponding to 20, 40, 60 and 120 min after glucose load administration. Serum was separated for determination of glucose levels and change in area under curve for glucose was calculated.

5.2.2.3 Oral Glucose Tolerance Tests (oGTT) in *db*/*db* mice:

db/*db* Mice of 5–7-week age were used for this experiment. Animals were kept on fasting and were grouped based on fasting serum glucose levels and after grouping OGTT was performed. Each animal received a single dose of vehicle/test compounds (50 mg/kg) administered orally, 30 min post dosing animals were bled for basal glucose level estimation followed by oral glucose load (2gm/kg) administration. Blood was collected at the time points corresponding to 30, 60 and

120 min after glucose load administration. Serum is separated for determination of glucose levels. Change in area under curve for glucose and glucose excursion was calculated from Vehicle control with glucose load *vs* water control group without glucose load. Provided in the **Figure 20** (see section 3.4.4.1) as % reduction in AUC glucose excursion *vs* vehicle control is calculated.

5.2.2.4 Body weight changes in diet induced obesity (DIO) rats:

The high fat diet induced obesity (DIO) in rats exhibits various features of metabolic syndrome in humans. The metabolic syndrome is characterized by abdominal obesity, high triglycerides, impaired fasting glucose and hyperinsulinemia. The animals with a uniform body weight were divided into two groups. The first group was provided with normal chow diet (NIN) and the 2nd group was provided with High Fat diet (HFD) for a period of 12 weeks. After 12 weeks diet feeding, the HFD fed animals were divided into 4 treatment groups. Formulations were prepared using vehicle [PEG400, Tween 80 and 0.5% sodium CMC (5:5:90)] and body weight was recorded daily for 28 days.

5.2.2.5 Active plasma GLP-1 and insulin secretion in db/db mice

On day 0 animals body weight was recorded and non-fasting blood collection was done for glucose analysis. grouping was done based on non-fasting glucose values in such a way that the average non-fasting blood glucose levels of each group does not differ significantly from others. On evening animals were kept on overnight fasting for the next day activity.

On oGTT day, the test compounds were formulated at specified dose. The animals were weighed and based on these weights the volume of administration was calculated so as to administer a single dose on mg/kg body weight basis, basal (-30min) blood collection was done; vehicle/test was administered per orally and then subjected for OGTT (oral glucose tolerance test). After 30 min dosing, glucose load (2 gm/kg/10ml) administered per orally. The blood (about 0.3 ml) was collected at the time points corresponding to 10 and 30 min after glucose load administration. The blood samples were collected into labelled microfuge tubes containing 5µl of DPP-IV inhibitors (to prevent degradation of GLP-1 after collection) and 30µl of 2% Na-EDTA (as anticoagulant). Immediately after collection, the blood samples were centrifuged

to collect plasma, estimation of GLP-1 and insulin in plasma samples was carried out using ELISA kit.

5.2.2.6 Caco-2 permeability assay:

The Caco-2 cell line is derived from a human colon adenocarcinoma and has been widely used as an *in-vitro* model for the prediction of intestinal drug permeability and absorption.[202] The cells were seeded in Transwells (Millipore, 0.4 µm pore size) and formed a confluent monolayer after 21 days culture. On day 21, the target compound **23c** (50 µM) was added into the apical side of the membrane and the concentration of the compound across Caco-2 cell monolayer was quantified by UPLC after 1 hour incubation at 37℃. Transepithelial electrical resistance (TEER) should be determined before as well as after transport experiments and should be over 500Ω×cm^2. The apparent permeability coefficient (P_{app}) for the compound was calculated from the following equation: (P_{app} = (dQ/dt)/(C_0×A)). Where dQ/dt is the rate of permeation of the drug across the cells, C_0 is the initial concentration and A is the area of the cell monolayer.

5.2.2.7 Liver microsome stability assay

Mouse liver microsome stability assay was performed as described.[203] Briefly, mouse liver microsomal incubation contained microsomal protein (0.5 mg/mL), the lead compound **23c** (10 µmol/L), Tris-HCl buffer and a NADPH-generating system. Incubations in duplicate were performed at 37 ℃ for 30 min. Reactions were initialed by addition of NADPH-generating system and terminated by adding equal volume of ice-cold acetonitrile which contained internal standard. The mixtures were centrifuged and the supernatants were analyzed by LC-MS/MS. Incubations with inactive liver microsomes served as negative controls.

5.2.2.8 Plasma protein binding

The extent of plasma protein binding for the tested compound was determined by equilibrium dialysis. The lead compound **23c** was added to pre-warmed (37 °C) human plasma and mixed (2.5 µM, 1% (vol/vol) DMSO). Dialysis plate was prepared by adding 350 µL of phosphate buffer (1% (vol/vol) DMSO) to the buffer compartment and 200 µL of the tested compound plasma solution (2.5 µM) to the

red compartment. After incubating the plate at 37 °C for 5 hours at 100 rpm on orbital shaker, samples were removed from each compartment for LC-MS/MS analysis.

5.2.2.9 Repeated dose toxicity study or experiment

Repeated dose toxicity study of GPR119 in *Wistar* rats by oral (gavage) route was conducted for 28 days with 14 days recovery period. Three doses 50, 100 & 200 mg/kg were selected based on efficacy dose (ED_{50} as~ 2.0 mg) found in db/db mice. Each group contain 10 male and 10 female rats received GPR119 test item. Two groups, vehicle control and high dose group kept for 2-week recovery period to see any delayed or persistent or recovery of toxic effects, if any.

During the experiment following parameters/observation were carried out:

Mortality and Clinical Signs: Mortality check was performed twice daily. Cage-side observation was executed once daily.

Detailed Clinical Examination: All animals were subjected to detailed clinical examination towards the end of the treatment and the recovery periods.

Ophthalmic Examination: Ophthalmological examination was performed with an ophthalmoscope during the last week of the treatment and during the last week of recovery period.

Body Weight: Body weights were recorded for all the animals on receipt and prior to randomized assignment to dose groups for the purpose of weight stratification. Body weights were recorded on day 1 (prior to dosing) and thereafter-on weekly basis until the end of the treatment and the recovery period. Fasted body weights on the day of necropsy was recorded for the calculation of organ: body weight ratios.

Feed Consumption: The feed consumption was measured on weekly basis until the end of the treatment and the recovery period.

Neurobehavioral Observations: Neurobehavioral observations following modified Irwin test was performed on the animals from control and high dose groups near the end of the treatment and the recovery period.

Clinical Pathology: Clinical pathology investigations were carried out on all the surviving rats at the end of the treatment period and the recovery period.

Haematology: The following haematological parameters were determined using automated haematology analyzer (Cell-Dyn 3700).

Parameter	Units
Total Leukocyte Count (WBC)	10^3
Erythrocyte Count (RBC)	10^6
Platelet Count (PLT)	10^3
Hematocrit (HCT)	%
Hemoglobin Concentration (HGB)	g/dL
Mean Corpuscular Volume (MCV)	fL
Mean Corpuscular Hemoglobin (MCH)	pg
Mean Corpuscular Hemoglobin Concentration (MCHC)	g/dL
Reticulocyte Count (RETIC)	10^9 /L
Absolute Differential Leukocyte Count, Monocyte, Eosinophil, Basophil, Neutrophil, Lymphocyte	10^3 /µL

Clinical Chemistry: The following clinical chemistry parameters were determined using automated biochemical analyzer (Daytona).

Analyte	Unit	Analyte	Units
Glucose (GLU)	mg/dL	Urea	mg/dL
Triglycerides (TG)	mg/dL	Creatinine (CREA)	mg/dL
Total Cholesterol (TCHO)	mg/dL	Total Bilirubin (TBIL)	mg/dL
Aspartate aminotransferase (AST)	U/L	Calcium (Ca)	mg/dL
Alanine aminotransferase (ALT)	U/L	Inorganic Phosphorus (Phos)	mg/dL
Alkaline Phosphatase (ALP)	U/L	Sodium (Na^+)	mmol/L
Total Protein (TP)	g/dL	Potassium (K^+)	mmol/L
Albumin (ALB)	g/dL	Chloride (Cl^-)	mmol/L

Terminal Procedures: All the surviving animals were fasted overnight prior to euthanasia. Necropsy was performed on all surviving animals at the end of treatment and recovery periods. The animals were euthanized by carbon dioxide (CO_2) asphyxiation followed by exsanguination.

Necropsy Procedures: At necropsy, the animals were examined visually for external abnormalities. The abdominal, thoracic, and cranial cavities were examined for abnormalities and the organs were removed, examined, and weighed. The organs such as adrenals, Brain, Heart, Lung, Liver, Testis, Epididymides, Spleen, Thymus, Ovary, Uterus, and Kidneys were weighed for organ and body weight ratio.

Statistical Analysis: Statistical analysis were performed using Graph pad prism software. Normality within groups and homogeneity of variances across groups were checked by appropriate statistical test respectively. For more than two groups, one-way ANOVA was performed for analyzing equality of means across groups. Appropriate Post–hoc test was performed for pairwise comparison across groups. For two groups, Student's t-test was performed for analyzing equality of means across groups. All analysis and comparisons were evaluated at the 5% and 1% level of significance.