EXPERIMENTAL

3

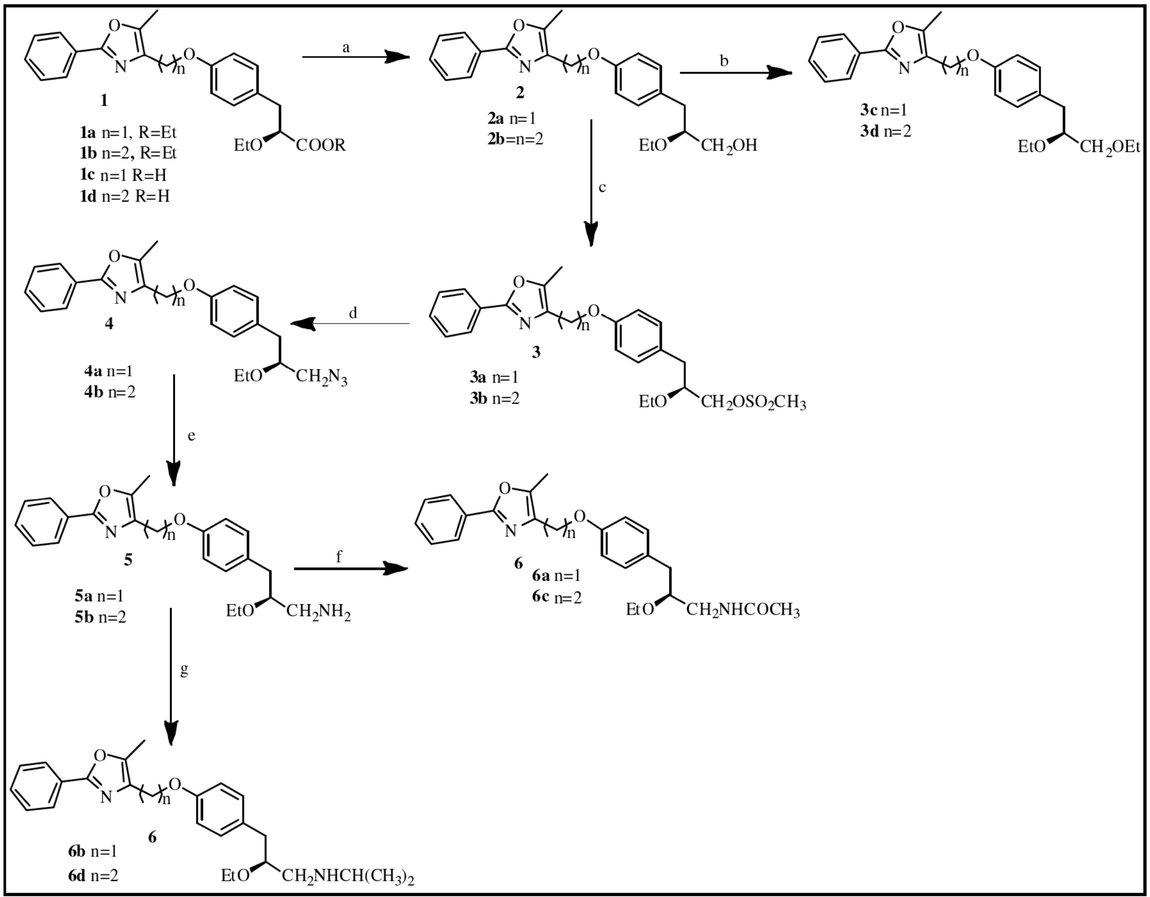
3 Experimental

Materials and methods

Reagents were obtained from Sigma Aldrich and 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 (λmax in cm^{-1}, as film 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 (d) 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), bs (broad singlet), and m (multiplet). D_2O exchange experiments were carried out to confirm the exchangeable protons when present. Mass spectra (ESI-MS) were obtained on Shimadzu LCMS 2010-A spectrometer. HPLC analyses were carried out at λmax 220 nm using column ODS C-18, 150nm * 4.6 nm * 4 m on AGILENT 1100. Progress of the reactions was monitored by TLC using precoated TLC plates (E. Merck Kieselgel 60 F254) and the spots were visualized by UV and/or iodine vapors. The chromatographic purification was performed on silica gel (230–400 mesh).

3.1 Synthesis of phenylpropane derivatives

Scheme : 1

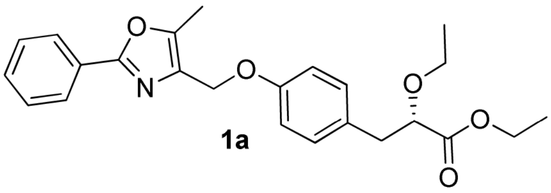


Reagents and conditions : (a) $LiAlH_4$, dry THF, 0-20 ^{o}C, 4h; (b) NaH, EtI, DMF, 25-28 ^{o}C, 4h; (c) Et_3N, CH_3SO_2Cl, CH_2Cl_2, 0-10 ^{o}C, 2h; (d) NaN_3, DMF, 100 ^{o}C, 6h; (e) Ph_3P, THF, 25-28 ^{o}C, 10h, H_2O, 10h; (f) Et_3N, CH_3COCl, CH_2Cl_2, 0-10 ^{o}C, 3h; (g) NaH, $ICH(CH_3)_2$, DMF, 25-28 ^{o}C, 8h.

3.1.1 Compounds

3.1.1.1 Compound 1a

Ethyl (2*S*)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl]-propanoate.



1a

To a solution of ethyl (2*S*)-ethoxy-3-(4-hydroxy-phenyl)-propanoate [1] (1.15 g, 4.83 mmol) and 4-chloromethyl-5-methyl-2-phenyl-oxazole [2] (1.0 g, 4.83 mmol) in dry DMF (10 mL), K_2CO_3 (1.33 g, 9.66 mmol) was added and the reaction mixture was stirred at 60-70 °C for 20 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water and brine, dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography using 8% ethyl acetate in hexane as eluent to give 1.79 g of title compound **1a** as thick liquid.

Purity by HPLC : 98 %

IR (Neat) : 820, 1071, 1160, 1251, 1341, 1515, 1587, 1720, 1741, 2881 cm^{-1}

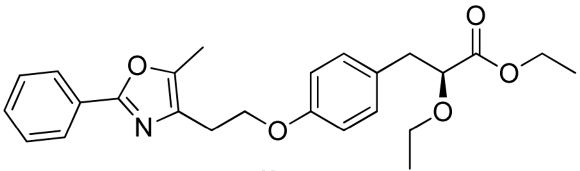
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 7.1 Hz, 3H), 1.2(t, *J* = 7.0 Hz, 3H), 2.4(s, 3H), 3.0-3.2(m, 2H), 3.5-3.6(m, 2H), 4.0(dd, *J* = 4.3 Hz & 7.4 Hz, 1H), 4.2-4.4(q, *J* = 7.1 Hz & 7.1 Hz, 2H), 4.9(s, 2H), 6.8(dd, *J* = 2.0 Hz & 6.7 Hz, 2H), 7.1(d, *J* = 1.9 Hz, 2H), 7.4-7.55(m, 3H), 8.0(dd, *J* = 1.8 Hz & 5.1 Hz, 2H).

ESI/MS (m/z) : 410 $(M+H)^+$

% Yield : 91 %

3.1.1.2 Compound 1b

Ethyl (2*S*)-ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propanoate.



1b

Title compound was prepared from ethyl (2*S*)-ethoxy-3-(4-hydroxy-phenyl)-propanoate [1] and 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethyl methanesulfonate [2] following the procedure described for compound **1a**. Thick liquid.

Purity by HPLC : 99 %

IR (Neat) : 821, 1064, 1176, 1245, 1344, 1513, 1583, 1744, 2877 cm^{-1}

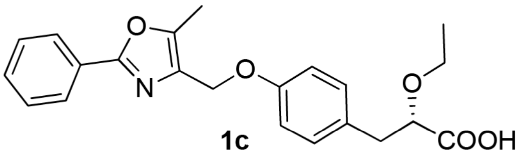
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 7.1 Hz, 3H), 1.2(t, *J* = 7.0 Hz, 3H), 2.4(s, 3H), 3.0-3.2(m, 4H), 3.5-3.7(m, 2H), 4.0(dd, *J* = 4.3 Hz & 7.4 Hz, 1H), 4.1-4.3(q, *J* = 7.1 Hz & 7.1Hz, 2H), 4.2(t, *J* = 6.7 Hz, 2H), 6.8(dd, *J* = 2.0 Hz & 6.7 Hz, 2H), 7.1(d, *J* = 1.9 Hz, 2H), 7.4-7.5(m, 3H), 8.0(dd, *J* = 1.8 Hz & 5.7 Hz, 2H).

ESI/MS (m/z) : 424 $(M+H)^+$

% Yield : 93 %

3.1.1.3 Compound 1c

(2*S*)-Ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-yl-methoxy]-phenyl] propanoic acid.



1c

To a solution of ethyl (2*S*)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-ylmethoxy]-phenyl]-propanoate **1a** (1.5 g, 3.66 mmol) in EtOH (10 mL), a solution of NaOH (0.29 g, 7.3 mmol) in H_2O (5 mL) was added and stirred at 25-28 °C for 18 h. The reaction mixture was concentrated in vacuum, diluted with water (20 mL), acidified by HCl and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with water (30 mL) and brine solution (30 mL), dried over sodium sulfate and evaporated in vacuum to give 1.27 g of title compound **1c** as white solid.

Purity by HPLC : 99 %

IR (KBr) : 1071, 1160, 1251, 1340, 1515, 1589, 1622, 1717, 2880, 3411 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.2(t, J = 7.0 Hz, 3H), 2.4(s, 3H), 3.0-3.2(m, 2H), 3.5-3.6(m, 2H), 4.0(dd, J = 4.3 Hz & 7.4 Hz, 1H), 4.9(s, 2H), 6.8(dd, J = 2.0 Hz & 6.7 Hz, 2H), 7.1(d, J = 1.9 Hz, 2H), 7.4-7.5(m, 3H), 8.0(dd, J = 1.8 Hz & 5.1 Hz, 2H).

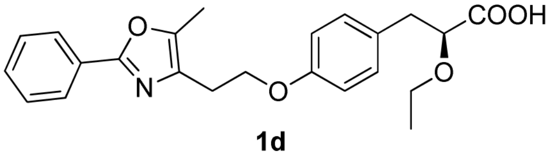
ESI/MS (m/z) : 382 (M+H)$^+$

% Yield : 91 %

mp : 103-104 °C

3.1.1.4 Compound 1d

(2*S*)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl] propanoic acid.



1d

Title compound was prepared from **1b** following the procedure described for compound **1c**. White solid.

Purity by HPLC : 99 %

IR (KBr) : 1064, 1176, 1245, 1342, 1512, 1583, 1612, 1706, 2877, 3409 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.2(t, J = 7.0 Hz, 3H), 2.4(s, 3H), 3.0-3-2(m, 4H), 3.5-3.6(m, 2H), 4.0(dd, J = 4.3 Hz & 7.4 Hz, 1H), 4.2(t, J = 6.7 Hz, 2H), 6.8(dd, J

= 2.0 Hz & 6.7 Hz, 2H), 7.1(d, *J* = 1.9 Hz, 2H), 7.4-7.6(m, 3H), 8.0(dd, *J* = 1.8 Hz & 5.1 Hz, 2H).

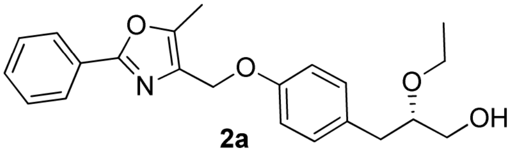
ESI/MS (m/z) : 396 $(M+H)^+$

% Yield : 93 %

mp : 97-98 °C

3.1.1.5 Compound 2a

(2*S*)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propan-1-ol.



2a

To a solution of ethyl (2*S*)-ethoxy-3-[4-[5-methyl-2-phenyl-oxazol-4-ylmethoxy]-phenyl]-propanoate **1a** (2.0 g, 4.89 mmol) in THF (10 mL), $LiAlH_4$ (0.185 g, 4.89 mmol) was added in small portions at 0 °C over a period of 30 min under nitrogen atmosphere and stirred at 20 °C for 4 h. Excess $LiAlH_4$ was quenched by dropwise addition of saturated aqueous Na_2SO_4 solution at 0-10 °C. Solid residue was filtered and washed with ethyl acetate. Filtrate was evaporated in vacuum to give 1.74 g of title compound **2a** as thick liquid.

Purity by HPLC : 97.66 %

IR (Neat) : 754, 1068, 1178, 1215, 1342, 1488, 1510, 2927, 3438 cm^{-1}

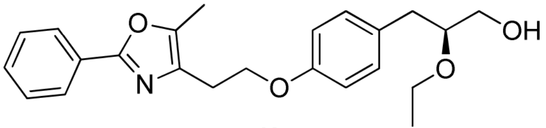
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.17(t, *J* = 6.99 Hz, 3H), 2.4(s, 3H), 2.6-2.8(m, 2H), 3.4-3.6(m, 5H), 4.9(s, 2H), 6.94(d, *J* = 8.64 Hz, 2H), 7.12(d, *J* = 8.58 Hz, 2H), 7.42-7.46(m, 3H), 8.0-8.03(m, 2H).

ESI/MS (m/z) : 368 $(M+H)^+$

% Yield : 97 %

3.1.1.6 Compound 2b

(2*S*)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propan-1-ol.



2b

Title compound was prepared from **1b** following the procedure described for compound **2a**. Off white solid.

Purity by HPLC : 97.28 %

IR (KBr) : 835, 1056, 1178, 1286, 1448, 1581, 2862, 3290 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.1(t, J = 6.9 Hz, 3H), 2.3(s, 3H), 2.5(dd, J = 6.7 Hz & 13.5 Hz, 1H), 2.7(dd, J = 6.9 Hz & 12.9 Hz, 1H), 2.9(t, J = 6.69 Hz, 2H), 3.5-3.6(m, 5H), 4.2(t, J = 6.69 Hz, 2H), 6.8(d, J = 8.55 Hz, 2H), 7.1(d, J = 8.5 Hz, 2H), 7.2-7.4(m, 3H), 7.9-8.0(m, 2H).

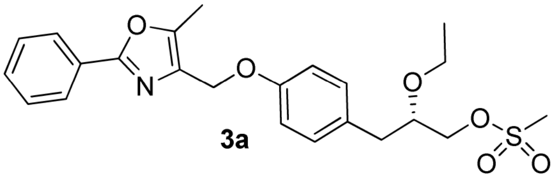
ESI/MS (m/z) : 382 (M+H)$^+$

% Yield : 84 %

m.p. : 45-47 °C

3.1.1.7 Compound 3a

(2*S*)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl methanesulfonate.



3a

To a solution of (2*S*)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propan-1-ol **2a** (1.0 g, 2.72 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.42 g, 4.08 mmol) was added followed by drop-wise addition of CH_3SO_2Cl (0.37 mg, 3.26 mmol) at 0-10 ^{o}C under nitrogen atmosphere and stirred at the same temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water, $NaHCO_3$ solution, dil HCl and brine, dried over sodium sulfate and evaporated in vacuum to give 1.18 g of title compound **3a** as thick liquid.

Purity by HPLC : 98 %

IR (Neat) : 828, 1069, 1095, 1159, 1215, 1250, 1345, 1530, 2929, 3122 cm^{-1}

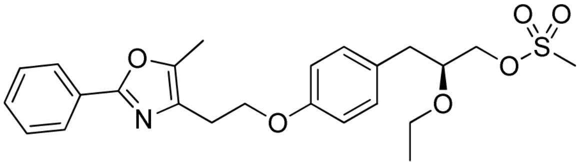
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.15(t, *J* = 6.99 Hz, 3H), 2.4(s, 3H), 2.7-2.8(m, 2H), 3.0(s, 3H), 3.4-3.6(m, 2H), 3.6-3.7(m, 1H), 4.0-4.2(m, 2H), 4.9(s, 2H), 6.95(d, *J* = 8.61 Hz, 2H), 7.14(d, *J* = 8.61 Hz, 2H), 7.41-7.46(m, 3H), 8.0-8.03(m, 2H).

ESI/MS (m/z) : 446 $(M+H)^+$

% Yield : 98 %

3.1.1.8 Compound 3b

(2*S*)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl methanesulfonate.



3b

Title compound was prepared from **2b** following the procedure described for compound **3a**. White solid.

Purity by HPLC : 96 %

IR (KBr) : 835, 1071, 1150, 1216, 1250, 1350, 1529, 2924, 3110 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 7.0 Hz, 3H), 2.3(s, 3H), 2.8-3.0(m, 2H), 2.9(t, *J* = 6.7 Hz, 2H), 3.0(s, 3H), 3.5-3.6(m, 2H), 3.6-3.8(m, 1H), 4.0(dd, *J* = 5.6 Hz & 10.9 Hz, 1H), 4.2-4.3(m, 3H), 6.8(d, *J* = 8.6 Hz, 2H), 7.1(d, *J* = 8.5 Hz, 2H), 7.4-7.6(m, 3H), 7.9-8.0(m, 2H).

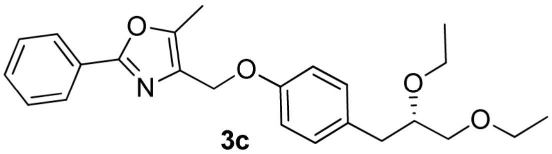
ESI/MS (m/z) : 460 $(M+H)^+$

% Yield : 84 %

m.p. : 62-64 °C

3.1.1.9 Compound 3c

4-[4-(2*S*,3-Diethoxy-propyl)-phenoxymethyl]-5-methyl-2-phenyl-oxazole.



3c

To an ice cold suspension of NaH (60%) (81.7 mg, 2.04 mmol) in DMF (1 mL), a solution of (2*S*)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)- phenyl]-propan-1-ol **2a** (500 mg, 1.36 mmol) in DMF (1 mL) was added drop wise at 10 °C under nitrogen atmosphere and stirred at 25-28 °C for 0.5 h. Ethyl iodide (254 mg, 1.63 mmol) was added at 25 °C and the reaction mixture was stirred at 25-28 °C for 4 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extract was washed with water and brine solution, dried over sodium sulfate and evaporated in vacuum to give 408 mg of title compound **3c** as thick liquid.

Purity by HPLC : 93.62 %

IR (Neat) : 754, 1110, 1215, 1298, 1398, 1488, 1610, 2804, 3016 cm^{-1}

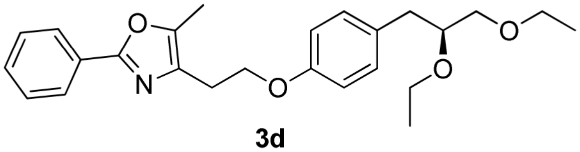
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.13(t, *J* = 6.9 Hz, 3H), 1.19(t, *J* = 6.9 Hz, 3H), 2.43(s, 3H), 2.77-3.01(m, 2H), 3.37-3.63(m, 7H), 4.97(s, 2H,), 6.9(d, *J* = 8.6 Hz, 2H), 7.17(d, *J* = 8.6 Hz, 2H), 7.42-7.47(m, 3H), 8.0-8.03(m, 2H).

ESI/MS (m/z) : 396 $(M+H)^+$

% Yield : 76 %

3.1.1.10 Compound 3d

4-[2-[4-(2*S*,3-Diethoxy-propyl)-phenoxy]-ethyl]-5-methyl-2-phenyloxazole.



3d

Title compound was prepared from **2b** following the procedure described for compound **3c**. Thick liquid.

Purity by HPLC : 99.47 %

IR (Neat) : 756, 1110, 1215, 1244, 1382, 1512, 1610, 2927, 3018 cm^{-1}

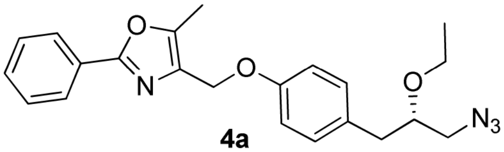
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 6.99 Hz, 3H), 1.2(t, *J* = 6.99 Hz, 3H), 2.4(s, 3H), 2.7(t, *J* = 6.6 Hz, 2H), 3.0(t, *J* = 6.69 Hz, 2H), 3.5-3.7(complex, 7H), 4.2(t, *J* = 6.69 Hz, 2H), 6.8(dd, *J* = 1.87 Hz & 6.65 Hz, 2H), 7.1(d, *J* = 8.55 Hz, 2H), 7.4-7.5(m, 3H), 7.9-8.1(m, 2H).

ESI/MS (m/z) : 410 $(M+H)^+$

% Yield : 57 %

3.1.1.11 Compound 4a

4-[4-(3-Azido-2*S*-ethoxy-propyl)-phenoxymethyl]-5-methyl-2-phenyl-oxazole.



4a

To a solution of (2*S*)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl methanesulfonate **3a** (1.0 g, 2.25 mmol) in dry DMF (2 mL), NaN_3 (0.73 g, 11.2 mmol) was added and the reaction mixture was stirred at 100 °C for 6 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extract was washed with water (30 mL) and brine solution (30 mL), dried over sodium sulfate and evaporated in vacuum to give 855 mg of title compound **4a** as thick liquid.

Purity by HPLC : 97.63 %

IR (Neat) : 669, 927, 1016, 1215, 1448, 1610, 2875, 2977 cm^{-1}

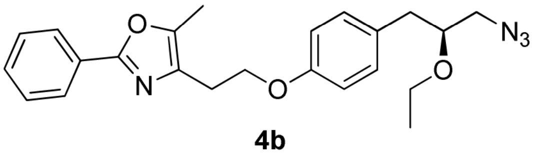
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.18(t, *J* = 6.99 Hz, 3H), 2.4(s, 3H), 2.7-2.85(m, 2H), 3.2-3.3(m, 2H), 3.45-3.65(m, 3H), 4.9(s, 2H), 6.95(d, *J* = 8.6 Hz, 2H), 7.14(d, *J* = 8.61 Hz, 2H), 7.41-7.46(m, 3H), 8.0-8.03(m, 2H).

ESI/MS (m/z) : 392 $(M+H)^+$

% Yield : 97 %

3.1.1.12 Compound 4b

4-[2-[4-(3-Azido-2*S*-ethoxy-propyl)-phenoxy]-ethyl]-5-methyl-2-phenyl-oxazole.



4b

Title compound was prepared from **3b** following the procedure described for compound **4a**. White solid.

Purity by HPLC : 99 %

IR (KBr) : 690, 947, 1091, 1170, 1278, 1384, 1463, 1510, 1610, 2854, 2979 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.2(t, *J* = 7.0 Hz, 3H), 2.3(s, 3H), 2.7(dd, *J* = 6.6 Hz & 13.5 Hz, 1H), 2.8(dd, *J* = 6.2 Hz & 13.5 Hz, 1H), 2.9(t, *J* = 6.7 Hz, 2H), 3.1-3.2(m, 2H), 3.5-3.7(m, 3H), 4.2(t, *J* = 6.7 Hz, 2H), 6.8(d, *J* = 9.5 Hz, 2H), 7.1(d, *J* = 8.5 Hz, 2H), 7.4-7.6(m, 3H), 7.9-8.11(m, 2H).

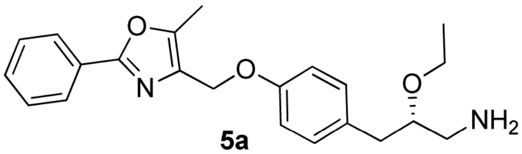
ESI/MS (m/z) : 407 $(M+H)^+$

% Yield : 71 %

mp : 60-63 °C

3.1.1.13 Compound 5a

(2*S*)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl amine.



5a

To a solution of (4-[4-(3-azido-2S-ethoxy-propyl)-phenoxymethyl]-5- methyl-2-phenyl-oxazole **4a** (1.2 g, 3.06 mmol) in dry THF (10 mL), Ph_3P (0.96 g, 3.67 mmol) was added and reaction mixture was stirred at 25-27 °C for 10 h. H_2O (10 mL) was added and the reaction mixture was stirred at 25-27 °C for 10 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extract was washed with water (30 mL) and brine solution (30 mL), dried over sodium sulfate and evaporated in vacuum. The crude product was purified by flash column chromatography using 1% MeOH in $CHCl_3$ as eluent to give 828 mg of title compound **5a** as thick liquid.

Purity by HPLC : 94 %

IR (Neat) : 669, 1089, 1179, 1388, 1466, 1510, 2360, 2979, 3411 cm^{-1}

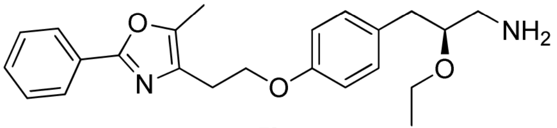
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.2(t, *J* = 6.9 Hz, 3H), 2.45(s, 3H), 2.68(d, *J* = 5.3 Hz, 2H), 2.70-2.84(m, 2H), 3.53-3.62(m, 2H), 3.74-4.05(m, 1H), 5.0(s, 2H), 6.9(d, *J* = 8.0 Hz, 2H), 7.1(d, *J* = 8.58 Hz, 2H), 7.42-7.45(m, 3H), 7.99-8.03(m, 2H).

ESI/MS (m/z) : 367 $(M+H)^+$

% Yield : 72 %

3.1.1.14 Compound 5b

(2*S*)-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl amine.



5b

Title compound was prepared from **4b** following the procedure described for compound **5a**. Thick liquid.

Purity by HPLC : 98 %

IR (Neat) : 669, 927, 1091, 1180, 1388, 1465, 1511, 2359, 2979, 3409 cm^{-1}

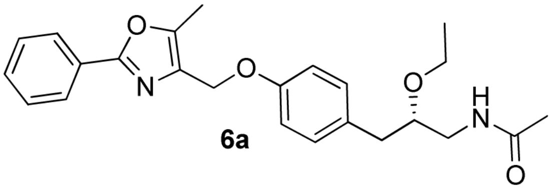
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 6.91 Hz, 3H), 2.3(s, 3H), 2.6-2.8(m, 4H), 2.9(t, *J* = 6.69 Hz, 2H), 3.4-3.5(m, 3H), 4.2(t, *J* = 6.69 Hz, 2H), 6.8(d, *J* = 8.5 Hz, 2H), 7.0(d, *J* = 8.4 Hz, 2H), 7.4-7.5(m, 3H), 7.9-8.01(m, 2H).

ESI/MS (m/z) : 381 $(M+H)^+$

% Yield : 76 %

3.1.1.15 Compound 6a

N-[(2*S*)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl] -acetamide.



6a

To a solution (2*S*)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)- phenyl]-propylamine **5a** (500 mg, 1.37 mmol) in CH_2Cl_2 (5 mL), Et_3N (207 mg, 2.05 mmol) was added followed by drop-wise addition of CH_3COCl (125 mg, 1.64 mmol) at 0-10 ^{o}C under nitrogen atmosphere and stirred at the same temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (35 mL), washed with water (25 mL), $NaHCO_3$ solution (25 mL), dil HCl (25 mL) and brine solution (35 mL), dried over sodium sulfate and evaporated in vacuum. The crude product was triturated with diethyl ether to give 247 mg of title compound **6a** as white solid.

Purity by HPLC : 97 %

IR (KBr) : 829, 1090, 1180, 1280, 1377, 1466, 1551, 1609, 1639, 2850, 2970, 3314 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.2(t, *J* = 6.9 Hz, 3H), 2.1(s, 3H), 2.43(s, 3H), 2.69-2.77(m, 2H), 2.78-3.44(m, 1H), 3.45-3.53(m, 4H), 4.97(s, 2H), 5.73(s, 1H), 6.93 (d, *J* = 8.61 Hz, 2H), 7.12(d, *J* = 8.58 Hz, 2H), 7.42-7.46(m, 3H), 8.00-8.03(m, 2H).

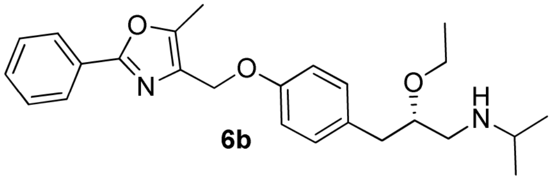
ESI/MS (m/z) : 409 $(M+H)^+$

% Yield : 37 %

mp : 111-112 °C

3.1.1.16 Compound 6b

N-[(2*S*)-Ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)-phenyl]-propyl-Isopropyl-amine.



6b

To an ice cold suspension of NaH (60%) (82 mg, 2.06 mmol) in DMF (1 mL), a solution of (2*S*)-ethoxy-3-[4-(5-methyl-2-phenyl-oxazol-4-ylmethoxy)- phenyl]-propylamine **5a** (500 mg, 1.37 mmol) in DMF (1 mL) was added drop wise at 10 °C under nitrogen atmosphere and stirred at 25-28 °C for 30 min. Isopropyl iodide (279 mg, 1.64 mmol) was added at 25-28 °C and the reaction mixture was stirred at 25-28 °C for 8 h. The reaction mixture was poured into ice cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extract was washed with water (20 mL) and brine solution (20 mL), dried over sodium sulfate and evaporated in vacuum to give 475 mg of title compound **6b** as thick liquid.

Purity by HPLC : 96 %

IR (Neat) : 1010, 1099, 1188, 1388, 1466, 1551, 2359, 2880, 2979, 3421 cm^{-1}

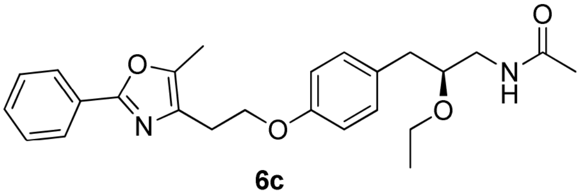
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.09(t, *J* = 6.8 Hz, 3H), 1.17(d, *J* = 5.52 Hz, 6H), 2.77-2.92(m, 4H), 2.43(s, 3H), 3.16-3.20(m, 1H), 3.25(t, *J* = 6.16 Hz, 1H), 3.43-3.92(m, 2H), 4.96(s, 2H), 6.97(d, *J* = 8.25 Hz, 2H), 7.17(d, *J* = 8.19 Hz, 2H), 7.50-7.92(m, 5H).

ESI/MS (m/z) : 409 $(M+H)^+$

% Yield : 85 %

3.1.1.17 Compound 6c

N-(2*S*-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl)-acetamide.



6c

Title compound was prepared from **5b** following the procedure described for compound **6a**. White solid.

Purity by HPLC : 98.46 %

IR (KBr) : 829, 1099, 1176, 1294, 1373, 1463, 1550, 1610, 1641, 2856, 2974, 3311 cm^{-1}

^1H NMR ($CDCl_3$, 300 MHz) : δ 1.1(t, *J* = 7.0 Hz, 3H), 1.9(s, 3H), 2.3(s, 3H), 2.6-2.8(m, 2H), 2.9(t, *J* = 6.7 Hz, 2H), 3.1-3.25(m, 1H), 3.5-3.76(m, 4H), 4.2(t, *J* = 6.7 Hz, 2H), 6.8(d, *J* = 8.6 Hz, 2H), 7.0(d, *J* = 8.5 Hz, 2H), 7.4-7.58(m, 3H), 8.0(dd, *J* = 2.3 Hz & 7.9 Hz, 2H).

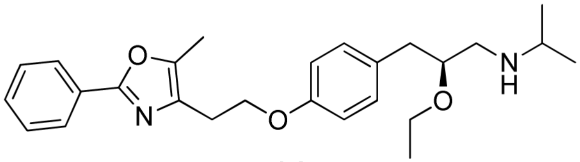
ESI/MS (m/z) : 423 $(M+H)^+$

% Yield : 64 %

mp : 101-102 °C

3.1.1.18 Compound 6d

(2*S*-Ethoxy-3-[4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl]-propyl)-isopropyl-amine.



6d

Title compound was prepared from **5b** following the procedure described for compound **6b**. White solid.

Purity by HPLC : 95 %

IR (KBr) : 692, 1022, 1099, 1220, 1245, 1484, 1512, 1612, 1702, 2345, 2977, 3433 cm^{-1}

^{1}H NMR (DMSO-d$_6$, 300 MHz) : δ 1.0-1.1(m, 9H), 2.3(s, 3H), 2.7-2.85(m, 3H), 2.9-3.1(m, 3H), 3.23-3.33(m, 1H), 3.4-3.6(complex, 3H), 4.1(t, *J* = 6.0 Hz, 2H), 6.8(d, *J* = 8.1 Hz, 2H), 7.1(d, *J* = 8.1 Hz, 2H), 7.5-7.7(m, 3H), 7.8-8.0(m, 2H).

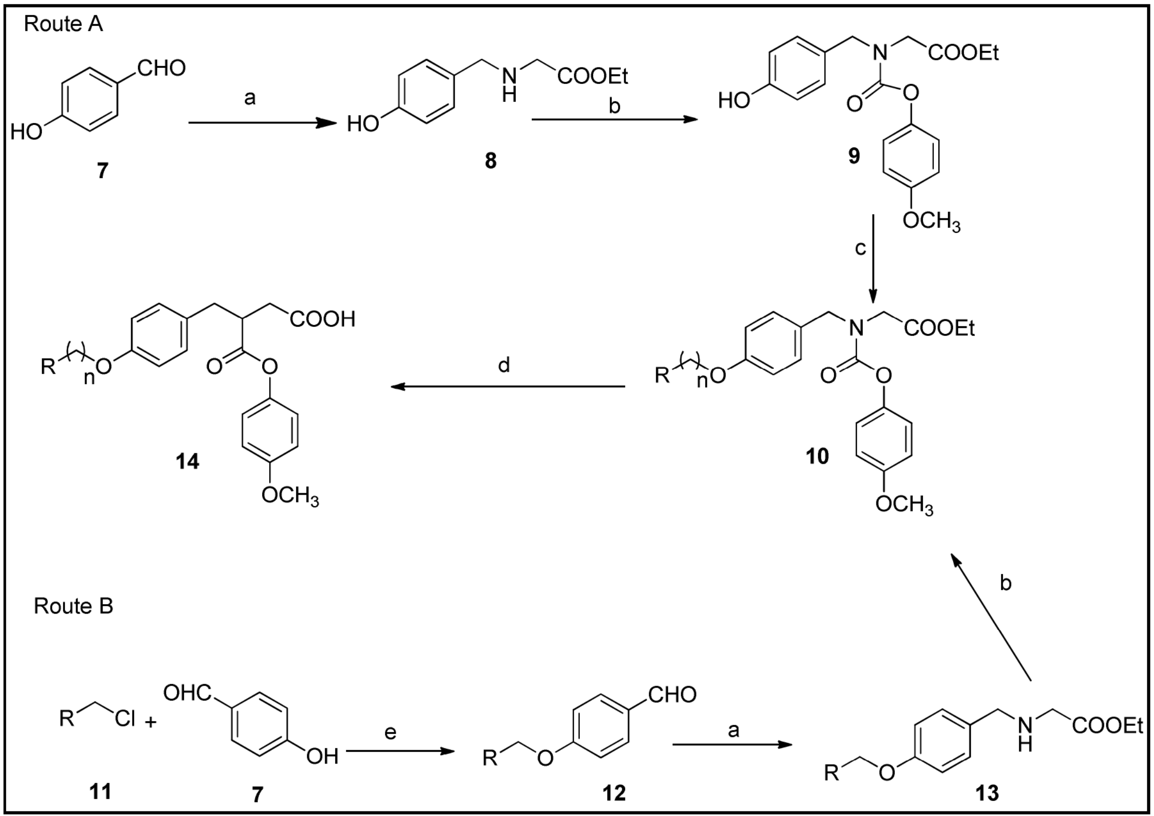
ESI/MS (m/z) : 423 (M+H)$^+$

% Yield : 82 %

mp : 122-125 °C

3.2 Synthesis oxybenzylglycine derivatives

Scheme : 2

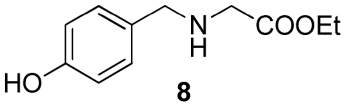


Reagents and conditions : (a) Glycin ester.HCl, TEA, $NaBH_4$, MeOH, 20-25 °C, 1h. (b) 4-OMe-PhOCOCl, Pyridine, DCM, 0-5 °C, 2h. (c) R-$(CH_2)_n$-X(n=2, X=OMs, Cl), K_2CO_3 , DMF, 60 °C, 5h. (d) NaOH, H_2O, MeOH, 20-25 °C, 4h. (e) K_2CO_3 , DMF, 60 °C, 5h.

3.2.1 Compounds of Route A

3.2.1.1 Intermediates 8

Ethyl 2-((4-hydroxybenzyl)amino)acetate.



8

To a solution of 4-hydroxy benzaldehyde **7** (10.0 g, 0.081mole) and glycine ethyl ester hydrochloride (12.7 g, 0.091mole) in methanol (100 mL) was added triethyl amine (9.81 g, 0.097 mole) at 20-25 °C and the reaction mixture was cooled in an ice bath. To this was added sodium borohydride (4.61 g, 0.121mole) and stirred for one hour at 20-25 °C. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate (100 mL). The combined organic extract was washed with water (75 mL), brine (75 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude product was flash chromatographed over silica gel using 25-40 % ethyl acetate in petroleum ether as an eluent to yield title product as an oil.

IR (Neat) : 1024, 1105, 1172, 1375, 1446, 1515, 1614, 1735, 2345, 3313 cm^{-1}

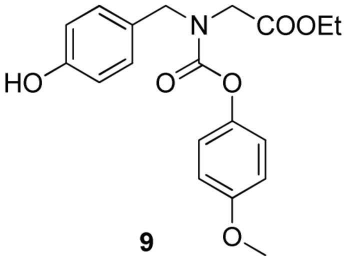
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.2(t, *J* = 7.1 Hz, 3H), 3.4(d, *J* = 5.0 Hz, 2H), 3.7(d, *J* = 6.3 Hz, 2H), 4.2(q, *J* = 7.2 Hz & 7.2 Hz, 2H), 6.7(d, *J* = 8.4 Hz, 2H), 7.1(d, *J* = 8.4 Hz, 2H).

ESI/MS (m/z) : 210 $(M+H)^+$

% Yield : 42 %.

3.2.1.2 Intermediates 9

Ethyl 2-((4-hydroxybenzyl)((4-methoxyphenoxy)carbonyl)amino)acetate.



9

To an ice cold solution of Ethyl 2-((4-hydroxybenzyl)amino)acetate **8** (7.19 g, 0.034 mole) and 4-methoxyphenyl chloroformate (6.34 g, 0.034 mole) in dichloromethane (36 mL) was added pyridine (3.22 g, 0.04 mole) and the reaction mixture was stirred at 0-5 °C for 2 h. The reaction mixture was diluted with dichloromethane (50 mL), washed with water (35 mL), 1.0 N HCl (35 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude product was chromatographed over silica gel using 10-20 % ethyl acetate in petroleum ether as an eluent to yield pure title product as an oil.

IR (Neat) : 1180, 1215, 1433, 1508, 1614, 1714, 3390 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.2(t, *J* = 7.1Hz, 3H), 3.7(s, 3H), 3.9(d, *J* = 3.6 Hz, 2H), 4.2(q, *J* = 7.1 Hz & 7.1Hz, 2H), 4.5(s, 1H), 4.6(s, 1H), 6.8(d, *J* = 7.9 Hz, 2H), 6.9(d, *J* = 8.9 Hz, 2H), 7.0-7.2(m, 2H), 7.3(d, *J* = 8.2 Hz, 2H).

ESI/MS (m/z) : 360 $(M+H)^+$

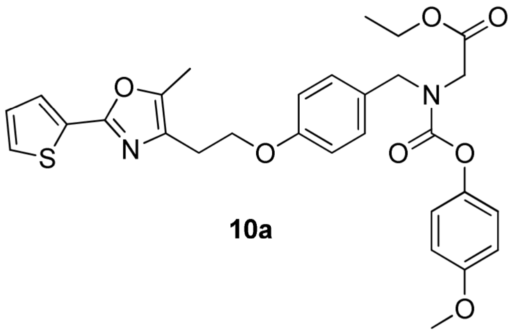
% Yield : 50 %

Procedure for Intermediates 10a-f

R-$(CH_2)_n$-X(n=2, X=OMs, Cl) [synthesis given in scheme 4 intermediate **25**] **(**1.0 g, 0.0034 mole) was added to mixture of Ethyl 2-((4-hydroxybenzyl)((4-methoxyphenoxy)carbonyl)amino)acetate **9** (1.46 g, 0.004 mole), potassium carbonate (0.703 g, 0.0051 mole) and tetrabutylammonium bromide (1 mg) in dimethyl formamide (10 mL) was stirred at 60 °C for 5 hours. The reaction mixture was cooled to 25 °C and poured in to ice cold water (25 mL), extracted with ethyl acetate (2 x 30 mL). The combined organic extract was washed with water (25 mL), brine (25 mL), dried over sodium sulfate and evaporated under reduced pressure. The crude product was (flash) chromatographed over silica gel using 10 % ethyl acetate in petroleum ether as an eluent to yield pure product as thick oil.

3.2.1.3 Intermediate 10a

Ethyl 2-(((4-methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(thiophen-2-yl) oxazol-4-yl)ethoxy)benzyl)amino)acetate.



10a

Purity by HPLC : 93.98 %

IR (Neat) : 758, 1215, 1718, 2927 cm^{-1}

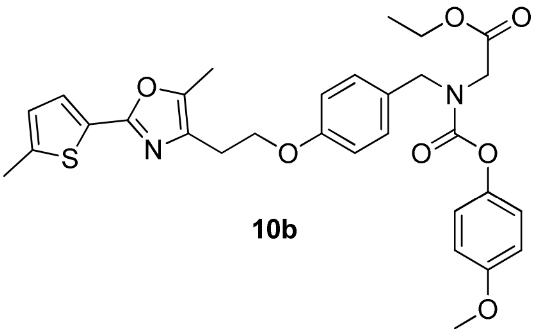
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.25(t, *J* = 7.11 Hz, 3H), 2.36(s, 3H), 2.95(t, *J* = 6.48 Hz, 2H), 3.79(s, 3H), 3.97(s, 2H), 4.14-4.24(m, 4H), 4.55(s, 1H), 4.66(s, 1H), 6.85-6.90(m, 4H), 7.01-7.09(m, 3H), 7.20-7.22(m, 2H), 7.35(m, 1H), 7.57(m, 1H).

ESI/MS (m/z) : 551.3 (M+H)$^+$

% Yield : 44 %

3.2.1.4 Intermediate 10b

Ethyl 2-(((4-methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(5-methyl-thiophen -2-yl)oxazol-4-yl)ethoxy)benzyl)amino)acetate.



10b

Purity by HPLC : 92.69 %

IR (Neat) : 667, 1216, 1719, 3018 cm^{-1}

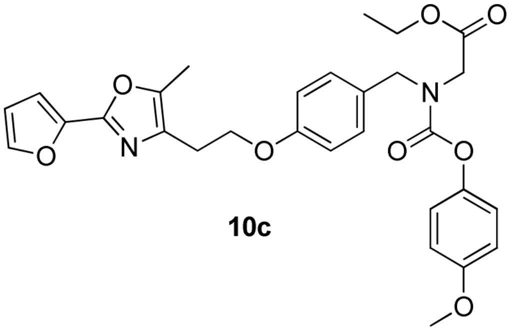
^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.22-1.27(m, 3H), 2.33(s, 3H), 2.51(s, 3H), 2.91-2.96(t, *J* = 6.45 Hz, 2H), 3.79(s, 3H), 3.98(s, 2H), 4.11-4.23(m, 4H), 4.55(s, 1H), 4.66(s, 1H), 6.72-6.73(dd, *J* = 0.9 Hz & 3.6 Hz, 1H), 6.84-6.89(m, 4H), 7.01-7.07(m, 2H), 7.20-7.26(m, 2H), 7.37(d, *J* = 3.6 Hz, 1H).

ESI/MS (m/z) : 565.4 (M+H)$^+$

% Yield : 52 %

3.2.1.5 Intermediate 10c

Ethyl 2-((4-(2-(2-(furan-2-yl)-5-methyloxazol-4-yl)ethoxy)benzyl)((4-methoxy phenoxy)carbonyl)amino)acetate.



10c

Purity by HPLC : 91.8 %

IR (Neat) : 670, 1302, 1701, 1710, 3075 cm^{-1}

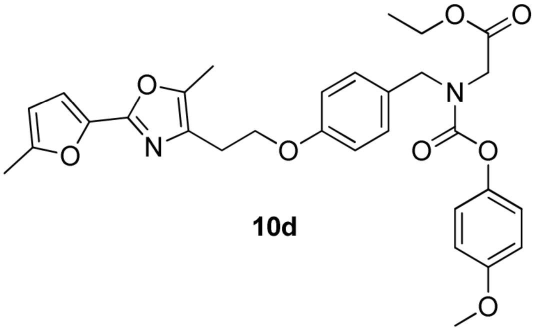
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.24-1.30(m, 3H), 2.31(s, 3H), 2.95(t, *J* = 6.8 Hz, 2H), 3.77(s, 3H), 4.01(s, 2H), 4.15-4.26(m, 4H), 4.59(s, 1H), 4.69(s, 1H), 6.48-6.50(dd, *J* = 1.8 Hz & 3.7 Hz, 1H), 6.84-6.88(m, 2H), 7.02-7.06(m, 2H), 7.26-7.40(m, 2H), 7.43-7.48(m, 1H), 7.51-7.52(m, 1H), 7.53-7.56(m, 2H).

ESI/MS (m/z) : 535.3 $(M+H)^+$

% Yield : 51 %

3.2.1.6 Intermediate 10d

Ethyl 2-(((4-methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)ethoxy)benzyl)amino)acetate.



10d

Purity by HPLC : 94.5 %

IR (Neat) : 661, 1300, 1698, 1705, 3100 cm^{-1}

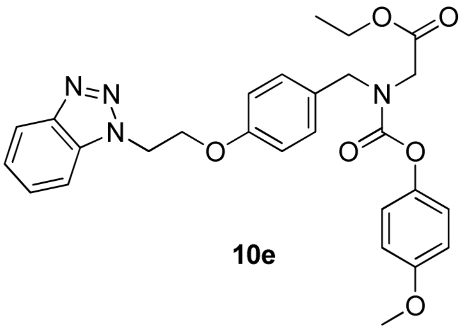
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 0.82-0.90(m, 3H), 2.35(s, 3H), 2.38(s, 3H), 2.95(t, *J* = 6.15 Hz, 2H), 3.79(s, 3H), 3.98(s, 2H), 4.16-4.25(m, 4H), 4.55(s, 1H), 4.65(s, 1H), 6.1(d, *J* = 2.4 Hz, 1H), 6.80-6.81(m, 2H), 6.84-6.88(m, 2H), 7.01-7.07(m, 3H), 7.20-7.26(m, 2H).

ESI/MS (m/z) : 549.3 $(M+H)^+$

% Yield : 46 %

3.2.1.7 Intermediate 10e

Ethyl 2-((4-(2-(1H-benzo[d][1,2,3]triazol-1-yl)ethoxy)benzyl)((4-methoxy phenoxy)carbonyl)amino)acetate.



10e

Purity by HPLC : 97.52 %

IR (Neat) : 725, 1508, 1720, 2927 cm^{-1}

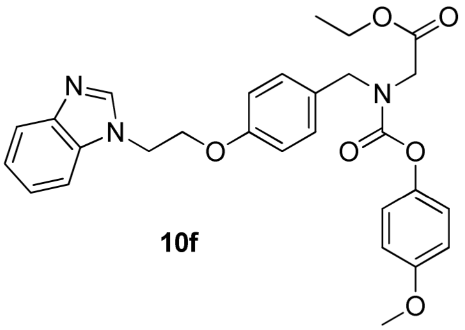
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.22-1.25(m, 3H), 3.79(s, 3H), 3.96(s, 2H), 4.13-4.18(m, 2H), 4.54-4.67(m, 4H), 5.11(t, *J* = 5.50 Hz, 2H), 6.85-6.90(m, 4H), 7.01(d, *J* = 7.2 Hz, 2H), 7.20(d, *J* = 8.59 Hz, 2H), 7.38-7.41(m, 2H), 7.86-7.89(m, 2H).

ESI/MS (m/z) : 505 (M+H)$^+$

% Yield : 50 %

3.2.1.8 Intermediate 10f

Ethyl 2-((4-(2-(1H-benzo[d]imidazol-1-yl)ethoxy)benzyl)((4-methoxy phenoxy)carbonyl)amino)acetate.



10f

Purity by HPLC : 87.53 %

IR (Neat) : 1377, 1508, 1720, 1751 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.20-1.28(m, 3H), 3.78(s, 3H), 3.96(s, 2H), 4.15-4.18(m, 2H), 4.30-4.32(m, 2H), 4.54(s, 1H), 4.56-4.59(m, 2H), 4.64(s, 1H), 6.81(d, *J* = 8.49 Hz, 2H), 6.85(d, *J* = 9.15 Hz, 2H), 7.02(d, *J* = 8.97 Hz, 2H), 7.22(d, *J* = 8.58 Hz, 2H), 7.26-7.81(m, 4H), 8.06(s, 1H).

ESI/MS (m/z) : 504 $(M+H)^+$

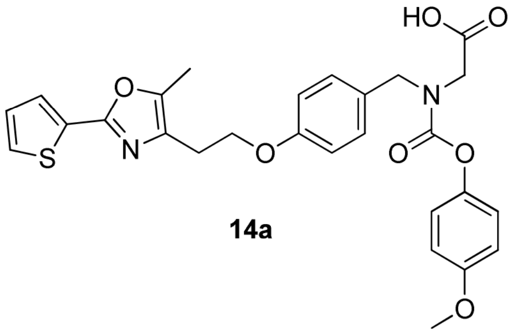
% Yield : 39 %

Procedure of Compound 14a

To a solution of ester compound **10a** (0.4 g, 0.72 mmole) in ethanol (2.4 mL) was added another solution of sodium hydroxide (37 mg, 0.94mmole) in water (1.2 mL) and the reaction mixture was stirred at ambient temperature for 4 hours. Solvents were evaporated under reduced pressure. Residue was dissolved in water (4 mL), acidified with 1N HCl and extracted with ethylacetate (25 mL). The combined organic extract was washed with water (20 mL), brine (20 mL), dried over sodium sulfate and evaporated under reduced pressure to afford crude product. The crude product was chromatographed (flash) over silica gel using 3.5 % methanol in chloroform as an eluent to obtain pure product as a solid.

3.2.1.9 Compound 14a

2-(((4-Methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(thiophen-2-yl)oxazol-4-yl)ethoxy)benzyl)amino)acetic acid.



14a

Purity by HPLC : 98.57 %

IR (KBr) : 725, 1170, 1512, 1720, 2927, 3433 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.35(s, 3H), 2.96(t, J = 6.48 Hz, 2H), 3.77(s, 3H), 4.02(s, 2H), 4.18-4.21(m, 2H), 4.55(s, 1H), 4.64(s, 1H), 6.83-6.89(m, 4H), 7.01-7.08(m, 3H), 7.20(d, J = 7.5 Hz, 2H), 7.35(d, J = 4.14 Hz, 1H), 7.59(d, J = 3.54 Hz, 1H).

ESI/MS (m/z) : 523.2 (M+H)$^+$

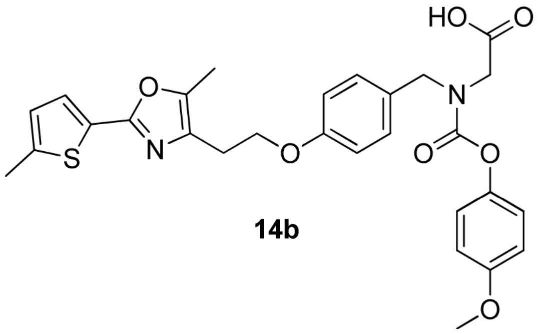
% Yield : 84 %

mp : 150-151 °C

Compounds **14b-f** were prepared by following the procedure of Compound **14a** using appropriate starting materials.

3.2.1.10 Compound 14b

2-(((4-Methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(5-methylthiophen-2-yl) oxazol-4-yl)ethoxy)benzyl)amino)acetic acid.



14b

Purity by HPLC : 98.42 %

IR (KBr) : 754, 1029, 1284, 1510, 1728, 2526, 3429 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 2.35(s, 3H), 2.49(s, 3H), 2.96(s, 2H), 3.77(s, 3H), 4.0(s, 2H), 4.18(t, J = 6.4 Hz, 2H), 4.54(s, 1H), 4.64(s, 1H), 6.72(d, J = 3.08 Hz, 1H), 6.72-6.87(m, 4H), 7.03(d, J = 8.6 Hz, 2H), 7.21(d, J = 8.29 Hz, 2H), 7.41(d, J = 3.58 Hz, 1H).

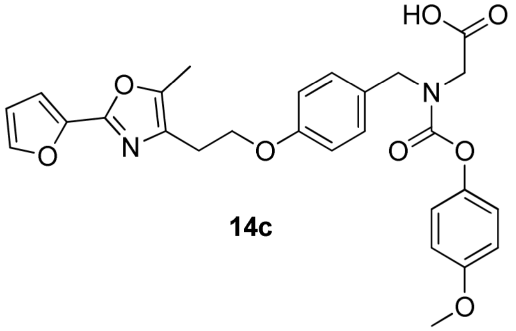
ESI/MS (m/z) : 537 (M+H)$^+$

% Yield : 35 %

mp : 139-140 °C

3.2.1.11 Compound 14c

2-((4-(2-(2-(Furan-2-yl)-5-methyloxazol-4-yl)ethoxy)benzyl)((4-methoxy phenoxy)carbonyl)amino)acetic acid.



14c

Purity by HPLC : 97.75 %

IR (KBr) : 823, 1028, 1195, 1596, 1631, 1724, 2943, 3427 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 2.36(s, 3H), 2.97(t, *J* = 5.15 Hz, 2H), 3.77(s, 3H), 4.01(s, 2H), 4.22(t, *J* = 5.8 Hz, 2H), 4.55(s, 1H), 4.63(s, 1H), 6.48-6.50(m, 1H), 6.83-6.88(m, 4H), 6.96(d, *J* = 3.37 Hz, 1H), 7.01-7.07(m, 2H), 7.21(d, *J* = 8.04 Hz, 2H), 7.5(s, 1H).

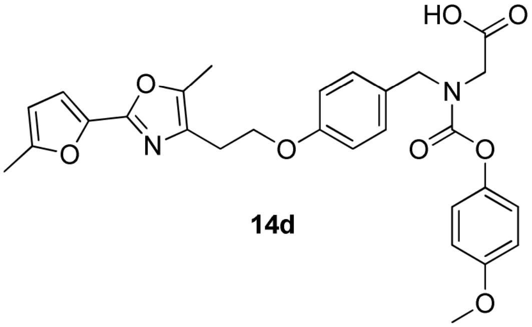
ESI/MS (m/z) : 506.9 (M+H)$^+$

% Yield : 77 %

mp : 137-138 °C

3.2.1.12 Compound 14d

2-(((4-Methoxyphenoxy)carbonyl)(4-(2-(5-methyl-2-(5-methylfuran-2-yl) oxazol-4-yl)ethoxy)benzyl)amino)acetic acid.



14d

Purity by HPLC : 93.88 %

IR (KBr) : 756, 1568, 1716, 2935 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.37(s, 3H), 2.42(s, 3H), 2.96(t, *J* = 5.65 Hz, 2H), 3.78(s, 3H), 4.02(s, 2H), 4.20(t, *J* = 5.64 Hz, 2H), 4.55(s, 1H), 4.65(s, 1H), 6.08(d, *J* = 2.63 Hz, 1H), 6.83-6.91(m, 5H), 7.05(t, *J* = 9.0 Hz, 2H), 7.20(d, *J* = 8.30 Hz, 2H).

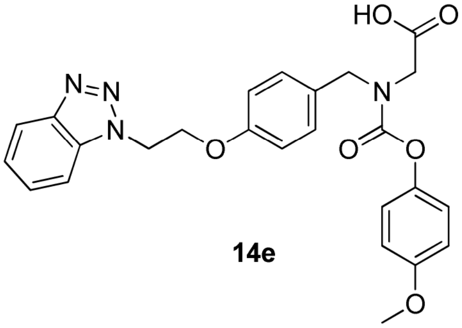
ESI/MS (m/z) : 521 (M+H)$^+$

% Yield : 81 %

mp : 118-120 °C

3.2.1.13 Compound 14e

2-((4-(2-(1H-Benzo[d][1,2,3]triazol-1-yl)ethoxy)benzyl)((4-methoxy phenoxy) carbonyl)amino)acetic acid.



14e

Purity by HPLC : 99.17 %

IR (KBr) : 730, 1508, 1720, 2927 cm^{-1}

^{1}H NMR (CDCl3, 300 MHz) : δ 3.76(s, 3H), 4.08(s, 2H), 4.53(s, 2H), 4.64(t, J = 5.59 Hz, 2H), 5.10(t, J = 5.52 Hz, 2H), 6.82-6.85(m, 4H), 7.00(d, J = 8.80 Hz, 2H), 7.19(d, J = 8.07 Hz, 2H), 7.37-7.41(m, 2H), 7.86-7.89(m, 2H).

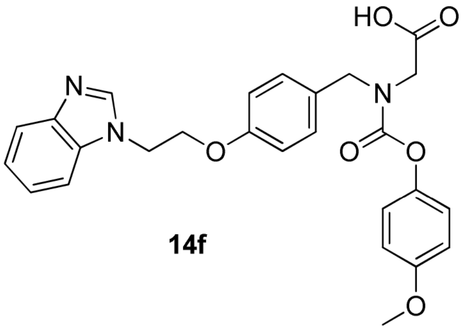
ESI/MS (m/z) : 477 (M+H)$^{+}$

% Yield : 62 %

mp : 117-118°C

3.2.1.14 Compound 14f

2-((4-(2-(1H-Benzo[d]imidazol-1-yl)ethoxy)benzyl)((4-methoxy phenoxy) carbonyl)amino)acetic acid.



14f

Purity by HPLC : 94.94 %

IR (KBr) : 721, 1436, 1508, 1718 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ3.78(s, 3H), 4.04(s, 2H), 4.38-4.39(m, 2H), 4.53-4.56(m, 3H), 4.66(s, 1H), 6.62(d, *J* = 8.28 Hz, 2H), 6.85(d, *J* = 8.94 Hz, 2H), 7.06(d, *J* = 9.03 Hz, 2H), 7.18(d, *J* = 8.55 Hz, 2H), 7.32-7.39(m, 2H), 7.47(d, *J* = 7.47 Hz, 1H), 7.80(d, *J* = 7.8 Hz, 1H), 8.02(s, 1H).

ESI/MS (m/z) : 476 (M+H)$^+$

% Yield : 64 %

mp : 98-99 °C

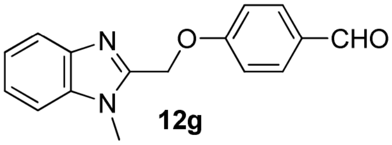
3.2.2 Compounds of Route B

Procedure of Intermediates 12g-i

To a solution 4-hydroxy benzaldehyde **7** (1.62 g, 0.013 mole) in dimethyl formamide (20 mL) was added chloro compound **11** [3] (2.0 g, 0.011 mole), and potassium carbonate (2.27 g, 0.016 mole). The reaction was stirred at 60 °C for 5 hours. The reaction mixture was cooled to 30 °C and poured in to ice cold water (50 mL), extracted with ethyl acetate (2 x 60 mL). The combined organic extract was washed with water (50 mL), brine (50 mL) , dried over sodium sulfate and evaporated under reduced pressure. The crude product was (flash) chromatographed over silica gel using 10 % ethyl acetate in petroleum ether as an eluent to yield liquid product.

3.2.2.1 Intermediates 12g

4-((1-Methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzaldehyde.



12g

Purity by HPLC : 98.4 %

IR (Neat) : 1199, 1339, 1740 cm^{-1}

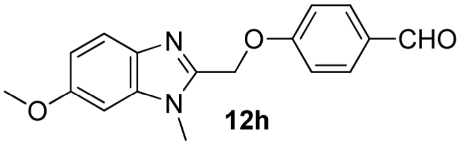
^{1}H NMR (CDCl$_3$, 300 MHz) : δ3.8(s, 3H), 4.05(s, 2H), 6.83(d, *J* = 7.2 Hz, 2H), 7.02-7.08(m, 4H), 7.28-7.30(m, 2H), 9.86(s, 1H).

ESI/MS (m/z) : 267 (M+H)$^+$

% Yield : 60 %

3.2.2.2 Intermediates 12h

4-((6-Methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzaldehyde.



12h

Purity by HPLC : 96 %

IR (Neat) : 1132, 1190, 1320, 1698 cm^{-1}

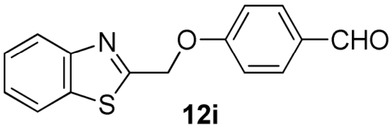
^{1}H NMR (CDCl$_3$, 300 MHz) : δ3.70(s, 3H), 3.82(s, 3H), 5.2(s, 2H), 6.81-6.89(m, 4H), 7.2-7.35(m, 3H), 10.01(s, 1H).

ESI/MS (m/z) : 297 (M+H)$^+$

% Yield : 65 %

3.2.2.3 Intermediates 12i

4-(Benzo[d]thiazol-2-ylmethoxy)benzaldehyde.



12i

Purity by HPLC : 91.89 %

IR (Neat) : 1438, 1695, 3423 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 5.57(s, 2H), 7.16(d, J = 8.7 Hz, 2H), 7.42-7.45(m, 1H), 7.49-7.54(m, 1H), 7.85-7.92(m, 3H), 8.05(d, J = 8.1 Hz, 1H), 9.9(s, 1H).

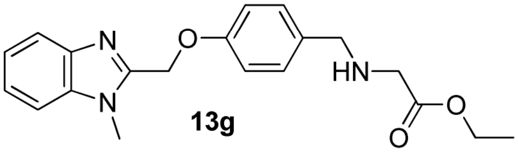
ESI/MS (m/z) : 270 (M+H)$^+$.

% Yield : 63 %

Intermediates **13g-i** were prepared by following the procedure of intermediate **8** using appropriate starting materials.

3.2.2.4 Intermediates 13g

Ethyl 2-((4-((1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzyl)amino) acetate.



13g

Purity by HPLC : 88.5 %

IR (Neat) : 1159, 1253, 1572, 1710, 3440 cm^{-1}

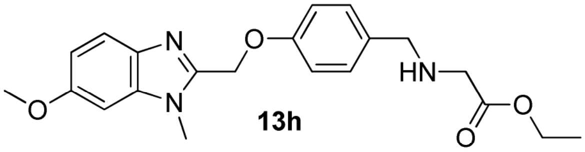
^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.96(t, J = 7.2 Hz, 3H), 3.87(s, 3H), 3.98(s, 2H), 4.12-4.18(m, 2H), 4.52(s, 2H), 4.62(s, 1H), 5.43(s, 1H), 6.88(d, J = 9.0 Hz, 2H), 7.22-7.24(m, 2H), 7.29-7.36(m, 3H), 7.79-7.81(m, 1H).

ESI/MS (m/z) : 354 $(M+H)^+$

% Yield : 74 %

3.2.2.5 Intermediates 13h

Ethyl 2-((4-((6-methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzyl) amino)acetate.



13h

Purity by HPLC : 83 %

IR (Neat) : 1152, 1320, 1600, 1704, 3430 cm^{-1}

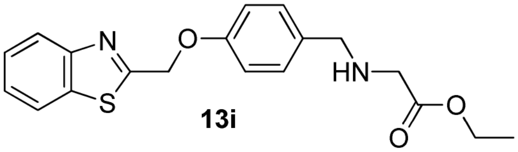
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.97(t, *J* = 7.0 Hz, 3H), 3.77(s, 3H), 3.86(s, 3H), 4.01(s, 2H), 4.03-4.06(m, 2H), 4.60(s, 1H), 4.68(s, 1H), 5.30(s, 2H), 6.82-6.87(m, 4H), 7.10-7.23(m, 3H).

ESI/MS (m/z) : 384 $(M+H)^+$

% Yield : 78 %

3.2.2.6 Intermediates 13i

Ethyl 2-((4-(benzo[d]thiazol-2-ylmethoxy)benzyl)amino)acetate.



13i

Purity by HPLC: 72.5 %

IR (Neat) : 1249, 1732, 2852, 3411 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.24-1.26(m, 3H), 3.38(s, 2H), 3.74(s, 2H), 4.14-4.21(q, *J* = 7.2 Hz & 7.2 Hz, 2H), 5.48(s, 2H), 7.0(d, *J* = 8.6 Hz, 2H), 7.28-

7.31(m, 2H), 7.37-7.42(m, 1H), 7.47-7.52(m, 1H), 7.89(d, *J* = 7.5 Hz, 1H), 8.03(d, *J* = 7.9 Hz, 1H).

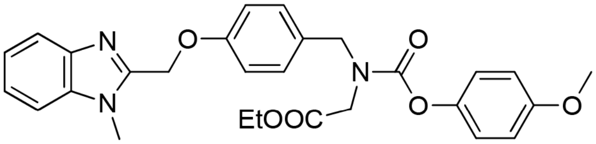
ESI/MS (m/z) : 357 $(M+H)^+$

% Yield : 82 %

Intermediates **10g-i** were prepared by following the procedure of intermediate **9** using appropriate starting materials

3.2.2.7 Intermediates 10g

Ethyl 2-(((4-methoxyphenoxy)carbonyl)(4-((1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzyl)amino)acetate.



10g

Purity by HPLC : 97.06 %

IR (Neat) : 757, 1362, 1509, 1716 cm^{-1}

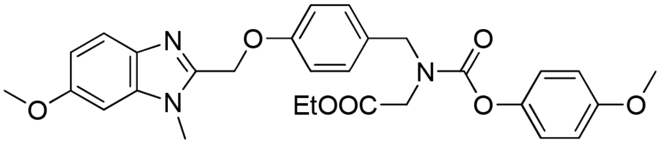
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.98(t, *J* = 7.38 Hz, 3H), 3.79(s, 3H), 3.89(s, 3H), 3.97(s, 2H), 4.11-4.18(m, 2H), 4.55(s, 1H), 4.66(s, 1H), 5.42(s, 2H), 6.86(d, *J* = 9.03 Hz, 2H), 7.02(d, *J* = 8.28 Hz, 2H), 7.06(d, *J* = 8.75 Hz, 2H), 7.23-7.26(m, 2H), 7.28-7.77(m, 3H), 7.78-7.80(m, 1H).

ESI/MS (m/z) : 504 $(M+H)^+$

Yield : 43 %

3.2.2.8 Intermediates 10h

Ethyl 2-((4-((6-methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzyl)((4-methoxyphenoxy)carbonyl)amino)acetate.



10h

Purity by HPLC : 87 %

IR (Neat) : 1350, 1362, 1380, 1702 cm^{-1}

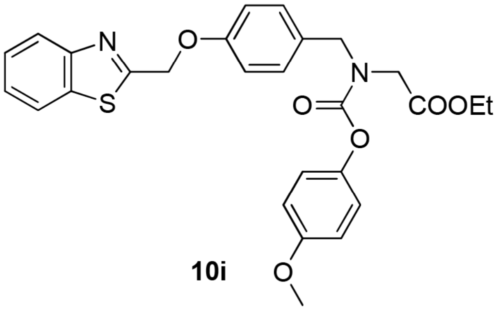
^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.97(t, J = 7.1 Hz, 3H), 3.78(s, 3H), 3.88(s, 6H), 4.03(s, 2H), 4.13-4.16(m, 2H), 4.62(s, 1H), 4.71(s, 1H), 5.35(s, 2H), 6.78-6.83(m, 4H), 6.92-7.03(m, 4H), 7.25-7.39(m, 3H).

ESI/MS (m/z) : 534 (M+H)$^+$

% Yield : 72 %

3.2.2.9 Intermediates 10i

Ethyl 2-((4-(benzo[d]thiazol-2-ylmethoxy)benzyl)((4-methoxyphenoxy) carbonyl)amino)acetate.



10i

Purity by HPLC : 84.21 %

IR (Neat) : 1436, 1739, 3432 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ0.82-0.87(m, 3H), 3.79(s, 3H), 3.99(s, 2H), 4.14-4.20(m, 2H), 4,57(s, 1H), 4.67(s, 1H), 5.5(s, 2H), 6.85-6.88(m, 2H), 7.01-7.05(m, 4H), 7.26-7.28(m, 2H), 7.41(t, *J* = 7.3 Hz, 1H), 7.5-7.53(m, 1H), 7.9(d, *J* = 8.0 Hz, 1H), 8.0(d, *J* = 8.0 Hz, 1H).

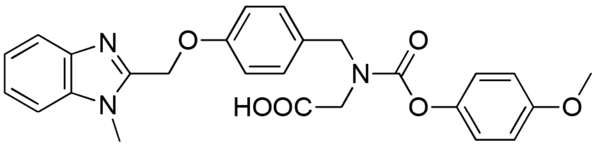
ESI/MS (m/z) : 507 $(M+H)^+$

% Yield : 78 %

Compounds **14g-i** were prepared by following the procedure of Compounds **14a-f** using appropriate starting materials.

3.2.2.10 Compound 14g

2-(((4-Methoxyphenoxy)carbonyl)(4-((1-methyl-1H-benzo[d]imidazol-2-yl) methoxy)benzyl)amino)acetic acid.



14g

Purity by HPLC : 98.46 %

IR (KBr) : 683, 1350, 1508, 1718 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ3.78(s, 3H), 3.93(s, 3H), 4.05(s, 2H), 4.60(s, 1H), 4.71(s, 1H), 5.51(s, 2H), 6.85(d, *J* = 7.38 Hz, 2H), 7.03-7.09(m, 4H), 7.27-7.28(m, 2H), 7.31-7.83(m, 4H).

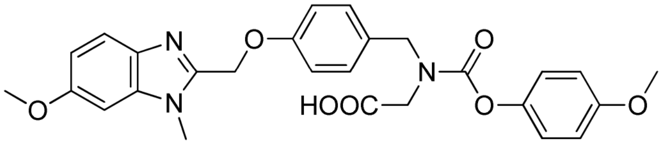
ESI/MS (m/z) : 476 $(M+H)^+$

% Yield : 69 %

mp : 140-144 °C

3.2.2.11 Compound 14h

2-((4-((6-Methoxy-1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)benzyl)((4-methoxyphenoxy)carbonyl)amino)acetic acid.



14h

Purity by HPLC : 94.64 %

IR (KBr) : 670, 1349, 1508, 1718 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ3.77(s, 3H), 3.87(s, 6H), 4.05(s, 2H), 4.60(s, 1H), 4.70(s, 1H), 5.42(s, 2H), 6.79-6.87(m, 4H), 6.90-7.07(m, 4H), 7.26-7.69(m, 3H).

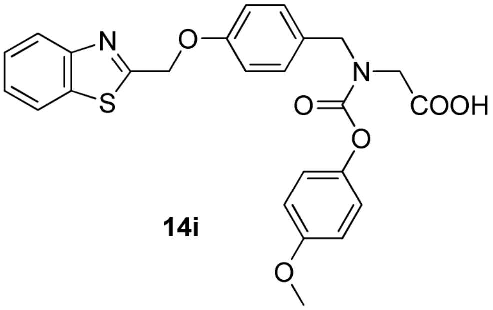
ESI/MS (m/z) : 506 (M+H)$^+$

% Yield : 50 %

mp : 152-155 °C

3.2.2.12 Compound 14i

2-((4-(Benzo[d]thiazol-2-ylmethoxy)benzyl)((4-methoxyphenoxy)carbonyl) amino)acetic acid.



14i

Purity by HPLC : 95.92 %

IR (KBr) : 729, 1434, 1724, 3435 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ3.78(s, 3H), 4.04(s, 2H), 4.58(s, 2H), 5.5(s, 2H), 6.86(d, *J* = 8.1 Hz, 2H), 7.0-7.03(m, 4H), 7.26-7.29(m, 2H), 7.38-7.43(m, 1H), 7.48-7.53(m, 1H), 7.89(d, *J* = 8.0 Hz, 1H), 8.03(d, *J* = 8.1 Hz, 1H).

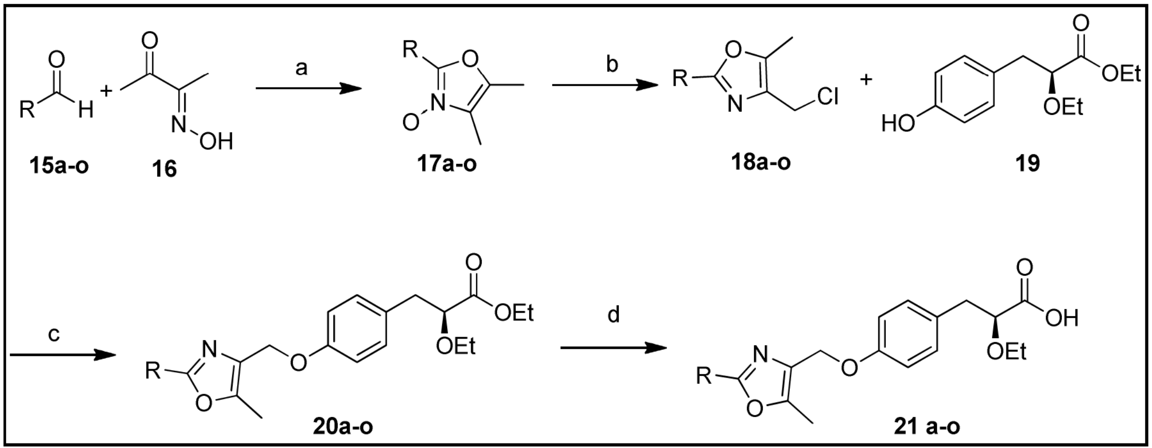
ESI/MS (m/z) : 479 $(M+H)^+$

% Yield : 90 %

mp : 148-150 °C

3.3 Synthesis of thiophene substituted oxazoles one carbon linker chain analogues

Scheme : 3



Reagents and conditions : (a) AcOH/HCl gas, 0 °C, 3h, 20-25 %; (b) $POCl_3$, Dichloroethane, 60 °C, 3h, 50-70 %; (c) K_2CO_3, DMF, 80-90 °C, 2h, 40-50 %; (d) NaOH/MeOH/H_2O, 20-25 °C, 4h, 60-80%.

3.3.1 Compounds

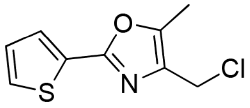
Procedure of Intermediate 18a

To an ice-cold solution of freshly distilled thiophene 2 carboxaldehyde **15a** (5.45 g, 0.048 mole) and diacetylmonoxime **16** (4.91 g, 0.048 mole) in AcOH (17 mL), dry HCl gas was passed for 3 h at 0 °C. The reaction mixture was diluted with diethyl ether (34 mL). Separated solid was filtered, washed with diethylether and dried under vacuum to obtain the title product **17a** as white solid. The product was directly used for the next reaction.

To an ice-cold suspension of N-oxide **17a** (9.5 g, 47.99 mmole) prepared in step I above in dichloroethane (50 mL) was added $POCl_3$ (8.46 g, 55.19 mmole) dropwise over a period of 2 hours at 10 °C. Reaction mixture was slowly heated to 60 °C and stirred at that temperature for 3 hours. Reaction mixture was cooled to room temperature, poured into ice-cold water (100 mL) and extracted with dichloroethane (150 mL). The combined organic extract was washed with water, dried over sodium sulfate and concentrated under vacuum to furnish title product **18a** as a solid.

3.3.1.1 Intermediate 18a

4-(Chloromethyl)-5-methyl-2-(thiophen-2-yl)oxazole.



18a

Purity by HPLC : 90.41 %

IR (KBr) : 700, 768, 1640, 2923, 3083 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.40(s, 3H), 4.52(s, 2H), 7.08(t, J = 8.58 Hz, 1H), 7.40(d, J = 4.89 Hz, 1H), 7.62(d, J = 3.45 Hz, 1H).

ESI/MS (m/z) : 214 $(M+H)^+$

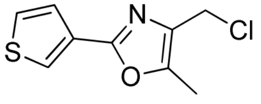
% Yield : 85 %

mp : 70-71 °C

Intermediates **18b-o** were prepared by following the procedure of intermediate **18a** using appropriate starting materials.

3.3.1.2 Intermediate 18b

4-(Chloromethyl)-5-methyl-2-(thiophen-3-yl)oxazole.



18b

Purity by HPLC : 88.56 %

IR (KBr) : 729, 1598, 1747, 3109 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 4.53(s, 2H), 7.35-7.38(m, 1H), 7.58-7.60(m, 1H), 7.89-7.90(m, 1H).

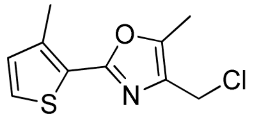
ESI/MS (m/z) : 214 (M+H)$^+$

% Yield : 71 %

mp : 101-102 °C

3.3.1.3 Intermediate 18c

4-(Chloromethyl)-5-methyl-2-(3-methylthiophen-2-yl)oxazole.



18c

Purity by HPLC : 77.46 %

IR (KBr) : 1529, 1635, 2922 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 2.57(s, 3H), 4.53(s, 2H), 6.90(d, *J* = 5.1Hz, 1H), 7.27(d, *J* = 5.1Hz, 1H).

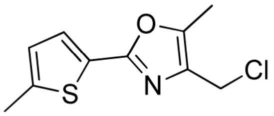
ESI/MS (m/z) : 228 (M+H)$^+$

% Yield : 82 %

mp : 98-101 °C

3.3.1.4 Intermediate 18d

4-(Chloromethyl)-5-methyl-2-(5-methylthiophen-2-yl)oxazole.



18d

Purity by HPLC : 91.54 %

IR (KBr) : 1521, 1633, 2920 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.45(s, 3H), 2.50(s, 3H), 4.51(s, 2H), 6.73(d, J = 2.73 Hz, 1H), 7.42(d, J = 3.54 Hz, 1H).

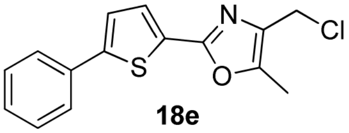
ESI/MS (m/z) : 228 (M+H)$^+$

% Yield : 84 %

mp : 92-95 °C

3.3.1.5 Intermediate 18e

4-(Chloromethyl)-5-methyl-2-(5-phenylthiophen-2-yl)oxazole.



18e

Purity by HPLC : 86 %

IR (KBr) : 675, 1550, 2950 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.48(s, 3H), 4.53(s, 2H), 7.30-7.40(m, 4H), 7.60(d, J = 3.8 Hz, 1H), 7.70(d, J = 6.8 Hz, 2H).

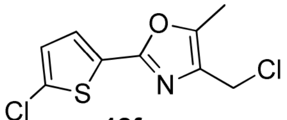
ESI/MS (m/z) : 290 (M+H)$^+$

% Yield : 75 %

mp : 103-106 °C

3.3.1.6 Intermediate 18f

2-(5-Chlorothiophen-2-yl)-4-(chloromethyl)-5-methyloxazole.



18f

Purity by HPLC : 92 %

IR (KBr) : 1506, 1627, 2925 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.39(s, 3H), 4.50(s, 2H), 6.91(d, J = 3.96 Hz, 1H), 7.39(d, J = 3.96 Hz, 1H).

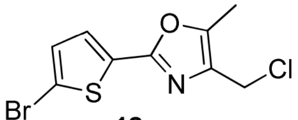
ESI/MS (m/z) : 249 (M+H)$^+$

% Yield : 37 %

mp : 92-95 ^{o}C

3.3.1.7 Intermediate 18g

2-(5-Bromothiophen-2-yl)-4-(chloromethyl)-5-methyloxazole.



18g

Purity by HPLC : 98.12 %

IR (KBr) : 1504, 1625, 2925, 2964 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.39(s, 3H), 4.50(s, 2H), 7.05(d, J = 3.92 Hz, 1H), 7.36(d, J = 3.93 Hz, 1H).

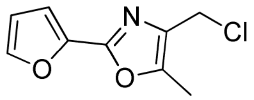
ESI/MS (m/z) : 293 (M+H)$^+$

% Yield : 76 %

mp : 97-98 ^{o}C

3.3.1.8 Intermediate 18h

4-(Chloromethyl)-2-(furan-2-yl)-5-methyloxazole.



18h

Purity by HPLC : 87 %

IR (KBr) : 1510, 1660, 2901, 2913 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.40(s, 3H), 4.52(s, 2H), 7.07-7.10(m, 1H), 7.40(d, *J* = 4.90 Hz, 1H), 7.62(d, *J* = 3.4 Hz, 1H).

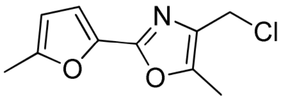
ESI/MS (m/z) : 198 $(M+H)^+$

% Yield : 83 %

mp : 110-114 °C

3.3.1.9 Intermediate 18i

4-(Chloromethyl)-5-methyl-2-(5-methylfuran-2-yl)oxazole.



18i

Purity by HPLC : 89.81 %

IR (KBr) : 1577, 1743, 3105 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.39(s, 6H), 4.57(s, 2H), 6.11(d , *J* = 2.54 Hz, 1H), 6.87(d, *J* = 3.3 Hz, 1H).

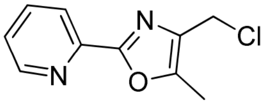
ESI/MS (m/z) : 212.5 $(M+H)^+$

% Yield : 47 %

mp : 112-115 °C

3.3.1.10 Intermediate 18j

4-(Chloromethyl)-5-methyl-2-(pyridin-2-yl)oxazole.



18j

Purity by HPLC : 90 %

IR (KBr) : 680, 1330, 1650, 2206 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.50(s, 3H), 4.51(s, 2H), 7.70-7.73(m, 1H), 7.78(t, J = 7.6 Hz, 1H), 8.0(d, J = 7.6 Hz, 1H), 8.5(d, J = 4.3 Hz, 1H).

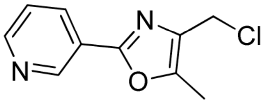
ESI/MS (m/z) : 209 (M+H)$^+$

% Yield : 91 %

mp : 121-124 ^{o}C

3.3.1.11 Intermediate 18k

4-(Chloromethyl)-5-methyl-2-(pyridin-3-yl)oxazole.



18k

Purity by HPLC : 93 %

IR (KBr) : 650, 1170, 1600, 2230 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.48(s, 3H), 4.49(s, 2H), 7.45(dd, J = 5.0 Hz & 7.6 Hz, 1H), 8.35(d, J = 7.8 Hz, 1H), 8.7(d, J = 4.4 Hz, 1H), 9.3(s, 1H).

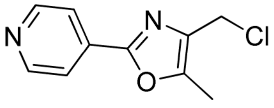
ESI/MS (m/z) : 209 (M+H)$^+$

% Yield : 78 %

mp : 117-120 ^{o}C

3.3.1.12 Intermediate 18l

4-(Chloromethyl)-5-methyl-2-(pyridin-4-yl)oxazole.



18l

Purity by HPLC : 89 %

IR (KBr) : 680, 1210, 1590, 2210 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.47(s, 3H), 4.51(s, 2H), 8.39(d, *J* = 3.0 Hz, 2H), 8.80(d, *J* = 5.1 Hz, 2H).

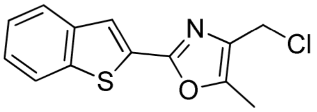
ESI/MS (m/z) : 209 (M+H)$^+$

% Yield : 90 %

mp : 118-122 °C

3.3.1.13 Intermediate 18m

2-(Benzo[b]thiophen-2-yl)-4-(chloromethyl)-5-methyloxazole.



18m

Purity by HPLC : 83.89 %

IR (KBr) : 717, 831, 1161, 1431, 1629, 1691, 1961, 2968 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.45(s, 3H), 4.55(s, 2H), 7.37-7.41(m, 2H), 7.81-7.87(m, 3H).

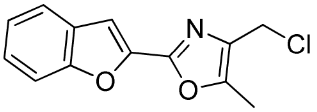
ESI/MS (m/z) : 264 (M+H)$^+$

% Yield : 67 %

mp : 90-92 °C

3.3.1.14 Intermediate 18n

2-(Benzofuran-2-yl)-4-(chloromethyl)-5-methyloxazole.



18n

Purity by HPLC : 82 %

IR (KBr) : 732, 850, 1190, 1600, 2850 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.47(s, 3H), 4.57(s, 2H), 7.26-7.36(m, 2H), 7.38-7.41(m, 1H), 7.57-7.60(m, 1H), 7.64-7.66(m, 1H).

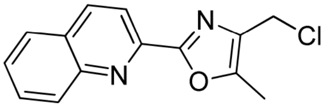
ESI/MS (m/z) : 248 (M+H)$^+$

% Yield : 84 %

mp : 101-105 °C

3.3.1.15 Intermediate 18o

4-(Chloromethyl)-5-methyl-2-(quinolin-2-yl)oxazole.



18o

Purity by HPLC : 90 %

IR (KBr) : 680, 1192, 1621, 2217 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.50(s, 3H), 4.53(s, 2H), 7.53(t, *J* = 7.1 Hz, 1H), 7.76(t, *J* = 7.2 Hz, 1H), 7.80(d, *J* = 7.3 Hz, 1H), 8.25-8.29(m, 3H).

ESI/MS (m/z) : 259 (M+H)$^+$

% Yield : 87 %

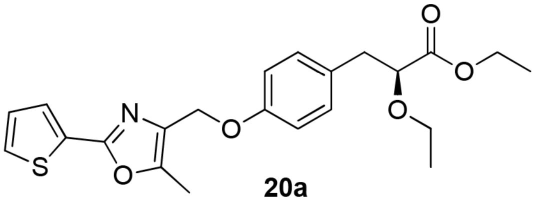
mp : 112-115 °C

Procedure of intermediate 20a

K_2CO_3 (1.51 g, 10.97 mmole) was added to hydroxy compound **19** [1] (1.86 g, 7.83 mmole) in DMF (20 mL) at 20-25 °C. To that chloromethyloxazole **18a** (2.25g, 7.83 mmole) was added. The reaction mixture was stirred at 80-90 °C for 2 h. The reaction mixture was poured into ice water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extract was successively washed with water (50 mL) & brine (50 mL), dried over sodium sulfate, filtered and concentrated under vacuum to furnish corresponding crude ester derivative. The crude ester derivative was purified by column chromatography using Hexane : Ethylacetate (9:1) as an eluent to furnish title product **20a** as solid.

3.3.1.16 Intermediate 20a

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(thiophen-2-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20a

Purity by HPLC : 95.45 %

IR (KBr) : 725, 954, 1240, 1465, 1579, 1739, 2956, 2981 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, J = 7.0 Hz, 3H), 1.22(t, J = 7.14 Hz, 3H), 2.40(s, 3H), 2.95(d, J = 6.6 Hz, 2H), 3.32-3.37(m, 1H), 3.57-3.62(m, 1H), 3.97(t, J = 6.3 Hz, 1H), 4.15-4.19(q, J = 7.12 Hz & 7.1Hz, 2H), 4.95(s, 2H), 6.9(d, J = 8.58 Hz, 2H), 7.08-7.11(m, 1H), 7.15(d, J = 8.52 Hz, 2H), 7.40(dd, J = 0.82 Hz & 4.14 Hz, 1H), 7.65(dd, J = 0.75 Hz & 2.82 Hz, 1H).

ESI/MS (m/z) : 416 $(M+H)^+$

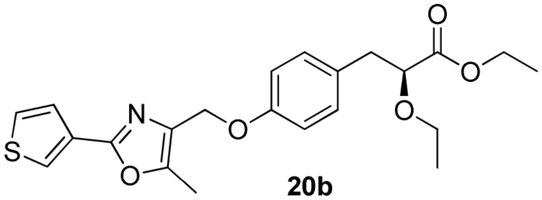
% Yield : 51 %

mp : 72-73 °C

Intermediates **20b-o** were prepared by following the procedure of intermediate **20a** using appropriate starting materials.

3.3.1.17 Intermediate 20b

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(thiophen-3-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20b

Purity by HPLC : 98.10 **%.**

IR (KBr) : 756, 1741, 1512, 1598, 2979 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 7.01 Hz, 3H), 1.2(t, *J* = 7.14 Hz, 3H), 2.40(s, 3H), 2.97(d, *J* = 6.60 Hz, 2H), 3.32-3.40(m, 1H), 3.55-3.62(m, 1H), 3.97(t, *J* = 6.65 Hz, 1H), 4.19-4.20(q, *J* = 7.12 Hz & 7.12Hz, 2H), 4.94(s, 2H), 6.93(d, *J* = 8.5 Hz, 2H), 7.18(d, *J* = 8.5 Hz, 2H), 7.35-7.37(m, 1H), 7.61(d, *J* = 5.02 Hz, 1H), 7.88-7.89(m, 1H).

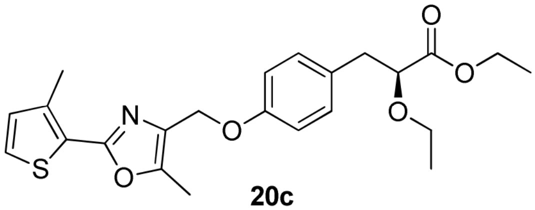
ESI/MS (m/z) : 416 $(M+H)^+$

% Yield : 78 %

mp : 85-90 °C

3.3.1.18 Intermediate 20c

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl) methoxy)phenyl)propanoate.



20c

Purity by HPLC : 98.69 %

IR (KBr) : 736, 1118, 1512, 1745, 2927 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.16(t, *J* = 7.05 Hz, 3H), 1.22(t, *J* = 7.12 Hz, 3H), 2.40(s, 3H), 2.57(s, 3H), 2.96(d, *J* = 6.66 Hz, 2H), 3.32-3.37(m, 1H), 3.57-3.62(m, 1H), 3.97(t, *J* = 6.64 Hz, 1H), 4.17-4.19(q, *J* = 7.2 Hz & 7.2 Hz, 2H), 4.95(s, 2H), 6.88-6.92(m, 1H), 6.94(d, *J* = 8.61 Hz, 2H), 7.17(d, *J* = 8.55 Hz, 2H), 7.26(d, *J* = 4.0 Hz, 1H).

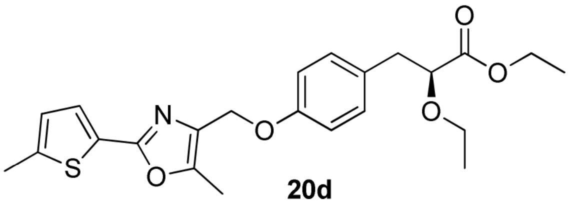
ESI/MS (m/z) : 430 (M+H)$^+$

% Yield : 82 %

mp : 104-105 ^{o}C

3.3.1.19 Intermediate 20d

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl) methoxy)phenyl)propanoate.



20d

Purity by HPLC : 99.02 %

IR (KBr) : 1238, 1512, 1745, 2977 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 7.0 Hz, 3H), 1.24(t, *J* = 7.14 Hz, 3H), 2.38(s, 3H), 2.52(s, 3H), 2.96(d, *J* = 6.63 Hz, 2H), 3.32-3.37(m, 1H), 3.57-3.62(m, 1H), 3.97(t, *J* = 6.66 Hz, 1H), 4.17-4.20(q, *J* = 7.11 Hz & 7.1Hz, 2H), 4.92(s, 2H), 6.73-6.76(m, 1H), 6.92(d, *J* = 8.61 Hz, 2H), 7.17(d, *J* = 8.55 Hz, 2H), 7.42(d, *J* = 3.6 Hz, 1H).

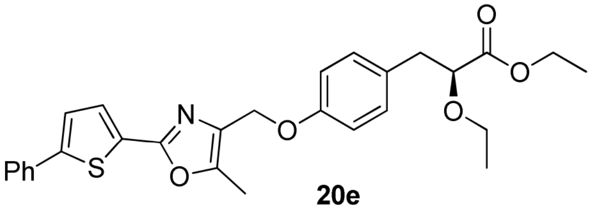
ESI/MS (m/z) : 430 $(M+H)^+$

% Yield : 82 %

mp : 106-110 °C

3.3.1.20 Intermediate 20e

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl) methoxy)phenyl)propanoate.



20e

Purity by HPLC : 96.60 %

IR (KBr) : 1515, 1747, 2933 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 6.99 Hz, 3H), 1.22(t, *J* = 6.98 Hz, 3H), 2.41(s, 3H), 2.96(d, *J* = 6.66 Hz, 2H), 3.32-3.63(m, 2H), 3.97(t, *J* = 6.66 Hz, 1H), 4.16-4.19(q, *J* = 7.05 Hz & 7.14 Hz, 2H), 4.95(s, 2H), 6.92(d, *J* = 8.64 Hz, 2H), 7.17(d, *J* = 8.58 Hz, 2H), 7.26-7.43(m, 4H), 7.58(d, *J* = 3.87 Hz, 1H), 7.63(d, *J* = 7.14 Hz, 2H).

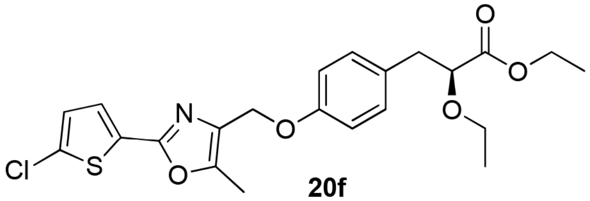
ESI/MS (m/z) : 492 $(M+H)^+$

% Yield : 34 %

mp : 100-101 °C

3.3.1.21 Intermediate 20f

(*S*)-Ethyl 3-(4-((2-(5-chlorothiophen-2-yl)-5-methyloxazol-4-yl)methoxy) phenyl)-2-ethoxypropanoate.



20f

Purity by HPLC : 98.66 %

IR (KBr) : 1510, 1741, 2873, 2981 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 7.00 Hz, 3H), 1.22(t, *J* = 7.15 Hz, 3H), 2.39(s, 3H), 2.95(d, *J* = 6.6 Hz, 2H), 3.32-3.62(m, 2H), 3.94(t, *J* = 6.63 Hz, 1H), 4.12-4.19(q, *J* = 7.11 Hz & 7.11 Hz, 2H), 4.92(s, 2H), 6.89-6.92(m, 3H), 7.17(d, *J* = 8.58 Hz, 2H), 7.37(d, *J* = 3.96 Hz, 1H).

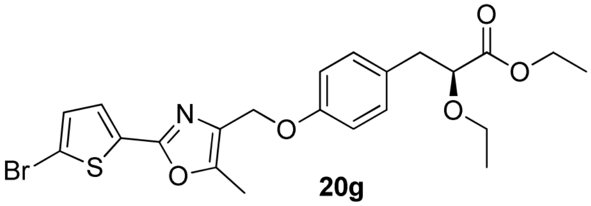
ESI/MS (m/z) : 450 (M+H)$^+$

% Yield : 55 %

mp : 101-105 °C

3.3.1.22 Intermediate 20g

(*S*)-Ethyl 3-(4-((2-(5-bromothiophen-2-yl)-5-methyloxazol-4-yl)methoxy) phenyl)-2-ethoxypropanoate.



20g

Purity by HPLC : 94.86 %

IR (KBr) : 1521, 1737, 2873, 2979 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 7.00 Hz, 3H), 1.22(t, *J* = 7.14 Hz, 3H), 2.39(s, 3H), 2.95(d, *J* = 6.57 Hz, 2H), 3.32-3.63(m, 2H), 3.97(t, *J* = 6.64 Hz, 1H), 4.12-4.19(q, *J* = 7.11 Hz & 7.14 Hz, 2H), 4.92(s, 2H), 6.91(d, *J* = 8.58 Hz, 2H), 7.04(d, *J* = 3,93 Hz, 1H), 7.17(d, *J* = 8.54 Hz, 2H), 7.35(d, *J* = 3.93 Hz, 1H).

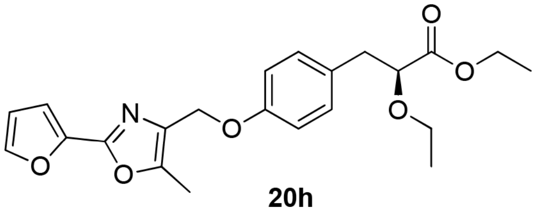
ESI/MS (m/z) : 495 (M+H)$^+$

% Yield : 40 %

mp : 112-116 °C

3.3.1.23 Intermediate 20h

(*S*)-Ethyl 2-ethoxy-3-(4-((2-(furan-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl) propanoate.



20h

Purity by HPLC : 89.88 %

IR (KBr) : 685, 1175, 1250, 1346, 1710, 3200 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.12-1.19(m, 3H), 1.22-1.27(m, 3H), 2.37(s, 3H), 2.92-2.97(m, 4H), 3.06-3.10(m, 1H), 3.36-3.41(m, 1H), 3.56-3.58(m, 1H), 4.96(s, 2H), 6.55(dd, *J* = 1.8 Hz & 3.6 Hz, 1H), 6.92(d, *J* = 8.58 Hz, 2H), 6.98(d, *J* = 3.40 Hz, 1H), 7.18(d, *J* = 8.55 Hz, 2H), 7.56(d, *J* = 1.2 Hz, 1H).

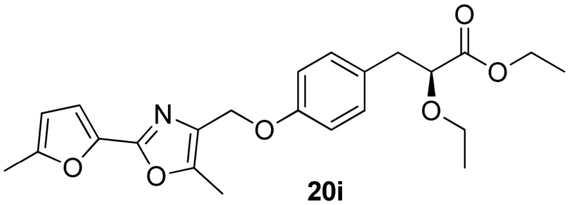
ESI/MS (m/z) : 400 (M+H)$^+$

% Yield : 78 %

mp : 97-104 °C

3.3.1.24 Intermediate 20i

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl) methoxy)phenyl)propanoate.



20i

Purity by HPLC : 86.31 %

IR (KBr) : 1579, 1737, 2339, 3018 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, J = 6.99 Hz, 3H), 1.21(t, J = 6.26 Hz, 3H), 2.41(s, 6H), 2.95(d, J = 6.48 Hz, 2H), 3.35-3.37(m, 2H), 3.59(t, J = 4.55 Hz, 1H), 4.11-4.19(m, 2H), 4.98(s, 2H), 6.13(d, J = 2.68 Hz, 1H), 6.75(d, J = 8.46 Hz, 2H), 6.96(d, J = 3.91 Hz, 1H), 7.10(d, J = 8.46 Hz, 2H).

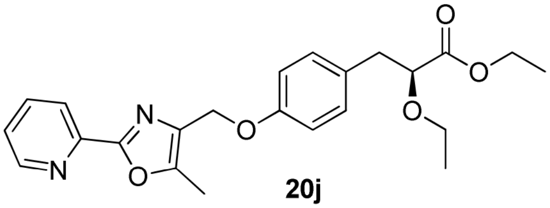
ESI/MS (m/z) : 414 $(M+H)^+$

% Yield : 31 %

mp : 120-123 °C

3.3.1.25 Intermediate 20j

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(pyridin-2-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20j

Purity by HPLC : 94.98 %

IR (KBr) : 678, 1350, 1737, 3016, 3583 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 6.99 Hz, 3H), 1.23(t, *J* = 7.1 Hz, 3H), 2.10(s, 3H), 2.48-2.50(m, 2H), 3.35-3.46(m, 1H), 3.6-3.72(m, 1H), 3.97-3.99(m, 1H), 4.1-4.2(q, *J* = 7.1 Hz, 2H), 5.05(s, 2H), 6.92(d, *J* = 8.6 Hz, 2H), 7.18(d, *J* = 8.5 Hz, 2H), 7.80-7.82(m, 1H), 7.9(t, *J* = 7.8 Hz, 1H), 8.1(d, *J* = 7.9 Hz, 1H), 8.7(d, *J* = 4.4 Hz, 1H).

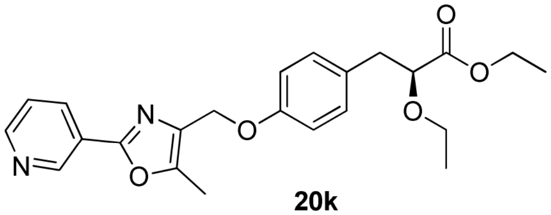
ESI/MS (m/z) : 411 $(M+H)^+$

% Yield : 35 %

mp : 114-117 °C

3.3.1.26 Intermediate 20k

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(pyridin-3-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20k

Purity by HPLC : 89.33 %

IR (KBr) : 669, 927, 1512, 1610, 1737, 2875, 2981, 3018, 3390 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.20(t, *J* = 6.9 Hz, 3H), 1.22(t, *J* = 7.0 Hz, 3H), 2.46(s, 3H), 2.96(d, *J* = 6.51 Hz, 2H), 3.32-3.38(m, 1H), 3.58-3.63(m, 1H), 3.97(t, *J* = 6.8 Hz, 1H), 4.17-4.19(q, *J* = 7.14 Hz & 7.18 Hz , 2H), 4.98(s, 2H), 6.92(d, *J* = 8.55 Hz, 2H), 7.17(d, *J* = 8.52 Hz, 2H), 7.47(dd, *J* = 5.02 Hz & 7.84 Hz, 1H), 8.39(d, *J* = 8.01 Hz, 1H), 8.68(d, *J* = 4.32 Hz, 1H), 9.25(s, 1H).

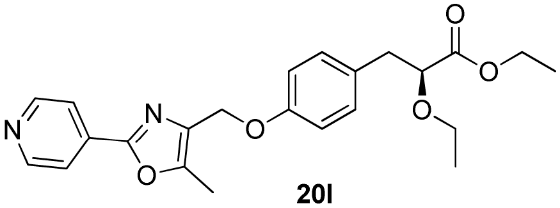
ESI/MS (m/z) : 411 $(M+H)^+$

% Yield : 68 %

mp : 124-128 °C

3.3.1.27 Intermediate 20l

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(pyridin-4-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20l

Purity by HPLC : 92.70 %

IR (KBr) : 1737, 2292, 2950, 3263 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.90 Hz, 3H), 1.24(t, *J* = 7.1 Hz, 3H), 2.55(s, 3H), 2.95-2.98(m, 2H), 3.33-3.61(m, 2H), 3.96-4.0(m, 1H), 4.14-4.21(q, *J* = 7.14 Hz & 7.12 Hz, 2H), 5.03(s, 2H), 6.90(d, *J* = 8.58 Hz, 2H), 7.19(d, *J* = 8.56 Hz, 2H), 8.40-8.41(m, 2H), 8.80-8.82(m, 2H).

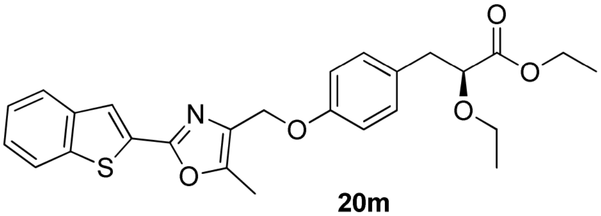
ESI/MS (m/z) : 411 (M+H)$^+$

% Yield : 32 %

mp : 118-121 °C

3.3.1.28 Intermediate 20m

(*S*)-Ethyl 3-(4-((2-(benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)methoxy) phenyl)-2-ethoxypropanoate.



20m

Purity by HPLC : 97.92 %

IR (KBr) : 729, 1028, 1298, 1641, 1732, 2933, 2976, 3382 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.99 Hz, 3H), 1.22(t, *J* = 7.12 Hz, 3H), 2.44(s, 3H), 2.96(d, *J* = 6.69 Hz, 2H), 3.32-3.38(m, 1H), 3.57-3.63(m, 1H), 3.97(t, *J* = 6.63 Hz, 1H), 4.16-4.19(q, *J* = 7.12 Hz & 7.18 Hz, 2H), 4.97(s, 2H), 6.93(d, *J* = 8.61 Hz, 2H), 7.18(d, *J* = 8.58 Hz, 2H), 7.36-7.51(m, 2H), 7.79-7.87(m, 3H).

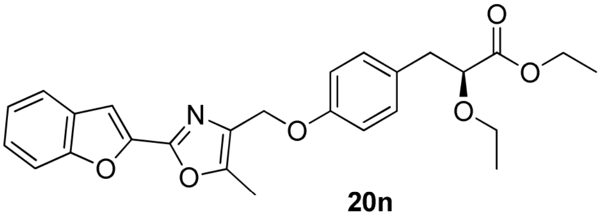
ESI/MS (m/z) : 466 (M+H)$^+$

% Yield : 62 %

mp : 94-96 °C

3.3.1.29 Intermediate 20n

(*S*)-Ethyl 3-(4-((2-(benzofuran-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl)-2-ethoxypropanoate.



20n

Purity by HPLC : 97.03 %

IR (KBr) : 731, 1030, 1650, 1720, 2958 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.14(t, *J* = 7.00 Hz, 3H), 1.17(t, *J* = 6.95 Hz, 3H), 2.43(s, 3H), 2.47-2.67(m, 2H), 3.35-3.50(m, 4H), 3.90-3.97(m, 1H), 4.96(s, 2H), 6.93(d, *J* = 8.05 Hz, 2H), 7.20(d, *J* = 8.30 Hz, 2H), 7.34-7.80(m, 5H).

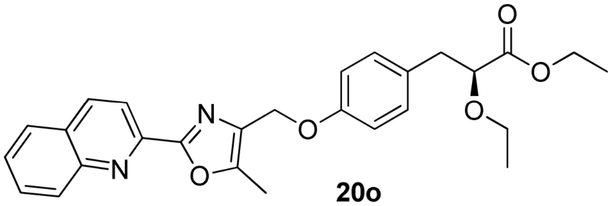
ESI/MS (m/z) : 450 $(M+H)^+$

% Yield : 76 %

mp : 111-115 °C

3.3.1.30 Intermediate 20o

(*S*)-Ethyl 2-ethoxy-3-(4-((5-methyl-2-(quinolin-2-yl)oxazol-4-yl)methoxy) phenyl)propanoate.



20o

Purity by HPLC : 84.16 %

IR (KBr) : 730, 1051, 1635, 1725, 2899 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.16(t, *J* = 7.05 Hz, 3H), 1.22(t, *J* = 7.2 Hz, 3H), 2.53(s, 3H), 2.96(d, *J* = 6.6 Hz, 2H), 3.32-3.38(m, 1H), 3.55-3.63(m, 1H), 3.97(t, *J* = 6.45 Hz, 1H), 4.13-4.20(q, *J* = 7.2 Hz & 7.2 Hz, 2H), 5.05(s, 2H), 6.95(d, *J* = 8.4 Hz, 2H), 7.18(d, *J* = 8.4 Hz, 2H), 7.59(t, *J* = 7.5 Hz, 1H), 7.76(t, *J* = 7.65 Hz, 1H), 7.85(d, *J* = 8.1 Hz, 1H), 8.23-8.28(m, 3H).

ESI/MS (m/z) : 461 $(M+H)^+$

% Yield : 51 %

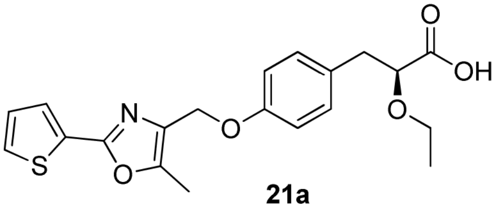
mp : 116-120 °C

Process of compound 21a

To a solution of ester compound **20a** (1.0g, 0.0024 mole) in methanol (6 mL) was added another solution of sodium hydroxide (0.119 g, 0.0029 mole) in water (3 mL) and the reaction mixture was stirred at ambient temperature for 4 hours. Solvents were evaporated under reduced pressure. Residue was dissolved in water (10 mL), acidified with 1N HCl and extracted with diethyl ether (2 X 25 mL). The combined organic extract was washed with water (35 mL), brine (35 mL) dried over sodium sulfate and evaporated under reduced pressure. Crude product was recrystalized from mixture of diisopropyl ether or petroleum ether to yield title product **21a** as solid.

3.3.1.31 Compound 21a

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(thiophen-2-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21a

Purity by HPLC : 98.46 %

IR (KBr) : 729, 1130, 1232, 1512, 1728, 2497, 2979, 3087 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 7.0 Hz, 3H), 2.4(s, 3H), 2.91-2.98(m, 2H), 3.35-3.49(m, 1H), 3.54-3.64(m, 1H), 4.03(t, *J* = 3.78 Hz, 1H), 4.95(s, 2H), 6.93(d, *J* = 8.47 Hz, 2H), 7.01(t, *J* = 3.69 Hz, 1H), 7.15(d, *J* = 8.47 Hz, 2H), 7.4(d, *J* = 4.89 Hz, 1H), 7.65(d, *J* = 3.45 Hz, 1H).

ESI/MS (m/z) : 388 (M+H)$^+$

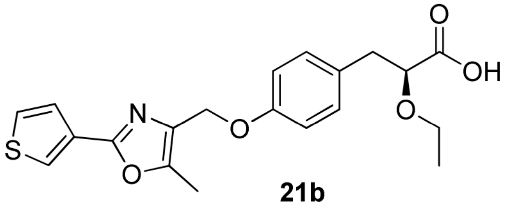
% Yield : 95 %

mp : 127-129 °C

Compounds **21b-o** were prepared by following the procedure of compound **21a** using appropriate starting materials.

3.3.1.32 Compound 21b

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(thiophen-3-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21b

Purity by HPLC : 99.47 %

IR (KBr) : 866, 1282, 1512, 1737, 3095 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 6.96 Hz, 3H), 2.40(s, 3H), 2.90-2.97(m, 1H), 3.03-3.09(m, 1H), 3.39-3.44(m, 1H), 3.57-3.62(m, 1H), 4.01-4.05(m, 1H), 4.94(s, 2H), 6.93(d, *J* = 8.5 Hz, 2H), 7.18(d, *J* = 8.5 Hz, 2H), 7.35-7.38(m, 1H), 7.59-7.61(m, 1H), 7.91-7.92(m, 1H).

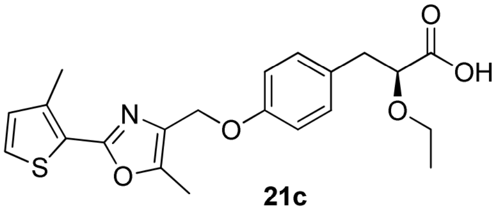
ESI/MS (m/z) : 388 $(M+H)^+$

% Yield : 73 %

mp : 115-118 °C

3.3.1.33 Compound 21c

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)methoxy) phenyl)propanoic acid.



21c

Purity by HPLC : 99.76 %

IR (KBr) : 1110, 1242, 1512, 1589, 1735, 2923, 3411 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 7.0 Hz, 3H), 2.40(s, 3H), 2.57(s, 3H), 2.90-2.98(m, 1H), 3.05-3.10(m, 1H), 3.41-3.46(m, 1H), 3.58-3.61(m, 1H), 4.02-4.13(m, 1H), 4.95(s, 2H), 6.92(d, *J* = 5.0 Hz, 1H), 6.94(d, *J* = 8.6 Hz, 2H), 7.18(d, *J* = 8.55 Hz, 2H), 7.27(d, *J* = 4.9 Hz, 1H).

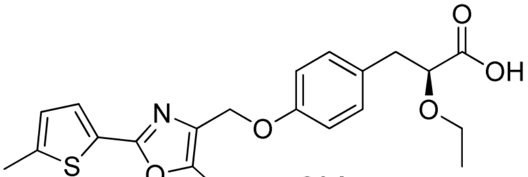
ESI/MS (m/z) : 402 (M+H)$^+$

% Yield : 97 %

mp : 131-135 °C

3.3.1.34 Compound 21d

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)methoxy) phenyl)propanoic acid.



21d

Purity by HPLC : 99.76 %

IR (KBr) : 1110, 1242, 1512, 1589, 1735, 2923, 3411 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.96 Hz, 3H), 2.38(s, 3H), 2.51(s, 3H), 2.90-2.97(m, 1H), 3.03-3.09(m, 1H), 3.38-3.43(m, 1H), 3.57-3.62(m, 1H), 4.00-

4.04(m, 1H), 4.92(s, 2H), 6.73-6.75(m, 1H), 6.92(d, *J* = 8.58 Hz, 2H), 7.18(d, *J* = 8.58 Hz, 2H), 7.44(d, *J* = 3.6 Hz, 1H).

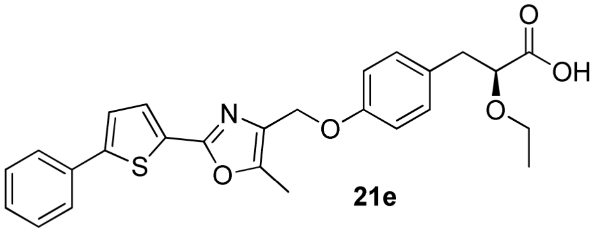
ESI/MS (m/z) : 402 $(M+H)^+$

% Yield : 73 %

mp : 133-134 °C

3.3.1.35 Compound 21e

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl)methoxy) phenyl) propanoic acid.



21e

Purity by HPLC : 97.46 %

IR (KBr) : 866, 1282, 1512, 1737, 3095 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.22(t, *J* = 6.98 Hz, 3H), 2.41(s, 3H), 2.96(d, *J* = 6.66 Hz, 2H), 3.32-3.63(m, 2H), 3.97(t, *J* = 6.66 Hz, 1H), 4.95(s, 2H), 6.92(d, *J* = 8.64 Hz, 2H), 7.17(d, *J* = 8.58 Hz, 2H), 7.26-7.43(m, 4H), 7.58(d, *J* = 3.87 Hz, 1H), 7.63(d, *J* = 7.14 Hz, 2H).

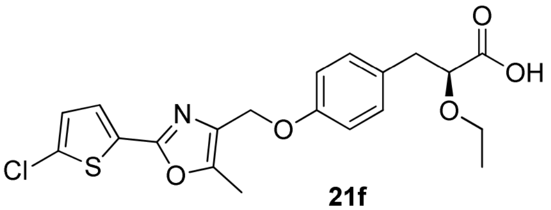
ESI/MS (m/z) : 464 $(M+H)^+$

% Yield : 52 %

mp : 152-156 °C

3.3.1.36 Compound 21f

(*S*)-3-(4-((2-(5-Chlorothiophen-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl)-2-ethoxypropanoic acid.



21f

Purity by HPLC : 98.99 %

IR (KBr) : 1573, 1647, 2925, 3379 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.18(t, J = 7.00 Hz, 3H), 2.39(s, 3H), 2.91-3.13(m, 2H), 3.44-3.61(m, 2H), 4.05(t, J = 5.82 Hz, 1H), 4.92(s, 2H), 6.90-6.93(m, 3H), 7.16(d, J = 8.58 Hz, 2H), 7.38(d, J = 3.96 Hz, 1H).

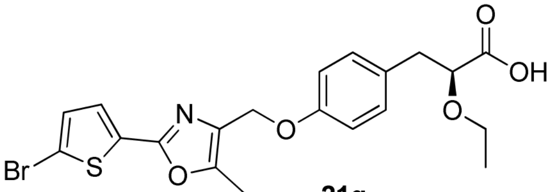
ESI/MS (m/z) : 422 (M+H)$^+$

% Yield : 82 %

mp : 98-102 °C

3.3.1.37 Compound 21g

(*S*)-3-(4-((2-(5-Bromothiophen-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl)-2-ethoxypropanoic acid.



21g

Purity by HPLC : 99.17 %

IR (KBr) : 672, 1348, 1589, 1683, 2925, 3381 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.18(t, J = 7.00 Hz, 3H), 2.35(s, 3H), 2.91-3.13(m, 2H), 3.14-3.44(m, 2H), 4.06(t, J = 5.8 Hz, 1H), 4.92(s, 2H), 6.92(d, J = 8.55 Hz, 2H), 7.05(d, J = 3.93 Hz, 1H), 7.16(d, J = 8.58 Hz, 2H), 7.36(d, J = 3.93 Hz, 1H).

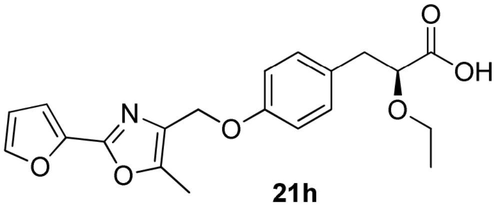
ESI/MS (m/z) : 467 $(M+H)^+$

% Yield : 66 %

mp : 107-111 °C

3.3.1.38 Compound 21h

(*S*)-2-Ethoxy-3-(4-((2-(furan-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl) propanoic acid.



21h

Purity by HPLC : 96.34 %

IR (KBr) : 767, 995, 1228, 1461, 1620, 1726, 2954, 3124 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.16(t, *J* = 6.99 Hz, 3H), 2.41(s, 3H), 2.9-2.98(m, 1H), 3.04-3.10(m, 1H), 3.40-3.45(m, 1H), 3.57-3.62(m, 1H), 4.04-4.06(m, 1H), 4.96(s, 2H), 6.52(dd, *J* = 1.68 Hz & 3.42 Hz, 1H), 6.92(d, *J* = 8.58 Hz, 2H), 6.98(d, *J* = 3.39 Hz, 1H), 7.17(d, *J* = 8.55 Hz, 2H), 7.54(s, *J* = 1.17 Hz, 1H).

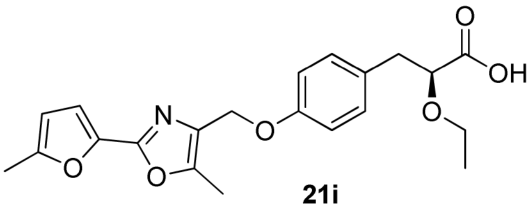
ESI/MS (m/z) : 372 $(M+H)^+$

% Yield : 76 %

mp : 112-113 °C

3.3.1.39 Compound 21i

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)methoxy) phenyl)propanoic acid.



21i

Purity by HPLC : 97.21 %

IR (KBr) : 1575, 1685, 2879, 2970 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.99 Hz, 3H), 2.41(s, 6H), 2.97-3.11(m, 2H), 3.41-3.46(m, 2H), 4.04(t, *J* = 5.94 Hz, 1H), 4.96(s, 2H), 6.13(d, *J* = 2.68 Hz, 1H), 6.90-6.93(m, 3H), 7.16(d, *J* = 8.50 Hz, 2H).

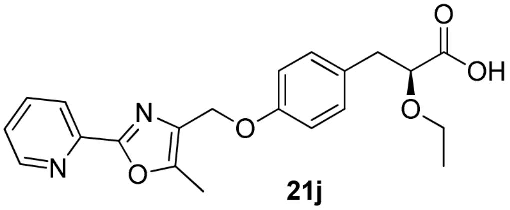
ESI/MS (m/z) : 386 (M+H)$^+$

% Yield : 64 %

mp : 108-112 ^{o}C

3.3.1.40 Compound 21j

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(pyridin-2-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21j

Purity by HPLC : 97.37 %

IR (KBr) : 681, 1343, 1737, 3016, 3583 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.18(t, *J* = 6.99 Hz, 3H), 2.46(s, 3H), 2.98(dd, *J* = 4.1 Hz & 7.3 Hz, 2H), 3.48-4.02(m, 2H), 4.09-4.12(m, 1H), 5.01(s, 2H), 6.96(d, *J*

= 8.6 Hz, 2H), 7.19(d, *J* = 8.5 Hz, 2H), 7.78-7.80(m, 1H), 7.81(t, *J* = 7.7 Hz, 1H), 8.1(d, *J* = 7.9 Hz, 1H), 8.7(d, *J* = 4.4 Hz, 1H).

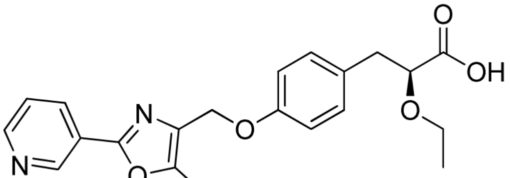
ESI/MS (m/z) : 383 $(M+H)^+$

% Yield : 35 %

mp : 135-139 °C

3.3.1.41 Compound 21k

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(pyridin-3-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21k

Purity by HPLC : 98.61 %

IR (KBr) : 962, 1512, 1608, 1718, 2297, 2507, 2873, 2977, 3402 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.19(t, *J* = 7.0 Hz, 3H), 2.47(s, 3H), 2.90(d, *J* = 7.0 Hz, 1H), 3.1(d, *J* = 4.38 Hz, 1H), 3.55-3.58(m, 2H), 4.08-4.12(m, 1H), 4.99(s, 2H), 6.95(d, *J* = 8.61 Hz, 2H), 7.17(d, *J* = 8.49 Hz, 2H), 7.59(d, *J* = 7.62 Hz, 1H), 8.48(d, *J* = 7.95 Hz, 1H), 8.69(s, 1H), 9.26(s, 1H).

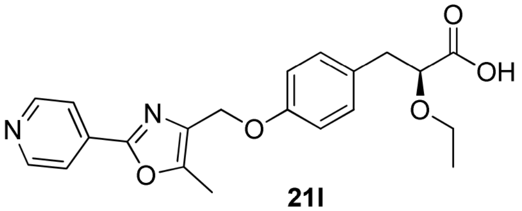
ESI/MS (m/z) : 383 $(M+H)^+$

% Yield : 72 %

mp : 117-118 °C

3.3.1.42 Compound 21l

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(pyridin-4-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21l

Purity by HPLC : 97.09 %

IR (KBr) : 1612, 1723, 2293, 2498, 2772, 2875, 3400 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.02(t, J = 6.96 Hz, 3H), 2.48(s, 3H), 2.81-2.91(m, 2H), 3.24-3.29(m, 1H), 3.53-3.90(m, 1H), 3.91(t, J = 6.39 Hz, 1H), 4.98(s, 2H), 6.92(d, J = 8.54 Hz, 2H), 7.14(d, J = 8.51 Hz, 2H), 7.83(d, J = 4.62 Hz, 2H), 8.72(d, J = 5.94 Hz, 2H).

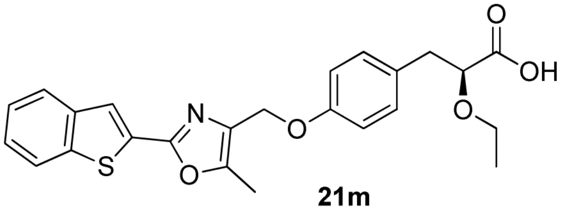
ESI/MS (m/z) : 383 (M+H)$^+$

% Yield : 50 %

mp : 132-134 °C

3.3.1.43 Compound 21m

(*S*)-3-(4-((2-(Benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl)-2-ethoxypropanoic acid.



21m

Purity by HPLC : 97.54 %

IR (KBr) : 833, 1002, 1298, 1641, 1701, 2524, 2931, 3516 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.18(t, J = 6.99 Hz, 3H), 2.45(s, 3H), 2.92-2.99(m, 1H), 3.08-3.14(m, 1H), 3.44-3.50(m, 1H), 3.56-3.61(m, 1H), 4.04-4.08(m, 1H), 4.98(s, 2H), 6.94(d, *J* = 8.55 Hz, 2H), 7.18(d, *J* = 8.52 Hz, 2H), 7.37-7.40(m, 2H), 7.79-7.86(m, 3H).

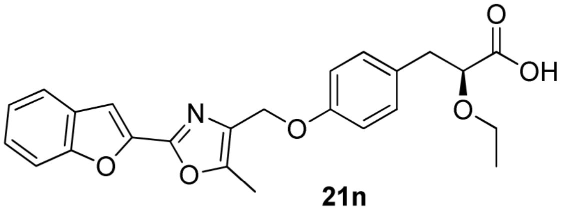
ESI/MS (m/z) : 438 $(M+H)^+$

% Yield : 88 %

mp : 108-110 °C

3.3.1.44 Compound 21n

(*S*)-3-(4-((2-(Benzofuran-2-yl)-5-methyloxazol-4-yl)methoxy)phenyl)-2-ethoxy propanoic acid.



21n

Purity by HPLC : 94.02 %

IR (KBr) : 677, 1348, 1512, 1708, 2337, 2927 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.03(t, *J* = 6.94 Hz, 3H), 2.46(s, 3H), 2.47-2.81(m, 2H), 3.44-3.53(m, 2H), 3.93-3.94(m, 1H), 4.98(s, 2H), 6.94(d, *J* = 8.55 Hz, 2H), 7.15(d, *J* = 8.52 Hz, 2H), 7.33-7.76(m, 5H), 12.59(s, 1H).

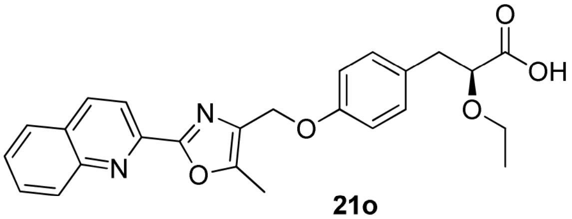
ESI/MS (m/z) : 422 $(M+H)^+$

% Yield : 59 %

mp : 110-112 °C

3.3.1.45 Compound 21o

(*S*)-2-Ethoxy-3-(4-((5-methyl-2-(quinolin-2-yl)oxazol-4-yl)methoxy)phenyl) propanoic acid.



21o

Purity by HPLC : 98.15 %

IR (KBr) : 758, 1122, 1244, 1512, 1600, 1710, 1735, 2925, 3440 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.18(t, *J* = 7.0 Hz, 3H), 2.53(s, 3H), 2.92-2.99(m, 1H), 3.07-3.13(m, 1H), 3.44-3.49(m, 1H), 3.57-3.62(m, 1H), 4.04-4.08(m, 1H), 5.05(s, 2H), 6.96(d, *J* = 8.52 Hz, 2H), 7.18(d, *J* = 8.52 Hz, 2H), 7.59(t, *J* = 7.42 Hz, 1H), 7.76(t, *J* = 7.4 Hz, 1H), 7.84(d, *J* = 8.04 Hz, 1H), 8.22-8.28(m, 3H).

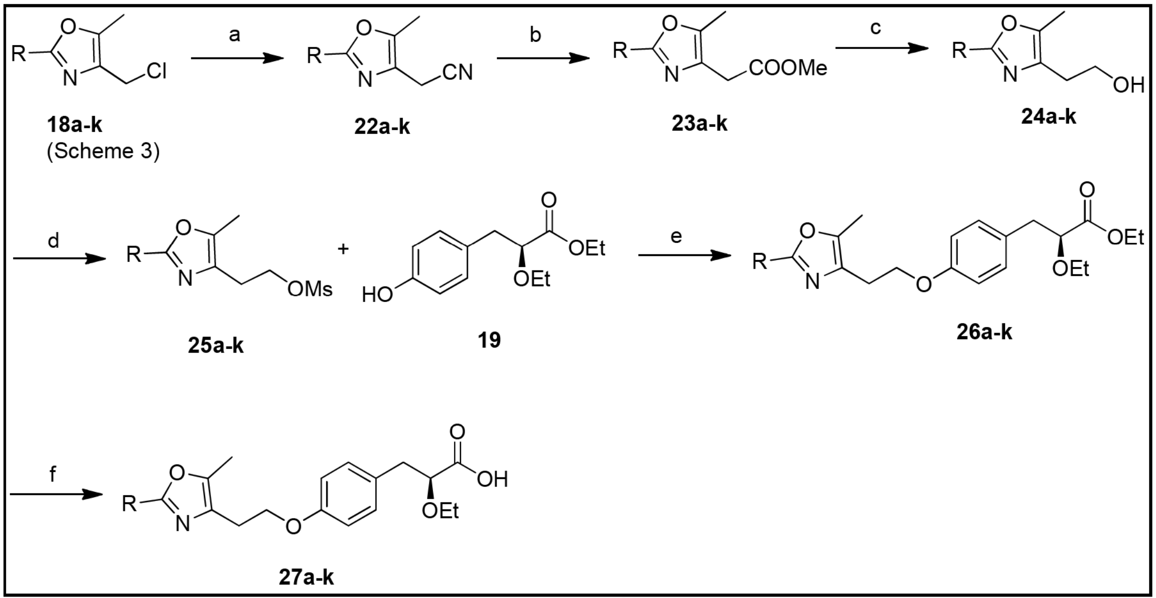
ESI/MS (m/z) : 433 $(M+H)^+$

% Yield : 67 %

mp : 151-152 °C

3.4 Synthesis of thiophene substituted oxazoles two carbon linker chain analogues

Scheme : 4



Reagents and conditions (a) NaCN, DMF, 25-30 °C, 4h, 80-90 %, (b) MeOH, H_2SO_4, catalytic H_2O, reflux, 16h, 60-70 %, (c) $LiAlH_4$, THF, 0-10 °C, 1h, 70-80 %, (d) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 25 °C, 4h, 85-90%, (e) K_2CO_3, DMF, 80-90 °C, 2h, 40-50%, (f) NaOH/MeOH/H_2O, 20-25 °C, 4h, 60-70 % .

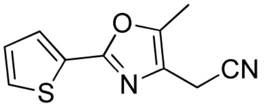
Procedure for intermediate 22a

To a solution of chloromethyloxazole **18a** (28.5 g, 133.8 mmole) in DMF (140 mL), NaCN (10.49 g, 2.14 mmole) was added and the reaction mixture was stirred at 25-30 °C for 4 hours. Reaction mixture was poured in water (450 mL), solid separated was filtered, washed with excess water and dried under vacuum to furnish the corresponding cyanomethyloxazole derivative **22a** as solid.

3.4.1 Compounds

3.4.1.1 Intermediate 22a

2-(5-Methyl-2-(thiophen-2-yl)oxazol-4-yl)acetonitrile.



22a

Purity by HPLC : 95.5 %

IR (KBr) : 700, 768, 1640, 2923, 3083 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.40(s, 3H), 3.67(s, 2H), 7.08(t, *J* = 8.58 Hz, 1H), 7.40(d, *J* = 4.89 Hz, 1H), 7.63(d, *J* = 3.45 Hz, 1H).

ESI/MS (m/z) : 205 $(M+H)^+$

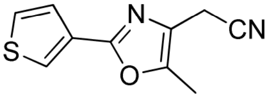
% Yield : 97 %

mp : 105-107 °C

Intermediates **22b-k** were prepared by following the procedure of intermediate **22a** using appropriate starting materials.

3.4.1.2 Intermediate 22b

2-(5-Methyl-2-(thiophen-3-yl)oxazol-4-yl)acetonitrile.



22b

Purity by HPLC : 98.60 %

IR (KBr) : 723, 860, 1595, 1645, 2250, 3109, 3411 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.42(s, 3H), 3.63(s, 2H), 7.37-7.39(m, 1H), 7.55-7.57(m, 1H), 7.88-7.89(m, 1H).

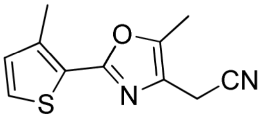
ESI/MS (m/z) : 205 $(M+H)^+$

% Yield : 99 %

mp : 112-113 °C

3.4.1.3 Intermediate 22c

2-(5-Methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)acetonitrile.



22c

Purity by HPLC : 97.8 %

IR (KBr) : 720, 860, 1600, 2250, 3099 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.40(s, 3H), 2.50(s, 3H), 3.61(s, 2H), 6.70(d, J = 2.7 Hz, 1H), 7.25(d, J = 3.0 Hz, 1H).

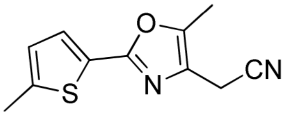
ESI/MS (m/z) : 219 $(M+H)^+$

% Yield : 97 %

mp : 121-124 °C

3.4.1.4 Intermediate 22d

2-(5-Methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)acetonitrile.



22d

Purity by HPLC : 97.75 %

IR (KBr) : 804, 1442, 1591, 1645, 2250, 2923, 3423 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.40(s, 3H), 2.52(s, 3H), 3.61(s, 2H), 6.74-6.76(m, 1H), 7.40(d, J = 3.60 Hz, 1H).

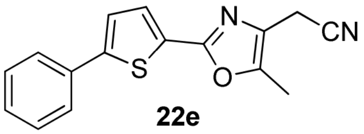
ESI/MS (m/z) : 219 $(M+H)^+$

% Yield : 85 %

mp : 76-77 °C

3.4.1.5 Intermediate 22e

2-(5-Methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl)acetonitrile.



22e

Purity by HPLC : 96.9 %

IR (KBr) : 801, 1441, 1642, 2247, 2900 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.42(s, 3H), 3.65(s, 2H), 7.28-7.38(m, 4H), 7.58(d, *J* = 3.6 Hz, 1H), 7.60(d, *J* = 7.0 Hz, 2H).

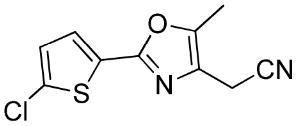
ESI/MS (m/z) : 281 (M+H)$^+$

% Yield : 86 %

mp : 81-85 ^{o}C

3.4.1.6 Intermediate 22f

2-(2-(5-Chlorothiophen-2-yl)-5-methyloxazol-4-yl)acetonitrile.



22f

Purity by HPLC : 98 %

IR (KBr) : 1332, 1600, 2253, 2858 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.35(s, 3H), 4.4(s, 2H), 7.05(d, *J* = 2.7 Hz, 1H), 7.28(d, *J* = 5.7 Hz, 1H).

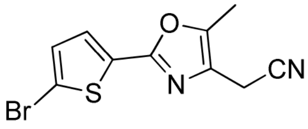
ESI/MS (m/z) : 239 (M+H)$^+$

% Yield : 92 %

mp : 99-103 ^{o}C

3.4.1.7 Intermediate 22g

2-(2-(5-Bromothiophen-2-yl)-5-methyloxazol-4-yl)acetonitrile.



22g

Purity by HPLC : 95.34 %

IR (KBr) : 1500, 1645, 2248, 2931, 2977 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.41(s, 3H), 3.61(s, 2H), 7.06(d, *J* = 3.92 Hz, 1H), 7.35(d, *J* = 3.93 Hz, 1H).

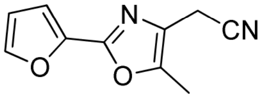
ESI/MS (m/z) : 284 $(M+H)^+$

% Yield : 100 %

mp : 118-119 °C

3.4.1.8 Intermediate 22h

2-(2-(Furan-2-yl)-5-methyloxazol-4-yl)acetonitrile.



22h

Purity by HPLC : 99 %

IR (KBr) : 1350, 1622, 2249, 2953 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.39(s, 3H), 3.67(s, 2H), 7.06-7.11(m, 1H), 7.41(d, *J* = 5.0 Hz, 1H), 7.64(d, *J* = 3.3 Hz, 1H).

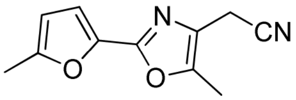
ESI/MS (m/z) : 189 $(M+H)^+$

% Yield : 89 %

mp : 115-119 °C

3.4.1.9 Intermediate 22i

2-(5-Methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)acetonitrile.



22i

Purity by HPLC : 98.72 %

IR (KBr) : 1332, 1645, 2253, 2977 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.39(s, 3H), 2.42(s, 3H), 3.63(s, 2H), 6.11(d, J = 2.7 Hz, 1H), 6.87(d, J = 3.3 Hz, 1H).

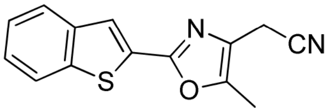
ESI/MS (m/z) : 203 (M+H)$^+$

% Yield : 78 %

mp : 118-121 °C

3.4.1.10 Intermediate 22j

2-(2-(Benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)acetonitrile.



22j

Purity by HPLC : 96.72 %

IR (KBr) : 870, 1350, 1620, 2248 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 3.64(s, 2H), 7.40-7.51(m, 2H), 7.80-7.89(m, 3H).

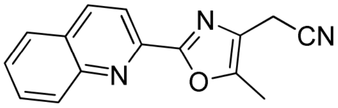
ESI/MS (m/z) : 255 (M+H)$^+$

% Yield : 72 %

mp : 116-118 °C

3.4.1.11 Intermediate 22k

2-(5-Methyl-2-(quinolin-2-yl)oxazol-4-yl)acetonitrile.



22k

Purity by HPLC : 95 %

IR (KBr) : 675, 1330, 1618, 2245 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.41(s, 3H), 3.63(s, 2H), 7.52-7.56(m, 1H), 7.71-7.81(m, 1H), 7.83(d, $J = 7.3$ Hz, 1H), 8.30-8.37(m, 3H).

ESI/MS (m/z) : 250 $(M+H)^+$

% Yield : 79 %

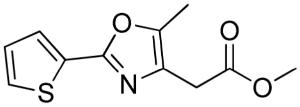
mp : 101-104 °C

Procedure for intermediate 23a

To a suspension of cyano compound prepared as above **22a** (27.0 g, 132.35 mole) in a mixture of methanol (270 mL) and water (catalytic) was added H_2SO_4 (21.6 mL) drop wise and the reaction mixture was refluxed for 16 hours. Solvent was evaporated under vacuum. The residue was poured into ice water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extract was successively washed with water (100 mL) & brine (100 mL), dried over sodium sulfate, filtered and concentrated under vacuum to furnish corresponding ester derivative **23a** as an oil, which was used further without purification.

3.4.1.12 Intermediate 23a

Methyl 2-(5-methyl-2-(thiophen-2-yl)oxazol-4-yl)acetate.



23a

Purity by HPLC : 97.02 %

IR (Neat) : 700, 768, 1640, 2923, 3083 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 3.51(s, 2H), 3.67(s, 3H), 7.08(t, *J* = 8.58 Hz, 1H), 7.40(d, *J* = 4.89 Hz, 1H), 7.63(d, *J* = 3.45 Hz, 1H).

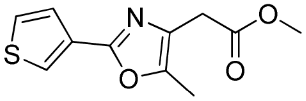
ESI/MS (m/z) : 238 (M+H)$^+$

% Yield : 95 %

Intermediates **23b-k** were prepared by following the procedure of intermediate **23a** using appropriate starting materials.

3.4.1.13 Intermediate 23b

Methyl 2-(5-methyl-2-(thiophen-3-yl)oxazol-4-yl)acetate.



23b

Purity by HPLC : 98.7 %

IR (Neat) : 701, 765, 1650, 2900 cm^{-1}

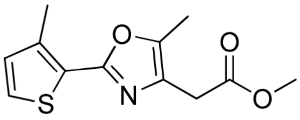
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 3.50(s, 2H), 3.77(s, 3H), 7.30-7.32(m, 1H), 7.66(d, *J* = 5.3 Hz, 1H), 7.84-7.92(m, 1H).

ESI/MS (m/z) : 238 (M+H)$^+$

% Yield : 80 %

3.4.1.14 Intermediate 23c

Methyl 2-(5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)acetate.



23c

Purity by HPLC : 93.7 %

IR (KBr) : 699, 755, 1661, 2899 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.38(s, 3H), 2.55(s, 3H), 3.52(s, 2H), 3.70(s, 3H), 6.70(d, J = 2.6 Hz, 1H), 7.42(d, J = 3.4 Hz, 1H).

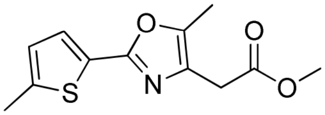
ESI/MS (m/z) : 252 $(M+H)^+$

% Yield : 92 %

mp : 75-78 °C

3.4.1.15 Intermediate 23d

Methyl 2-(5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)acetate.



23d

Purity by HPLC : 97.58 %

IR (KBr) : 804, 1163, 1743, 2922, 2952, 3465 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.32(s, 3H), 2.50(s, 3H), 3.53(s, 2H), 3.71(s, 3H), 6.71-6.73(m, 1H), 7.38(d, J = 3.60 Hz, 1H).

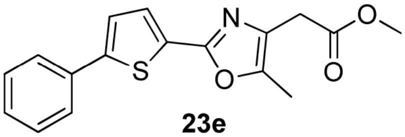
ESI/MS (m/z) : 252 $(M+H)^+$

% Yield : 80 %

mp : 68-69 °C

3.4.1.16 Intermediate 23e

Methyl 2-(5-methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl)acetate.



23e

Purity by HPLC : 94.7 %

IR (KBr) : 690, 802, 1150, 1730 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.42(s, 3H), 3.48(s, 2H), 3.67(s, 3H), 7.25-7.40(m, 4H), 7.56(d, *J* = 3.7 Hz, 1H), 7.58(d, *J* = 7.1 Hz, 2H).

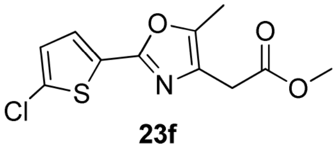
ESI/MS (m/z) : 314 (M+H)$^+$

% Yield : 88 %

mp : 78-82 °C

3.4.1.17 Intermediate 23f

Methyl 2-(2-(5-chlorothiophen-2-yl)-5-methyloxazol-4-yl)acetate.



23f

Purity by HPLC : 96.79 %

IR (KBr) : 1530, 1735, 2923, 2953 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 3.51(s, 2H), 3.67(s, 3H), 7.06(d, *J* = 2.7 Hz, 1H), 7.30(d, *J* = 6.0 Hz, 1H).

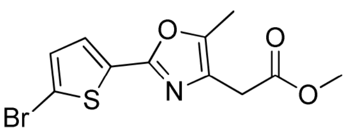
ESI/MS (m/z) : 272 (M+H)$^+$

% Yield : 81 %

mp : 72-76 °C

3.4.1.18 Intermediate 23g

Methyl 2-(2-(5-bromothiophen-2-yl)-5-methyloxazol-4-yl)acetate.



23g

Purity by HPLC : 94.35 %

IR (KBr) : 1515, 1739, 2925, 2954 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.3(s, 3H), 3.53(s, 2H), 3.72(s, 3H), 7.03(d, *J* = 3.9 Hz, 1H), 7.33(d, *J* = 3.93 Hz, 1H).

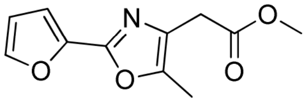
ESI/MS (m/z) : 318 (M+H)$^+$

% Yield : 76 %

mp : 80-84 °C

3.4.1.19 Intermediate 23h

Methyl 2-(2-(furan-2-yl)-5-methyloxazol-4-yl)acetate.



23h

Purity by HPLC : 93.7 %

IR (KBr) : 1321, 1739, 2922, 2950 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.40(s, 3H), 3.51(s, 2H), 3.67(s, 3H), 7.07-7.10(m, 1H), 7.40(d, *J* = 4.89 Hz, 1H), 7.62(d, *J* = 3.45 Hz, 1H).

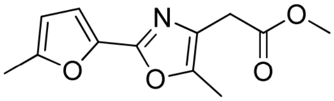
ESI/MS (m/z) : 222 (M+H)$^+$

% Yield : 90 %

mp : 86-88 °C

3.4.1.20 Intermediate 23i

Methyl 2-(5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)acetate.



23i

Purity by HPLC : 83 %

IR (KBr) : 1315, 1720, 2895, 3010 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.26(s, 3H), 2.33(s, 3H), 3.55(s, 3H), 3.71(s, 2H), 6.08(d, *J* = 3.0 Hz, 1H), 6.83(d, *J* = 3.3 Hz, 1H).

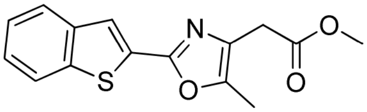
ESI/MS (m/z) : 236 (M+H)$^+$

% Yield : 90 %

mp : 100-103 ^{o}C

3.4.1.21 Intermediate 23j

Methyl 2-(2-(benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)acetate.



23j

Purity by HPLC : 89.92 %

IR (KBr) : 685, 1310, 1620, 1735, 2854 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.31(s, 3H), 3.48(s, 2H), 3.69(s, 3H), 7.38-7.42(m, 2H), 7.79-7.86(m, 3H).

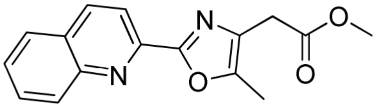
ESI/MS (m/z) : 288 (M+H)$^+$

% Yield : 79 %

mp : 92-95 ^{o}C

3.4.1.22 Intermediate 23k

Methyl 2-(5-methyl-2-(quinolin-2-yl)oxazol-4-yl)acetate.



23k

Purity by HPLC : 92 %

IR (KBr) : 685, 1301, 1600, 1740, 2922 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.31(s, 3H), 3.45(s, 2H), 3.70(s, 3H), 7.50(t, *J* = 7.2 Hz, 1H), 7.79(m, 1H), 7.77(d, *J* = 7.3 Hz, 1H), 8.20-8.30(m, 3H).

ESI/MS (m/z) : 283 (M+H)$^+$

% Yield : 87 %

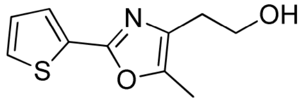
mp : 110-114 °C

Procedure for intermediate 24a

To an ice-cold solution of the ester **23a** prepared as above (29.77g, 0.132 mole) in THF (149 mL), LiAlH$_4$ (5.02 g, 0.132 mole) was added in portions over a period of 30 minutes and the reaction mixture was stirred below 10 °C for one hour. Reaction mixture was quenched with saturated aqueous solution of sodium sulfate till solid separated out. The solids were filtered and washed with hot ethyl acetate (2 x 125 mL). The combined filtrate was concentrated under vacuum to yield corresponding alcohol **24a**, which was directly taken for the next step.

3.4.1.23 Intermediate 24a

2-(5-Methyl-2-(thiophen-2-yl)oxazol-4-yl)ethanol.



24a

Purity by HPLC : 88.76 %

IR (KBr) : 756, 1641, 2927, 3018 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.32(s, 3H), 2.70(t, *J* = 5.5 Hz, 2H), 3.91(t, *J* = 5.5 Hz, 2H), 7.07-7.10(dd, *J* = 3.9 Hz & 5.1 Hz, 1H), 7.36-7.38(dd, *J* = 0.9 Hz & 5.1 Hz, 1H), 7.58-7.59(dd, *J* = 0.9 Hz & 3.6 Hz, 1H).

ESI/MS (m/z) : 210 $(M+H)^+$

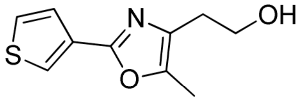
% Yield : 92 %

mp : 87-89 °C

Intermediates **24b-k** were prepared by following the procedure of intermediate **24a** using appropriate starting materials.

3.4.1.24 Intermediate 24b

2-(5-Methyl-2-(thiophen-3-yl)oxazol-4-yl)ethanol.



24b

Purity by HPLC : 90.11 %

IR (KBr) : 1341, 1622, 2918, 3540 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ2.43(s, 3H), 2.68(t, *J* = 4.3 Hz, 2H), 3.88(t, *J* = 5.9 Hz, 2H), 7.30-7.36(m, 1H), 7.63(d, *J* = 5.2 Hz, 1H), 7.84-7.87(m, 1H).

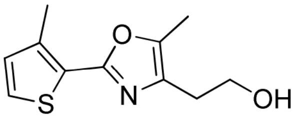
ESI/MS (m/z) : 210 $(M+H)^+$

% Yield : 90 %

mp : 100-103 °C

3.4.1.25 Intermediate 24c

2-(5-Methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)ethanol.



24c

Purity by HPLC : 92.73 %

IR (KBr) : 1347, 1622, 2942, 3590 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.37(s, 3H), 2.6(s, 3H), 2.68(t, *J* = 4.4 Hz, 2H), 3.70(t, *J* = 5.6 Hz, 2H), 7.00(d, *J* = 2.1 Hz, 1H), 7.31(d, *J* = 5.9 Hz, 1H).

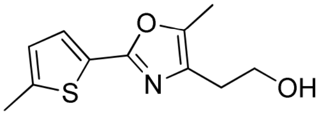
ESI/MS (m/z) : 224 (M+H)$^+$

% Yield : 78 %

mp : 89-92 °C

3.4.1.26 Intermediate 24d

2-(5-Methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)ethanol.



24d

Purity by HPLC : 95.45 %

IR (KBr) : 756, 1643, 2923, 3016 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.29(s, 3H), 2.51(s, 3H), 2.68(t, *J* = 5.64 Hz, 2H), 3.89-3.90(m, 2H), 6.72-6.74(m, 1H), 7.37(d, *J* = 3.6 Hz, 1H).

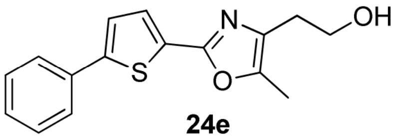
ESI/MS (m/z) : 224 (M+H)$^+$

% Yield : 76 %

mp : 89-91 ^{o}C

3.4.1.27 Intermediate 24e

2-(5-Methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl)ethanol.



24e

Purity by HPLC : 96.19 %

IR (KBr) : 1517, 2854, 3313 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.33(s, 3H), 2.71(t, *J* = 7.06 Hz, 2H), 3.91-3.93(m, 2H), 7.26-7.64(m, 7H).

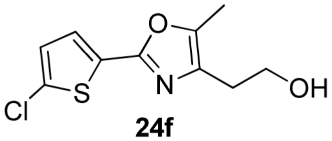
ESI/MS (m/z) : 286 (M+H)$^+$

% Yield : 100 %

mp : 99-102 ℃

3.4.1.28 Intermediate 24f

2-(2-(5-Chlorothiophen-2-yl)-5-methyloxazol-4-yl)ethanol.



24f

Purity by HPLC : 94.72 %

IR (KBr) : 1341, 1622, 2913, 3601 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.29(s, 3H), 2.69(t, *J* = 4.5 Hz, 2H), 3.88(t, *J* = 6.0 Hz, 2H), 7.05(d, *J* = 2.0 Hz, 1H), 7.31(d, *J* = 6.0 Hz, 1H).

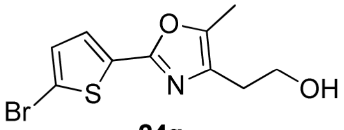
ESI/MS (m/z) : 244 (M+H)$^+$

% Yield : 98 %

mp : 104-108 ℃

3.4.1.29 Intermediate 24g

2-(2-(5-Bromothiophen-2-yl)-5-methyloxazol-4-yl)ethanol.



24g

Purity by HPLC : 88.8 %

IR (KBr) : 1278, 1350, 2847, 3350 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.30(s, 3H), 2.69(t, *J* = 4.5 Hz, 2H), 3.89(t, *J* = 6 Hz, 2H), 7.04(d, *J* = 2 Hz, 1H), 7.31(d, *J* = 6 Hz, 1H).

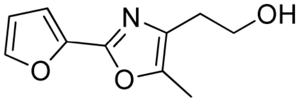
ESI/MS (m/z) : 289.9 (M+H)$^+$

% Yield : 93 %

mp : 107-110 ℃

3.4.1.30 Intermediate 24h

2-(2-(Furan-2-yl)-5-methyloxazol-4-yl)ethanol.



24h

Purity by HPLC : 87.67 %

IR (KBr) : 756, 1047, 1215, 1448, 1637, 3018, 3402 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.33(s, 3H), 2.72(t, *J* = 5.83 Hz, 2H), 3.92(t, *J* = 5.88 Hz, 2H), 6.51(m, 1H), 6.93(d, *J* = 3.39 Hz, 1H), 7.52(d, *J* = 1.11 Hz, 1H).

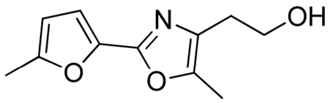
ESI/MS (m/z) : 194 (M+H)$^+$

% Yield : 93 %

mp : 108-111 ℃

3.4.1.31 Intermediate 24i

2-(5-Methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)ethanol.



24i

Purity by HPLC : 94.72 %

IR (KBr) : 1579, 2885, 3583 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.32(s, 3H), 2.39(s, 3H), 2.72(t, J = 6 Hz, 2H), 3.91(t, J = 6 Hz, 2H), 6.10(d, J = 3.0 Hz, 1H), 6.88(d, J = 3.0 Hz, 1H).

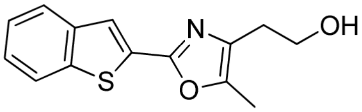
ESI/MS (m/z) : 208 (M+H)$^+$

% Yield : 79 %

mp : 95-98 ℃

3.4.1.32 Intermediate 24j

2-(2-(Benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)ethanol.



24j

Purity by HPLC : 93.11 %

IR (KBr) : 672, 1260, 1360, 3243 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.30(s, 3H), 2.63(t, J = 4.1 Hz, 2H), 3.89(t, J = 6.0 Hz, 2H), 7.40-7.47(m, 2H), 7.80-7.90(m, 3H).

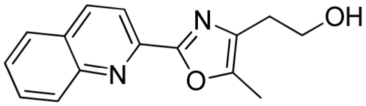
ESI/MS (m/z) : 260 (M+H)$^+$

% Yield : 91 %

mp : 101-104 ℃

3.4.1.33 Intermediate 24k

2-(5-Methyl-2-(quinolin-2-yl)oxazol-4-yl)ethanol.



24k

Purity by HPLC : 95.43 %

IR (KBr) : 680, 1247, 1372, 3347 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.35(s, 3H), 2.57(t, J = 4.3 Hz, 2H), 3.90(t, J = 5.9 Hz, 2H), 7.54(t, J = 7.3 Hz, 1H), 7.80(t, J = 7.5 Hz, 1H), 7.80(d, J = 7.8 Hz, 1H), 8.21-8.27(m, 3H).

ESI/MS (m/z) : 255 (M+H)$^+$

% Yield : 87 %

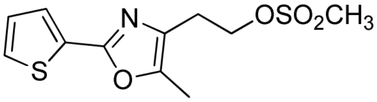
mp : 96-99 °C

Procedure for intermediates 25a

To an ice-cold solution of the alcohol compounds **24a** (26.06 g, 0.132 mole in dichloromethane (130 mL) were added triethylamine (15.99 g, 0.158 mole) followed by dropwise addition of methanesulfonylchloride (16.62 g, 0.145 mole) at 10 °C and the reaction mixture was stirred at ambient temperature for 4 hours. The reaction mixture was diluted with chloroform (200 mL) and successively washed with water (100 mL), 1N HCl (100 mL), again water (100 mL) and finally with sodium bicarbonate solution (100 mL). The organic extract was dried over sodium sulfate and concentrated under vacuum. The crude syrup so obtained was triturated with methanol to obtain corresponding mesylate derivative **25a** as an oil.

3.4.1.34 Intermediate 25a

2-(5-Methyl-2-(thiophen-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25a

Purity by HPLC : 97.02 %

IR (Neat) : 1589, 1639, 3433 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.34(s, 3H), 2.93(t, *J* = 6.45 Hz, 2H), 2.96(s, 3H), 4.50(t, *J* = 6.51 Hz, 2H), 7.08-7.11(m, 1H), 7.38-7.40(dd, *J* = 1.2 Hz & 5.1 Hz, 1H), 7.58-7.60(dd, *J* = 1.2 Hz & 3.9 Hz, 1H).

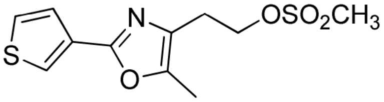
ESI/MS (m/z) : 288 (M+H)$^+$

% Yield : 86 %

Intermediates **25b-k** were prepared by following the procedure of intermediate **25a** using appropriate starting materials.

3.4.1.35 Intermediate 25b

2-(5-Methyl-2-(thiophen-3-yl)oxazol-4-yl)ethyl methanesulfonate.



25b

Purity by HPLC : 92.45 %

IR (Neat) : 1247, 1375, 3004 cm^{-1}

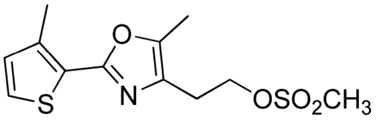
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.45(s, 3H), 3.0(s, 3H), 3.10(t, *J* = 5.9 Hz, 2H), 4.40(t, *J* = 6.2 Hz, 2H), 7.32-7.33(m, 1H), 7.58-7.6(d, *J* = 5.0 Hz, 1H), 7.83-7.86(m, 1H).

ESI/MS (m/z) : 288 (M+H)$^+$

% Yield : 85 %

3.4.1.36 Intermediate 25c

2-(5-Methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25c

Purity by HPLC : 93.44 %

IR (Neat) : 1274, 1345, 2845, 2915 cm^{-1}

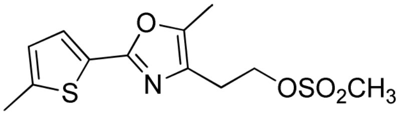
^{1}H NMR (CDCl3, 300 MHz) : δ2.40(s, 3H), 2.59(s, 3H), 2.69(t, J = 4.5 Hz, 2H), 2.95(s, 3H), 3.80(t, J = 6.0 Hz, 2H), 7.02(d, J = 4.2 Hz, 1H), 7.32(d, J = 3.5 Hz, 1H).

ESI/MS (m/z) : 302 (M+H)$^+$

% Yield : 83 %

3.4.1.37 Intermediate 25d

2-(5-Methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25d

Purity by HPLC : 99.20 %

IR (Neat) : 1589, 2917, 3018 cm^{-1}

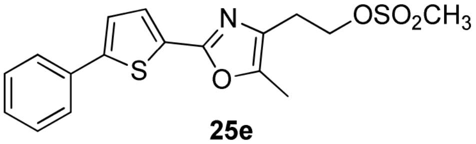
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.32(s, 3H), 2.51(s, 3H), 2.90(t, J = 6 Hz, 2H), 2.95(s, 3H), 4.49(t, J = 6 Hz, 2H), 6.73-6.74(m, 1H), 7.36(d, J = 3.57 Hz, 1H).

ESI/MS (m/z) : 302 (M+H)$^+$

% Yield : 60 %

3.4.1.38 Intermediate 25e

2-(5-Methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25e

Purity by HPLC : 94.07 %

IR (Neat) : 1523, 1637, 2854, 3080 cm^{-1}

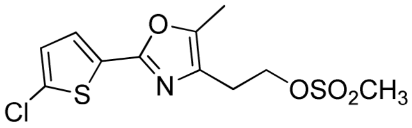
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.35(s, 3H), 2.97(s, 3H), 2.99(t, J = 6 Hz, 2H), 4.51(t, J = 6.40 Hz, 2H), 7.25-7.64(m, 7H).

ESI/MS (m/z) : 364 (M+H)$^+$

% Yield : 98 %

3.4.1.39 Intermediate 25f

2-(2-(5-Chlorothiophen-2-yl)-5-methyloxazol-4-yl)ethyl methanesulfonate.



25f

Purity by HPLC : 88.45 %

IR (Neat) : 1347, 1400, 2954, 3020 cm^{-1}

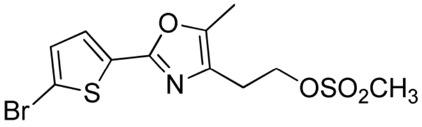
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.30(s, 3H), 2.69(t, J = 4.6 Hz, 2H), 3.1(s, 3H), 3.87(t, J = 6.0 Hz, 2H), 7.03(d, J = 2 Hz, 1H), 7.30(d, J = 5.8 Hz, 1H).

ESI/MS (m/z) : 322 (M+H)$^+$

% Yield : 85 %

3.4.1.40 Intermediate 25g

2-(2-(5-Bromothiophen-2-yl)-5-methyloxazol-4-yl)ethyl methanesulfonate.



25g

Purity by HPLC : 94.4 %

IR (Neat) : 1374, 1450, 2854, 3010 cm^{-1}

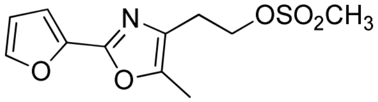
^{1}H NMR (CDCl$_3$, 300 MHz) **:** δ2.31(s, 3H), 2.68(t, *J* = 4.6 Hz, 2H), 3.0(s, 3H), 3.88(t, *J* = 6.1 Hz, 2H), 7.03(d, *J* = 2 Hz, 1H), 7.31(d, *J* = 6 Hz, 1H).

ESI/MS (m/z) : 367.9 (M+H)$^+$

% Yield : 84 %

3.4.1.41 Intermediate 25h

2-(2-(Furan-2-yl)-5-methyloxazol-4-yl)ethyl methanesulfonate.



25h

Purity by HPLC : 93.22 %

IR (Neat) : 1341, 1452, 2964, 3020 cm^{-1}

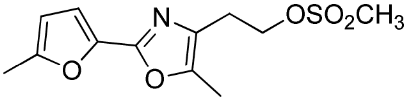
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.34(s, 3H), 2.93(t, *J* = 6.5 Hz, 2H), 2.96(s, 3H), 4.50(t, *J* = 6.5 Hz, 2H), 7.1-7.2(m, 1H), 7.4-7.45(dd, *J* = 1.2 Hz & 5.1 Hz, 1H), 7.6-7.64(dd, *J* = 1.3 Hz & 4.0 Hz, 1H).

ESI/MS (m/z) : 272 (M+H)$^+$

% Yield : 88 %

3.4.1.42 Intermediate 25i

2-(5-Methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25i

Purity by HPLC : 74.58 %

IR (Neat) : 1579, 2854, 3020 cm^{-1}

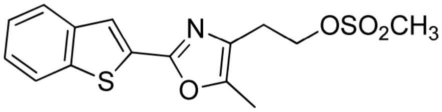
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.33(s, 3H), 2.39(s, 3H), 2.93(t, *J* = 6.0 Hz, 2H), 3.49(s, 3H), 4.49(t, *J* = 6.0 Hz, 2H), 6.10(d, *J* = 3.0 Hz, 1H), 6.82(d, *J* = 3.0 Hz, 1H).

ESI/MS (m/z) : 286 (M+H)$^+$

% Yield : 83 %

3.4.1.43 Intermediate 25j

2-(2-(Benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)ethyl methanesulfonate.



25j

Purity by HPLC : 87.42 %

IR (Neat) : 1620, 2950, 3010 cm^{-1}

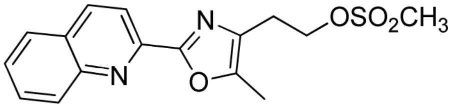
^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.34(s, 3H), 2.93(t, *J* = 6.4 Hz, 2H), 2.98(s, 3H), 4.48(t, *J* = 6.4 Hz, 2H), 7.38-7.48(m, 2H), 7.73-7.83(m, 3H).

ESI/MS (m/z) : 338 (M+H)$^+$

% Yield : 72 %

3.4.1.44 Intermediate 25k

2-(5-Methyl-2-(quinolin-2-yl)oxazol-4-yl)ethyl methanesulfonate.



25k

Purity by HPLC : 88.79 %

IR (Neat) : 672, 1370, 1620, 2978 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ2.43(s, 3H), 3.1(s, 3H), 3.25(t, *J* = 6.0 Hz, 2H), 4.39(t, *J* = 6.1 Hz, 2H), 7.55(t, *J* = 7.4 Hz, 1H), 7.75(t, *J* = 7.6 Hz, 1H), 7.83(d, *J* = 8.0 Hz, 1H), 8.25-8.29(m, 3H).

ESI/MS (m/z) : 333 (M+H)$^+$

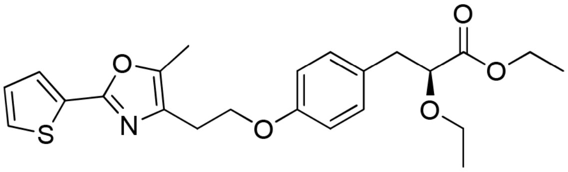
% Yield : 86 %

Procedure for intermediates 26a

K$_2$CO$_3$ (1.08 g, 7.83 mmol) was added to hydroxy compound **19** [1] (1.86 g, 7.83 mmole) in DMF (9.3 mL) at 20-25 °C. To that mesylate **25a** (2.25 g, 7.83 mmole) was added. The reaction mixture was stirred at 80-90 °C for 2 h. The reaction mixture was poured into water (35 mL) and extracted with ethyl acetate (2 X 25 mL). The combined organic extract was successively washed with water (25 mL) & brine (25 mL), dried over sodium sulfate, filtered and concentrated under vacuum to furnish corresponding crude ester derivative. The crude ester derivative was purified by column chromatography using Hexane : Ethylacetate as an eluent to furnish title product **26a** as an oil.

3.4.1.45 Intermediate 26a

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(thiophen-2-yl)oxazol-4-yl)ethoxy) phenyl)propanoate.



26a

Purity by HPLC : 95.49 %

IR (Neat) : 758, 1215, 1512, 1737, 2875, 2981 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.15(t, *J* = 6.93 Hz, 3H), 1.20(t, *J* = 7.14 Hz, 3H), 2.34(s, 3H), 2.92-2.96(m, 4H), 3.30-3.61(m, 2H), 3.95(t, *J* = 6.6 Hz, 1H), 4.12-4.21(m, 4H), 6.81(d, *J* = 8.64 Hz, 2H), 7.06-7.09(m, 1H), 7.12(d, *J* = 8.6 Hz, 2H), 7.35(dd, *J* = 1.11 Hz & 5.05 Hz, 1H), 7.57(dd, *J* = 1.14 Hz & 3.69 Hz, 1H).

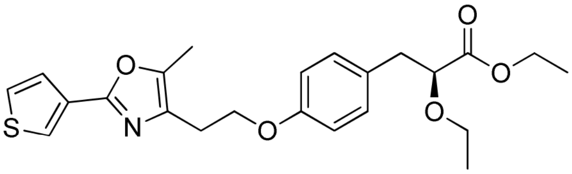
ESI/MS (m/z) : 430 (M+H)$^+$

% Yield : 78 %

Intermediates **26b-k** were prepared by following the procedure of intermediate **26a** using appropriate starting materials.

3.4.1.46 Intermediate 26b

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(thiophen-3-yl)oxazol-4-yl)ethoxy) phenyl)propanoate.



26b

Purity by HPLC : 95.5 %

IR (Neat) : 1245, 1512, 1745, 2977 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.15(t, *J* = 7.0 Hz, 3H), 1.21(t, *J* = 7.10 Hz, 3H), 2.34(s, 3H), 2.92-2.96(m, 4H), 3.30-3.36(m, 1H), 3.56-3.61(m, 1H), 3.92(t, *J* =

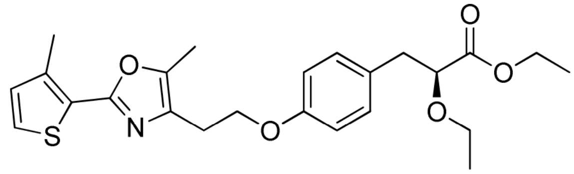
6.64 Hz, 1H), 4.12-4.16(m, 2H), 4.17-4.22(m, 2H), 6.82(d, *J* = 8.58 Hz, 2H), 7.14(d, *J* = 8.55 Hz, 2H), 7.33-7.36(m, 1H), 7.55-7.57(m, 1H), 7.83-7.84(m, 1H).

ESI/MS (m/z) : 430 $(M+H)^+$

% Yield : 63 %

3.4.1.47 Intermediate 26c

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl) ethoxy)phenyl)propanoate.



26c

Purity by HPLC : 95.45 %

IR (Neat) : 756, 1245, 1512, 1741, 2979 cm^{-1}

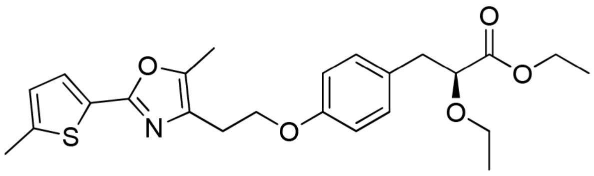
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.15(t, *J* = 7.0 Hz, 3H), 1.21(t, *J* = 7.10 Hz, 3H), 2.34(s, 3H), 2.55(s, 3H), 2.92-2.96(m, 4H), 3.31-3.36(m, 1H), 3.56-3.59(m, 1H), 3.95(t, *J* = 6.66 Hz, 1H), 4.12-4.18(m, 2H), 4.19-4.22(m, 2H), 6.82(d, *J* = 8.58 Hz, 2H), 6.89(d, *J* = 5.01 Hz, 1H), 7.14(d, *J* = 8.58 Hz, 2H), 7.23(d, *J* = 5.01 Hz, 1H).

ESI/MS (m/z) : 444 $(M+H)^+$

% Yield : 30 %

3.4.1.48 Intermediate 26d

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl) ethoxy)phenyl)propanoate.



26d

Purity by HPLC : 95.40 %

IR (Neat) : 804, 1512, 1747, 2977 cm^{-1}

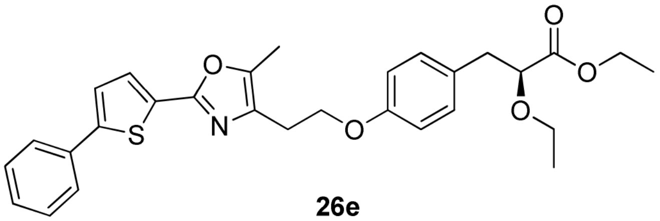
^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.15(t, J = 6.9 Hz, 3H), 1.20(t, J = 7.12 Hz, 3H), 2.30(s, 3H), 2.51(s, 3H), 2.90-2.94(m, 4H), 3.33-3.36(m, 1H), 3.56-3.58(m, 1H), 3.94(t, J = 6.67 Hz, 1H), 4.1-4.2(m, 4H), 6.71-6.73(m, 1H), 6.79(d, J = 8.4 Hz, 2H), 7.14(d, J = 8.61 Hz, 2H), 7.36(d, J = 3.6 Hz, 1H).

ESI/MS (m/z) : 444 (M+H)$^+$

% Yield : 75 %

3.4.1.49 Intermediate 26e

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl) ethoxy)phenyl)propanoate.



26e

Purity by HPLC : 97.01 %

IR (Neat) : 682, 1341, 1512, 1745, 2871 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.15(t, J = 6.99 Hz, 3H), 1.21(t, J = 6.94 Hz, 3H), 2.35(s, 3H), 2.92-2.97(m, 4H), 3.31-3.61(m, 2H), 3.95(t, J = 6.61 Hz, 1H), 4.08-

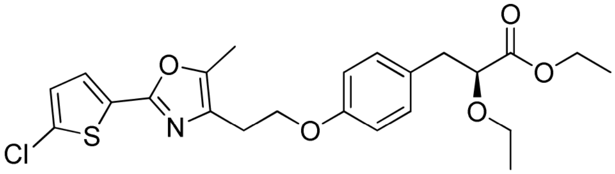
4.23(m, 4H), 6.81(d, *J* = 8.61 Hz, 2H), 7.13(d, *J* = 8.57 Hz, 2H), 7.26-7.64(m, 7H).

ESI/MS (m/z) : 506 $(M+H)^+$

% Yield : 48 %

3.4.1.50 Intermediate 26f

((*S*)-Ethyl 3-(4-(2-(2-(5-chlorothiophen-2-yl)-5-methyloxazol-4-yl)ethoxy) phenyl)-2-ethoxypropanoate.



26f

Purity by HPLC : 97.74 %

IR (Neat) : 690, 1349, 1512, 1735 cm^{-1}

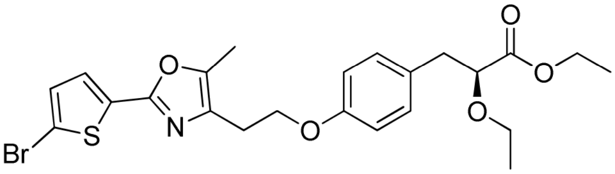
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.14(t, *J* = 6.96 Hz, 3H), 1.21(t, *J* = 5.6 Hz, 3H), 2.33(s, 3H), 2.89-2.94(m, 4H), 3.28-3.63(m, 2H), 3.93(t, *J* = 6.62 Hz, 1H), 4.08-4.20(m, 4H), 6.80(d, *J* = 7.39 Hz, 2H), 6.89(d, *J* = 3.96 Hz, 1H), 7.13(d, *J* = 8.58 Hz, 2H), 7.33(d, *J* = 3.96 Hz, 1H).

ESI/MS (m/z) : 464 $(M+H)^+$

% Yield : 39 %

3.4.1.51 Intermediate 26g

(*S*)-Ethyl 3-(4-(2-(2-(5-bromothiophen-2-yl)-5-methyloxazol-4-yl)ethoxy) phenyl)-2-ethoxypropanoate.



26g

Purity by HPLC : 94.18 %

IR (Neat) : 681, 1342, 1583, 1735, 2925 cm^{-1}

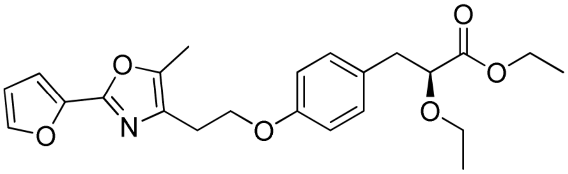
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.18(t, J = 6.15 Hz, 3H), 1.22(t, J = 7.06 Hz, 3H), 2.33(s, 3H), 2.90-2.94(m, 4H), 3.28-3.63(m, 2H), 3.95(t, J = 6.63 Hz, 1H), 4.12-4.20(m, 4H), 6.80(d, J = 8.60 Hz, 2H), 7.03(d, J = 3.92 Hz, 1H), 7.13(d, J = 8.53 Hz, 2H), 7.30(d, J = 3.93 Hz, 1H).

ESI/MS (m/z) : 509 $(M+H)^+$

% Yield : 26 %

3.4.1.52 Intermediate 26h

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(2-(furan-2-yl)-5-methyloxazol-4-yl)ethoxy)phenyl) propanoate.



26h

Purity by HPLC : 83.62 %

IR (Neat) : 758, 1215, 1512, 1737, 1639, 3018 cm^{-1}

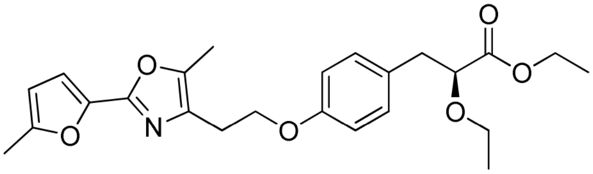
^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.15(t, J = 6.93 Hz, 3H), 1.2(t, J = 7.14 Hz, 3H), 2.34(s, 3H), 2.92-2.96(m, 4H), 3.30-3.40(m, 1H), 3.50-3.62(m, 1H), 3.95(t, J = 7.1 Hz, 1H), 4.14(t, J = 7.12 Hz, 2H), 4.22(t, J = 6.65 Hz, 2H), 6.49-6.51(m, 1H), 6.81(d, *J* = 8.6 Hz, 2H), 6.90(d, *J* = 3.2 Hz, 1H), 7.14(d, *J* = 8.6 Hz, 2H), 7.50(m, 1H).

ESI/MS (m/z) : 414 $(M+H)^+$

% Yield : 66 %

3.4.1.53 Intermediate 26i

(*S*)-Ethyl-2-ethoxy-3-(4-(2-(5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl) ethoxy)phenyl)propanoate.



26i

Purity by HPLC : 95.57 %

IR (Neat) : 1579, 1747, 2925, 2977, 3375 cm^{-1}

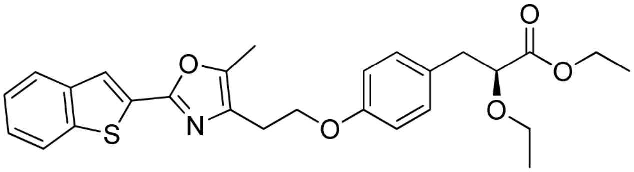
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.17(t, *J* = 6.15 Hz, 3H), 1.24(t, *J* = 6.03 Hz, 3H), 2.33(s, 3H), 2.38(s, 3H), 2.92-2.96(m, 4H), 3.33-3.59(m, 2H), 3.94(t, *J* = 6.54 Hz, 1H), 4.10-4.22(m, 4H), 6.08(d, *J* = 2.49 Hz, 1H), 6.78-6.81(m, 3H), 7.12(d, *J* = 8.43 Hz, 2H).

ESI/MS (m/z) : 428 $(M+H)^+$

% Yield : 38 %

3.4.1.54 Intermediate 26j

(*S*)-Ethyl 3-(4-(2-(2-(benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)ethoxy) phenyl)-2-ethoxypropanoate.



26j

Purity by HPLC : 89.20 %

IR (Neat) : 669, 1116, 1737, 2979, 3018 cm^{-1}

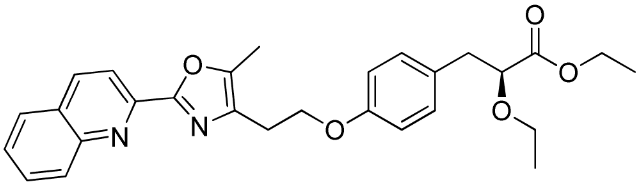
^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.14(t, *J* = 7.14 Hz, 3H), 1.21(t, *J* = 7.12 Hz, 3H), 2.39(s, 3H), 2.92-2.99(m, 4H), 3.33-3.36(m, 1H), 3.55-3.59(m, 1H), 3.94(t, *J* = 6.7 Hz, 1H), 4.14(t, *J* = 7.12 Hz, 2H), 4.22(t, *J* = 6.33 Hz, 2H), 6.81(d, *J* = 8.61 Hz, 2H), 7.13(d, *J* = 8.55 Hz, 2H), 7.34-7.4(m, 2H), 7.79-7.86(m, 3H).

ESI/MS (m/z) : 480 (M+H)$^+$

% Yield : 41 %

3.4.1.55 Intermediate 26k

(*S*)-Ethyl 2-ethoxy-3-(4-(2-(5-methyl-2-(quinolin-2-yl)oxazol-4-yl)ethoxy) phenyl)propanoate.



26k

Purity by HPLC : 97.8 %

IR (Neat) : 669, 1116, 1737, 2979, 3018 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.14(t, *J* = 7.0 Hz, 3H), 1.21(t, *J* = 7.1 Hz, 3H), 2.43(s, 3H), 2.87-2.93(m, 1H), 3.02(t, *J* = 6.2 Hz, 2H), 3.05-3.07(m, 1H), 3.43-3.53(m, 2H), 4.0-4.1(m, 1H), 4.13-4.20(q, *J* = 7.2 Hz & 7.2 Hz, 2H), 4.27(t, *J* =

6.3 Hz, 2H), 6.78(d, *J* = 8.5 Hz, 2H), 7.10(d, *J* = 8.4 Hz, 2H), 7.56(t, *J* = 7.27 Hz, 1H), 7.78(t, *J* = 7.6 Hz, 1H), 7.87(d, *J* = 8.0 Hz, 1H), 8.2-8.25(m, 3H).

ESI/MS (m/z) : 475 $(M+H)^+$

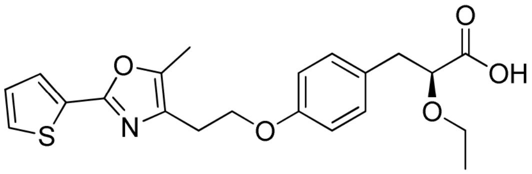
% Yield : 32 %

Procedure for compound 27a

To a solution of ester compound **26a** (1.0 g, 2.33 mmole) in methanol (6 mL) was added another solution of sodium hydroxide (0.139 g, 3.49 mmole) in water (3 mL) and the reaction mixture was stirred at ambient temperature for 4 hours. Solvents were evaporated under reduced pressure. Residue was dissolved in water (5 mL), acidified with 1N HCl and extracted with diethyl ether (2 x 20 mL). The combined organic extract was washed with water (25 mL), brine (25 mL) dried over sodium sulfate and evaporated under reduced pressure. Crude product was recrystalized from a mixture of diisopropyl ether or petroleum ether to give final product **27a** as a solid.

3.4.1.56 Compound 27a

(*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(thiophen-2-yl)oxazol-4-yl)ethoxy)phenyl) propanoic acid.



27a

Purity by HPLC : 98.75 %

IR (KBr) : 731, 1110, 1245, 1512, 1701, 2482, 2976, 3101, 3411 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.17(t, *J* = 6.99 Hz, 3H), 2.35(s, 3H), 2.92-2.97(m, 1H), 2.95(t, *J* = 6.6 Hz, 2H), 3.04-3.09(m, 1H), 3.41-3.47(m, 1H), 3.55-3.60(m, 1H), 4.01-4.05(m, 1H), 4.18(t, *J* = 6.6 Hz, 2H), 6.81(d, *J* = 8.6 Hz, 2H), 7.06-7.09(m, 1H), 7.13(d, *J* = 8.55 Hz, 2H), 7.37(dd, *J* = 1.0 Hz & 4.22 Hz, 1H), 7.48(dd, *J* = 1.0 Hz & 2.64 Hz, 1H).

ESI/MS (m/z) : 402 $(M+H)^+$

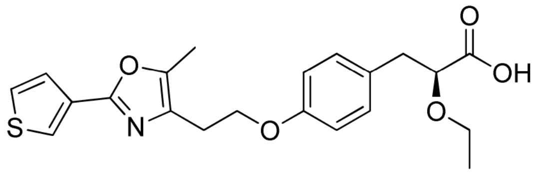
% Yield : 85 %

mp : 106-108 °C

Compounds **27b-k** were prepared by following the procedure of compound **27a** using appropriate starting materials.

3.4.1.57 Compound 27b

(*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(thiophen-3-yl)oxazol-4-yl)ethoxy)phenyl) propanoic acid.



27b

Purity by HPLC : 96.6 %

IR (KBr) : 756, 1217, 1245, 1512, 1724, 2977 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.15(t, *J* = 7.0 Hz, 3H), 2.34(s, 3H), 2.89-3.08(m, 4H), 3.40-3.45(m, 1H), 3.55-3.60(m, 1H), 4.00-4.04(m, 1H), 4.19(t, *J* = 6.66 Hz, 2H), 6.83(d, *J* = 8.55 Hz, 2H), 6.88(d, *J* = 5.01 Hz, 1H), 7.14(d, *J* = 8.58 Hz, 2H), 7.23(d, *J* = 5.01 Hz, 1H), 7.86(d, *J* = 2.58 Hz, 1H).

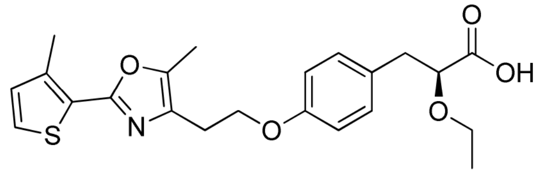
ESI/MS (m/z) : 402 $(M+H)^+$

% Yield : 73 %

mp : 122-125 °C

3.4.1.58 Compound 27c

(*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(3-methylthiophen-2-yl)oxazol-4-yl)ethoxy) phenyl)propanoic acid.



27c

Purity by HPLC : 96.84 %

IR (KBr) : 756, 1245, 1512, 1722, 2979 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 1.15(t, *J* = 7.0 Hz, 3H), 2.34(s, 3H), 2.55(s, 3H), 2.89-3.08(m, 4H), 3.40-3.45(m, 1H), 3.55-3.60(m, 1H), 4.00-4.04(m, 1H), 4.19(t, *J* = 6.66 Hz, 2H), 6.83(d, *J* = 8.55 Hz, 2H), 6.88(d, *J* = 5.01 Hz, 1H), 7.14(d, *J* = 8.58 Hz, 2H), 7.23(d, *J* = 5.01 Hz, 1H).

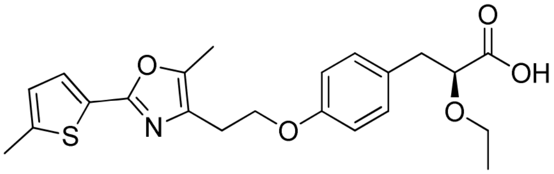
ESI/MS (m/z) : 416 (M+H)$^+$

% Yield : 90 %

mp : 116-119 °C

3.4.1.59 Compound 27d

(*S*)-2-ethoxy-3-(4-(2-(5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-yl)ethoxy) phenyl)propanoic acid.



27d

Purity by HPLC : 98.19 %

IR (KBr) : 798, 1213, 1510, 1701, 1724, 2873, 3410 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.15(t, *J* = 6.96 Hz, 3H), 2.32(s, 3H), 2.50(s, 3H), 2.89-2.96(m, 4H), 3.40-3.43(m, 1H), 3.56-3.59(m, 1H), 3.99-4.03(m, 1H), 4.16(t, *J* = 6.58 Hz, 2H), 6.72(d, *J* = 3.54 Hz, 1H), 6.81(d, *J* = 8.5 Hz, 2H), 7.15(d, *J* = 8.5 Hz, 2H), 7.39(d, *J* = 3.6 Hz, 1H).

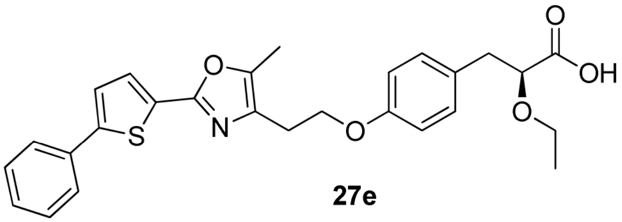
ESI/MS (m/z) : 416 $(M+H)^+$

% Yield : 76 %

mp : 88-91 °C

3.4.1.60 Compound 27e

((*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(5-phenylthiophen-2-yl)oxazol-4-yl) ethoxy)phenyl)propanoic acid.



27e

Purity by HPLC : 95.88 %

IR (KBr) : 927, 1512, 1730, 2927 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ1.16(t, *J* = 6.39 Hz, 3H), 2.89(s, 3H), 2.93-3.05(m, 4H), 3.41-3.58(m, 2H), 4.01-4.05(m, 1H), 4.20(t, *J* = 6.60 Hz, 2H), 6.81(d, *J* = 8.59 Hz, 2H), 7.14(d, *J* = 8.55 Hz, 2H), 7.26-7.42(m, 4H), 7.54(d, *J* = 3.86 Hz, 1H), 7.62(d, *J* = 7.26 Hz, 2H).

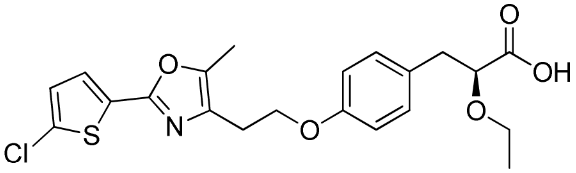
ESI/MS (m/z) : 478 $(M+H)^+$

% Yield : 88 %

mp : 108-109 °C

3.4.1.61 Compound 27f

(*S*)-3-(4-(2-(2-(5-Chlorothiophen-2-yl)-5-methyloxazol-4-yl)ethoxy)phenyl)-2-ethoxypropanoic acid.



27f

Purity by HPLC : 98.56 %

IR (KBr) : 692, 1341, 1512, 1735 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, J = 6.95 Hz, 3H), 2.33(s, 3H), 2.90-3.10(m, 4H), 3.40-3.63(m, 2H), 4.02-4.05(m, 1H), 4.17(t, J = 6.90 Hz, 2H), 6.80(d, J = 8.61 Hz, 2H), 6.89(d, J = 3.78 Hz, 1H), 7.13(d, J = 8.52 Hz, 2H), 7.33(d, J = 3.95 Hz, 1H).

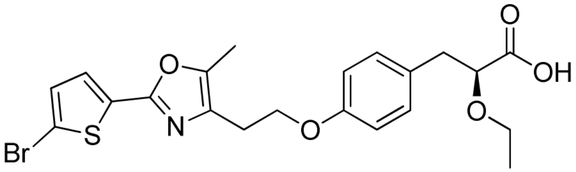
ESI/MS (m/z) : 436 (M+H)$^+$

% Yield : 98 %

mp : 111-114 °C

3.4.1.62 Compound 27g

(*S*)-3-(4-(2-(2-(5-Bromothiophen-2-yl)-5-methyloxazol-4-yl)ethoxy)phenyl)-2-ethoxypropanoic acid.



27g

Purity by HPLC : 96.17 %

IR (KBr) : 975, 1512, 1742, 2927 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.94 Hz, 3H), 2.33(s, 3H), 2.90-3.10(m, 4H), 3.42-3.59(m, 2H), 4.01-4.11(m, 1H), 4.17(t, *J* = 6.49 Hz, 2H), 7.03(d, *J* = 3.93 Hz, 1H), 6.80(d, *J* = 8.52 Hz, 2H), 7.13(d, *J* = 8.52 Hz, 2H), 7.31(d, *J* = 3.93 Hz, 1H).

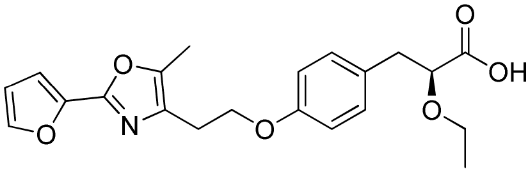
ESI/MS (m/z) : 481 (M+H)$^+$

% Yield : 71 %

mp : 123-126 °C

3.4.1.63 Compound 27h

(*S*)-2-Ethoxy-3-(4-(2-(2-(furan-2-yl)-5-methyloxazol-4-yl)ethoxy)phenyl) propanoic acid.



27h

Purity by HPLC : 98.02 %

IR (KBr) : 750, 819, 1062, 1193, 1512, 1612, 1703, 2929, 3400 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.96 Hz, 3H), 2.35(s, 3H), 2.92-2.97(m, 3H), 3.02-3.12(m, 1H), 3.41-3.44(m, 1H), 3.56-3.59(m, 1H), 4.0-4.04(m, 1H), 4.19(t, *J* = 6.64 Hz, 2H), 6.50(dd, *J* = 1.64 Hz & 3.36 Hz, 1H), 6.8(d, *J* = 8.52 Hz, 2H), 6.94(d, *J* = 3.39 Hz, 1H), 7.13(d, *J* = 8.55 Hz, 2H), 7.51(d, *J* = 1.1 Hz, 1H).

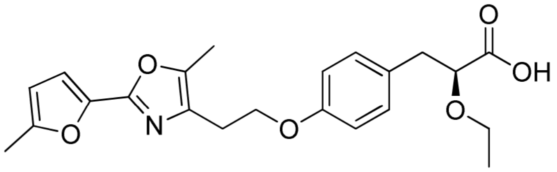
ESI/MS (m/z) : 386 (M+H)$^+$

% Yield : 68 %

mp : 83-85 °C

3.4.1.64 Compound 27i

(*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(5-methylfuran-2-yl)oxazol-4-yl)ethoxy) phenyl)propanoic acid.



27i

Purity by HPLC : 97.66 %

IR (KBr) : 1575, 1735, 2877, 2923, 3130 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.94 Hz, 3H), 2.34(s, 3H), 2.38(s, 3H), 2.92-2.96(m, 4H), 3.39-3.44(m, 2H), 4.02(t, *J* = 5.98 Hz, 1H), 4.19(t, *J* = 6.61 Hz, 2H), 6.09(d, *J* = 2.53 Hz, 1H), 6.79-6.81(m, 3H), 7.13(d, *J* = 8.54 Hz, 2H).

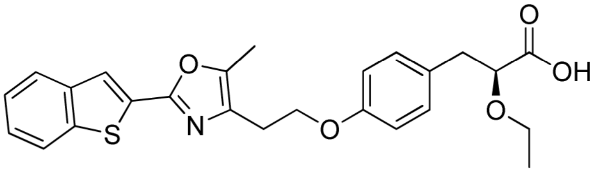
ESI/MS (m/z) : 399.9 (M+H)$^+$

% Yield : 72 %

mp : 99-100 °C

3.4.1.65 Compound 27j

(*S*)-3-(4-(2-(2-(Benzo[b]thiophen-2-yl)-5-methyloxazol-4-yl)ethoxy)phenyl)-2-ethoxypropanoic acid.



27j

Purity by HPLC : 95.55 %

IR (KBr) : 819, 1110, 1510, 1730, 2914, 3411 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 7.0 Hz, 3H), 2.38(s, 3H), 2.89-3.06(m, 4H), 3.42-3.57(m, 2H), 4.04-4.06(m, 1H), 4.22(t, *J* = 6.55 Hz, 2H), 6.82(d, *J* = 8.58 Hz, 2H), 7.13(d, *J* = 8.58 Hz, 2H), 7.34-7.40(m, 2H), 7.78-7.86(m, 3H).

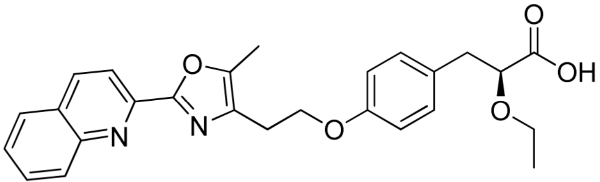
ESI/MS (m/z) : 451.9 $(M+H)^+$

% Yield : 67 %

mp : 154-157 °C

3.4.1.66 Compound 27k

(*S*)-2-Ethoxy-3-(4-(2-(5-methyl-2-(quinolin-2-yl)oxazol-4-yl)ethoxy)phenyl) propanoic acid.



27k

Purity by HPLC : 96.39 %

IR (KBr) : 756, 1118, 1217, 1512, 1598, 1732, 2927, 3583 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ1.16(t, *J* = 6.97 Hz, 3H), 2.44(s, 3H), 2.88-2.95(m, 1H), 3.04(t, *J* = 6.4,3Hz, 2H), 3.05-3.07(m, 1H), 3.45-3.57(m, 2H), 4.01-4.05(m, 1H), 4.28(t, *J* = 6.5 Hz, 2H), 6.8(d, *J* = 8.52 Hz, 2H), 7.11(d, *J* = 8.49 Hz, 2H) ,7.57(t, *J* = 7.29 Hz, 1H), 7.75(t, *J* = 7.7 Hz, 1H), 7.83(d, J = 8.13 Hz, 1H), 8.17-8.27(m, 3H).

ESI/MS (m/z) : 447 $(M+H)^+$

% Yield : 67 %

mp : 90-92 °C

3.5 *in vitro* PPAR transactivation assay

Principle : HepG2 cells are transfected with human full length PPARα, PPARβ (or δ) and PPARγ cloned in pSG5 expression vector. In presence of ligands, the PPAR will bind to PPAR response element (PPRE) cloned with the luciferase reporter vector that will lead to transactivation. The binding of ligand to the receptor would trigger the luciferin production in a dose dependent manner. Luciferin in the presence of Mg^{2+} and luciferase will be converted to oxyluciferin and will emit light which can be detected and quantified in luminometer. The luciferase values were normalized with β-galactosidase values and the values were obtained in terms of relative luciferase units (RLU)

Cell Culture : HepG2 cells (ATCC, USA) were maintained in growth medium composed of MEM (Sigma) supplemented with 10% FBS (Hyclone), 1 x MEM non essential amino acid (Sigma) and 1mM Sodium Pyruvate and 1% Penicillin /Streptomycin (Sigma).

Transient Transfection : HepG2 cells were seeded in 24 well plates at a density of 400000 cells / well in 1mL of medium per well. Cells were transfected using the transfection reagent Superfect (Qiagen). Cells were transfected with 0.08 μg of the pSG5 expression vector containing the cDNA of PPARα or PPARγ or PPARδ and cotransfected with PPRE3-TK-luc. Cells were incubated at 37 °C, 5% CO_2 for 3 hours. After this, 1.0 mL of the medium containing the respective ligands to the respective wells were added. The cells were then incubated at 37 °C, 5% CO_2 for 20-22 hours. After the incubation period, cells were first washed with PBS, lysed and the supernatant was collected. Supernatant was then assayed for luciferase and β-galactosidase activity. The Luciferase activity was determined using commercial fire-fly luciferase assay according to the suppliers's [Promega] instructions in white 96-well plate [Nunc]. β-Galactosidase activity was determined in ELISA reader at 415 nm. The ratio of luciferase versus bgalactosidase was calculated and fold induction was calculated with respect to DMSO. Fold inductions of the standard compounds were also calculated with respect to DMSO. EC_{50} values for the test compounds were calculated by nonlinear regression analysis using graph pad prism software. Each concentration point represents values in duplicates

3.6 *in vivo* experiments

All the animals were bred at animal breeding facility of 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

3.6.1 Triglyceride lowering activity in Swiss albino mice (SAM)

Male Swiss albino mice (SAM) of 6-8 week age and 20-30 g body weight with serum triglyceride levels in the range of 80-120 mg/dl have been used for screening the compounds. Animals were randomized based on pre-treatment (day 0) serum triglyceride levels and the test compounds were administered orally at an indicated dose for 6 days. On day 6 non-fasted blood samples were collected one hour after drug administration and serum triglyceride levels were measured. Reduction in serum triglycerides was calculated according to formula given below.

% Reduction= 1-[(TT/OT)/(TC/OC)]TT X 100, where,

TT= Serum TG level on test day of treated group.

OT= Serum TG level on day 0 of treatment of treated group.

TC= Serum TG level on test day of control group.

OC= Serum TG level on day 0 of treatment of control group.

3.6.2 Glucose and Triglyceride (TG) lowering activity in db/db mice

Male db/db mice of 8-12 weeks age and 30-45 g of body weight were selected for the study. The animals having serum glucose in the range 300-550 mg/dl on day 0 were randomized according to their non fasted serum glucose levels and divided into different groups having 6 animals in each group. All animals then were orally dosed once daily with vehicle (10 % PEG400 and 90% (0.5%) sodium carboxymethyl cellulose in water) and the test compounds for 6 days. All animals were fed ad libitum throughout the study. On day 6 exactly one hour after the last dose, the animals were bled and the serum was analyzed for glucose and triglycerides to calculate percent change due to drug treatment versus control group of animals using the formula mentioned in the previous experiment (This takes into account any changes that may have occurred in the vehicle-treated animals during the study).

3.7 Pharmacokinetics experiment

Pharmacokinetic behavior of the test compounds was studied via per-oral route of administration in Wistar rats of 8 to 10 weeks of age. 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 collected into heparinized micro centrifuge tubes. Plasma was separated by centrifugation at 4000 rpm for 5 min at ambient temperature and analyzed

immediately. Remaining samples were stored at -20 ℃ until analyzed. 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 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 ℃. Finally, the tubes were reconstituted with 0.1 mL diluent (acetonitrile: methanol: water 40:40:20, v/v/v). The reconstituted samples were analyzed 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 ℃. Chromatogrphic 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 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 ($t_{1/2}$) 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.

3.8 References

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