Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supplementary Information

(Experimental data, Material methods for invitro and in vivo assay)

Design, synthesis and biological evaluation of γ-lactam hydroxamate based TACE inhibitors

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Experimental

General

Melting points were recorded on open glass capillaries, using a scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR 8300 spectrophotometer (Vmax in cm^{-1}, using KBr pellets). The ^1H NMR spectra were recorded on a Brucker Avanc-300 spectrometer (300 MHz). The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, either in $CDCl_3$ or DMSO-d_6 solution. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), bs (broad singlet), and m (multiplet). Mass spectra (ESI-MS) were obtained on Shimadzu LCMS 2010-A spectrometer. Elemental analyses were carried out, using a Perkin-Elmer 2400 CHN analyzer and values within limit of ±0.4 % of the theoretical values were taken into consideration. Purity of synthesized compounds was checked by precoated TLC plates (E. Merck Kieselgel 60 F_{254}) and the spots were visualized by iodine vapors. The chromatographic purification was performed on silica gel (200-400 mesh). All the chemicals used for the synthesis were purchased from Aldrich Company Limited, Dorset (UK).

Chemistry

General procedure for the synthesis of methyl 2-substiuted quinoline-4-carboxylate (4a-r)

To the ice cold solution (8-10 ^0C) of 2-substiuted quinoline-4-carboxylic acids (**3a-r;** 3.8 mmol),[1,2] dissolved in CH_2Cl_2 (10 mL), $SOCl_2$ (5.0 mmol) was added dropwise, with constant stirring. The reaction mixture was stirred at room temperature (25 ^0C) for 30 min, refluxed for 2 h and quenched with MeOH (2 mL). Excess solvents were removed under reduced pressure and the residue obtained was dissolved in solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the

compounds **4a-r**. Using above procedure, total 18 derivatives methyl 2-substiuted quinoline-4-carboxylate (**4a**-**r**) was prepared and the physicochemical properties and spectral data of some of the representative compounds are listed below.

*Methyl 2-phenylquinoline-4-carboxylate **(4a)***

Yield = 57 % ; mp 52-54° C; IR (KBr, cm^{-1}): 1720, 1591, 1342; ESI (*m*/*z*) 263 (M+H); ^1H NMR ($CDCl_3$): δ 4.08 (s, 3H), 4.07 (s, 3H), 7.45 (m, 3H), 7.60 (m, 1H), 7.80 (t, 1H, *J* = 7.33 Hz), 8.22 (m, 3H), 8.41 (d, 1H, *J* = 8.53 Hz).

*Methyl 2-(m-tolyl)quinoline-4-carboxylate **(4b)***

Yield = 83 %; IR (KBr, cm^{-1}): 3423, 1718, 1596, 1523, 1442, 1348, 1276, 1103; ESI (*m*/*z*) 279.1 (M+H); ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H), 4.08 (s, 3H), 7.52 (m, 2H), 7.77 (m, 2H), 8.21 (d, 1H, *J* = 7.55 Hz), 8.44 (d, 1H, *J* = 8.80 Hz), 8.74 (d, 1H, *J* = 7.46 Hz), 9.08 (s, 1H).

*Methyl 2-(p-tolyl)quinoline-4-carboxylate **(4c)***

Yield = 82 %; mp 113° C; IR (KBr, cm^{-1}): 2943, 1720, 1591, 1504, 1440; ESI (*m*/*z*) 278.1 (M+H); ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 4.07 (s, 3H), 7.35 (d, 3H, *J* = 7.98 Hz), 7.63 (t, 1H, *J* = 7.11 Hz), 7.76 (t, 1H, *J* = 7.08 Hz), 8.12 (d, 1H, *J* = 8.10 Hz), 8.20 (d, 1H, *J* = 8.37 Hz), 8.39 (s, 1H), 8.72 8.72 (d, 1H, *J* = 8.37 Hz).

*Methyl 2-(4-chlorophenyl)quinoline-4-carboxylate **(4d)***

Yield = 77 %; IR (KBr, cm^{-1}): 2950, 1724, 1591, 1490, 1342; ESI (*m*/*z*) 298.2 (M+H); ^1H NMR ($CDCl_3$): δ 4.08 (s, 3H), 7.50 (d, 2H, *J* = 8.49 Hz), 7.66 (t, 2H, *J* = 7.91 Hz), 7.78 (t, 1H, *J* = 7.08 Hz), 8.18 (m, 2H), 8.37 (s, 1H), 8.75 (d, 1H, *J* = 8.49 Hz).

*Methyl 2-(4-fluorophenyl)quinoline-4-carboxylate **(4e)***

Yield = 86 %; IR (KBr, cm^{-1}): 3433, 1728, 1608, 1502, 1350; ESI (*m*/*z*) 282.1 (M+H); ^1H NMR ($CDCl_3$): δ 4.07 (s, 3H), 7.20 (d, 2H, *J* = 8.64 Hz), 7.63 (t, 1H, *J* = 7.26 Hz), 7.77 (t, 1H, *J* = 7.08 Hz), 8.21 (m, 3H), 8.36 (s, 1H), 7.74 (d, 1H, *J* = 8.55 Hz).

*Methyl 2-(4-methoxyphenyl)quinoline-4-carboxylate **(4f)***

Yield = 80 %; mp 102-103° C; IR (KBr, cm^{-1}): 3433, 1728, 1608, 1502, 1350; ESI (*m*/*z*) 370 (M+H); ^1H NMR ($CDCl_3$): δ 4.07 (s, 3H), 5.17 (s, 2H), 7.13 (d, 2H, *J* = 8.90 Hz), 7.42 (m, 5H), 7.60 (t, 1H, *J* = 7.56 Hz), 7.76 (t, 1H, *J* = 7.06 Hz), 7.18 (d, 3H, *J* = 8.49 Hz), 8.36 (s, 1H), 8.72 (d, 1H, *J* = 8.25 Hz).

General procedure for the synthesis of methyl 2-substiuted quinoline-4-yl methanol (5a-r)

To the ice cold solution (8-10 ^0C) of methyl 2-substiuted quinoline-4-carboxylate (**4a-r;** 4.2 mmol), dissolved in CH_2Cl_2 (10 mL), $NaBH_4$ (12.8 mmol) was added portion wise, with constant stirring. The reaction mixture was stirred at room temperature (25 ^0C) for 4h and quenched with water (100 mL). The

aqueous layer was extracted with $CHCl_3$ (3 x 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get compounds **5a-r**.Using above procedure, total 18 derivatives methyl 2-substiuted quinoline-4-yl methanol (**5a-r**) were prepared and the physicochemical properties and spectral data of some of the representative compounds are listed below.

(2-Phenylquinolin-4-yl)methanol ***(5a)***

Yield = 78 %; mp 94-96 °C; IR (KBr,cm^{-1}): 3398, 1602, 1444, 1352, 1093, 1006; ESI (*m/z*) 236. (M+H); ^{1}H NMR ($CDCl_3$): δ 5.27 (d, 2H, *J* = 4.92 Hz), 7.44-7.57 (m, 4H), 7.73 (t, 1H, *J* = 7.14 Hz), 7.94 (d, 1H, *J* = 8.37 Hz), 8.01 (s,1H), 8.16-8.22 (m, 3H).

(2-(m-Tolyl)quinolin-4-yl)methanol ***(5b)***

Yield = 66 %; mp 98-99 °C; IR (KBr,cm^{-1}): 3389, 1607, 1441, 1359, 1096, 1016; ESI (*m/z*) 236. (M+H); ^{1}H NMR ($CDCl_3$): δ 2.6 (s, 3H), 5.25 (s, 2H), 7.18 (s, 2H), 7.55 (s, 1H), 7.70 (m, 1H), 7.82 (m, 3H), 8.26 (s, 1H), 8.98 (s, 1H).

(2-(p-Tolyl)quinolin-4-yl)methanol ***(5c)***

Yield = 75 %; IR (KBr, cm^{-1}): 3348, 3018, 1728, 1602, 1552, 1506, 1446; ESI (*m/z*) 250.1 (M+H); ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 5.16 (s, 2H), 7.27 (d, 2H, *J* = 7.92 Hz), 7.55 (t, 1H, *J* = 7.35 Hz), 7.75 (t, 1H, *J* = 7.2 Hz), 7.86 (d, 2H, *J* = 9.48 Hz), 7.90 (d, 2H, *J* = 8.04 Hz), 8.17 (d, 1H, *J* = 8.43 Hz).

(2-(4-Chlorophenyl)quinolin-4-yl)methanol ***(5d)***

Yield = 52 %; IR (KBr, cm^{-1}): 3246, 3037, 2835, 2345, 1718, 1600, 1492, 1425, 1348; ESI (*m/z*) 270.2 (M+H); ^{1}H NMR ($CDCl_3$): δ 5.26 (s, 2H), 7.26 (m, 2H), 7.55 (m, 1H), 7.76 (m, 1H), 7.90 (m, 2H), 8.10 (d, 2H, *J* = 8.52 Hz), 8.21 (d, 1H, *J* = 6.15 Hz).

(2-(4-Fluorophenyl)quinolin-4-yl)methanol ***(5e)***

Yield = 60 %; IR (KBr, cm^{-1}): 3250, 3032, 2829, 2355, 1728, 1602, 1490, 1420, 1341; ESI (*m/z*) 254.2 (M+H); ^{1}H NMR ($CDCl_3$): δ 5.21 (s, 2H), 7.23 (m, 2H), 7.57 (m, 1H), 7.78 (m, 1H), 7.95 (m, 2H), 8.14 (d, 2H, *J* = 8.52 Hz), 8.25 (d, 1H, *J* = 6.15 Hz).

(2-(4-Methoxyphenyl)quinolin-4-yl)methanol ***(5f)***

Yield = 92.6 %; mp 102-103°C; IR (KBr, cm^{-1}): 3035, 3035, 2999, 1598, 1577, 1548, 1506, 1251, 1172; ESI (*m/z*) 266 (M+H); ^{1}H NMR ($CDCl_3$): δ 3.43 (s, 3H), 5.24 (s, 2H), 6.99 (d, 1H, *J* = 8.7 Hz), 7.49 (q, 1H, *J* = 7.2 Hz), 7.69 (t, 1H, *J* = 7.1 Hz), 7.86 (d, 2H, *J* = 8.1 Hz), 8.07 (d, 2H, *J* = 8.73 Hz), 8.15 (d, 1H, *J* = 8.43 Hz).

(2-(4-(Benzyloxy)phenyl)quinolin-4-yl)methanol ***(5g)***

Yield = 90.9 %; mp 98-99 °C; IR (KBr, cm^{-1}): 3448, 3340, 1641, 1604, 1581, 1552, 1421, 1355, 1244 ; ESI (*m/z*) 342 (M+H); ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 2H), 5.2 (s, 2H), 7.49 (m, 6H), 7.70 (t, 1H, *J* = 8.0 Hz), 7.93 (t, 2H, *J* = 8.48 Hz), 8.16 (t, 3H, *J* = 6.2 Hz).

(2-(Isopropoxymethyl)quinolin-4-yl)methanol ***(5k)***

Yield = 15.22 %; IR (KBr, cm^{-1}): 3400, 3192, 1647, 1608; ESI (*m/z*) 232.2. (M+H); ^{1}H NMR (DMSO-d_6): δ 1.18 (d, 6H, *J* = 6.07 Hz), 3.67 (m, 1H), 4.74 (s, 2H), 4.98 (d, 2H, *J* = 5.43 Hz), 5.56 (t, 1H, *J* = 5.42 Hz), 7.53 (t, 1H, *J* = 7.34 Hz), 7.69 (m, 2H), 7.94 (d, 1H, *J* = 8.53 Hz), 7.98 (d, 1H, *J*= 8.35 Hz).

(2-Cyclopropylquinolin-4-yl)methanol ***(5l)***

Yield = 82.2 %; mp 80-82 °C; IR (KBr, cm^{-1}): 3446, 3087, 1670, 1610, 1433, 1244, 812; ESI (*m/z*) 200.1. (M+H); ^{1}H NMR (DMSO-d_6): δ 1.05 (m, 4H, *J* = 7.84 Hz), 2.26 (m, 1H, *J* = 5.42 Hz), 4.94, (d, 3H, *J* = 2.87 Hz), 5.5 (s, 1H), 7.45 (m, 2H, *J* = 7.21 Hz), 7.65 (t, 1H, *J* = 7.029 Hz), 7.84 (d, 1H, *J* = 8.33 Hz). 7.95 (d, 1H, *J* = 8.22 Hz).

(2-(Methoxymethyl)quinolin-4-yl)methanol ***(5o)***

Yield = 85 %; IR (KBr, cm^{-1}): 1722, 1619, 1494, 1477, 1371, 1249.8; ESI (*m/z*) 203.9 (M+H); ^{1}H NMR (DMSO-d_6) : δ 1.22 (t, 3H, *J* = 7.14 Hz), 1.32 (t, 6H, *J* = 7.05 Hz), 4.17 (q, 4H, *J* = 7.05 Hz), 4.20 (q, 2H, *J* = 7.14 Hz), 7.41 (m, 5H), 7.61 (d, 1H, *J* = 24.18 Hz).

(2-(2-Methoxyethyl)quinolin-4-yl)methanol ***(5p)***

Yield = 36.7 %; IR (KBr, cm^{-1}): 3421, 3018, 1606, 1215, 771; ESI (*m/z*) 218.2 (M+H); ^{1}H NMR (DMSO-d_6): δ 3.23 (t, 2H, *J* = 6.66 Hz), 3.35 (s, 3H), 3.85 (t, 2H, *J* = 6.63 Hz), 5.25 (s, 2H), 7.55 (m, 3H), 7.65 (m, 1H), 7.95 (d, 1H, *J* = 8.13 Hz), 8.05 (d, 1H, *J* = 8.3 Hz).

General procedure for the synthesis of ester derivatives (7a-s)

To a stirred solution of phenol derivatives (**6a**-**b**; 2.3 mmol)[3] and alcohol derivatives (**5a-r**; 2.6 mmol), in dry toluene (15 mL), triphenylphosphine (TPP; 2.6 mmol) and diethylazodicarboxylate (DEAD; 2.6 mmol) was added at 0-5 ^{0}C under N_2. The reaction mixture was stirred at room temperature (25 ^{0}C) for 16 h, quenched with ice cold-water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get oily compound. The crude product was purified by column chromatography, using a mixture of ethyl acetate and hexane (1:3) as an eluant to get ester derivatives **7a**-**s**. Using above procedure, total 19 compounds (**7a**-**s**) were prepared and the physicochemical properties and spectral data of some of the representative compounds are listed below.

(R)-Methyl2-((R)-3-((tert-butoxycarbonyl) amino)-2-oxo-3-(4-((2-phenylquinolin-4-yl)methoxy) phenyl) pyrrolidin-1-yl)-4-methylpentanoate ***(7a)***

Yield = 54.5 %; IR (KBr, cm^{-1}): 3411, 2960, 2869, 1751, 1699, 1604, 1515, 1477, 1369,1282; ESI (*m/z*) 638.4 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.98 (m, 6H), 1.40 (s, 9H), 1.68 (m, 2H), 2.75 (m, 1H), 4.91 (m,

1H), 5.58 (s, 2H), 5.63 (s, 1H), 7.03 (d, 2H, *J* = 8.73 Hz), 7.4 (m, 4H), 7.53 (m, 2H), 7.73 (m, 1H), 7.99 (m, 2H), 8.16 (d, 2H, *J* = 7.05 Hz), 8.25 (d, 1H, *J* = 8.43 Hz), 8.16 (d, 1H, *J* = 7.05 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-2-oxo-3-(4-((2-(m-tolyl) quinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-4-methylpentanoate ***(7b)***

Yield = 50 %; mp 83-85 °C; IR (KBr, cm^{-1}): 3421, 2925, 1751, 1710, 1654, 1163, 1018; ESI (*m/z*) 652.4 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.96 (m, 6H), 1.41 (s, 3H), 1.41 (s, 9H), 1.72 (m, 2H), 2.47 (s, 3H), 2.84 (m, 1H), 2.89 (m, 1H), 3.38 (m, 2H), 3.53 (s, 3H), 4.91(m, 1H), 5.57 (s, 2H), 5.62 (s, 1H), 7.04 (d, 2H, J = 8.82 Hz), 7.31 (m, 2H), 7.45 (m, 2H), 7.57 (t, 1H, J = 7.91 Hz), 7.73 (t, 2H, J = 7.76 Hz), 7.57 (t, 1H), 7.90 (m, 1H), 8.0 (d, 1H, J = 5.29 Hz), 8.0 (d, 1H, J = 8.32 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-2-oxo-3-(4-((2-(p-tolyl) quinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-4-methylpentanoate ***(7c)***

Yield = 49 %; IR (KBr, cm^{-1}): 3433, 2956, 2871, 1720, 1693, 1604, 1492, 1388; ESI (*m/z*) 652.4 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.23 (m, 4H), 1.40 (s, 9H), 1.69 (m, 2H), 2.01 (s, 2H), 2.78 (s, 3H), 2.4 (s, 1H), 3.37 (m, 2H), 5.56 (m, 1H), 5.6 (s, 2H), 5.62 (s, 1H), 7.03 (d, 2H, *J* = 8.79 Hz), 7.38 (d, 2H, *J* = 7.98 Hz), 7.58 (d, 2H, *J* = 7.29 Hz), 7.72 (m, 1H), 7.74 (m, 1H), 7.9 (m, 3H), 8.22 (d, 1H, *J* = 8.25 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(4-chlorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7d)***

Yield = 67 %; IR (KBr, cm^{-1}): 3419, 2956, 1743, 1701, 1604, 1490, 1431; ESI (*m/z*) 672 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.88 (m, 6H), 1.40 (s, 9H), 1.75 (m, 2H), 2.26 (m, 1H), 7.79 (m, 1H), 2.89 (m, 1H), 3.4 (d, 2H, *J* = 7.89 Hz), 3.55 (s, 3H), 4.91 (m, 1H), 5.57 (s, 2H), 5.62 (s, 1H), 7.03 (d, 2H, *J* = 8.76 Hz), 7.48 (m, 4H), 7.58 (t, 1H, *J* = 7.14 Hz), 7.76 (t, 1H, *J* = 7.35 Hz), 8.12 (d, 2H, *J* = 8.46 Hz), 8.20 (d, 1H, *J* = 8.31 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(4-fluorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7e)***

Yield = 46 %; IR (KBr, cm^{-1}): 2956, 2869, 2927, 1741, 1701, 1604, 1488; ESI (*m/z*) 656 (MH^+); ^{1}H NMR ($CDCl_3$): δ 0.88 (d, 6H, *J* = 6.24 Hz), 1.28 (s, 2H), 1.71 (m, 2H), 2.83 (m, 2H), 3.40 (d, 2H, *J* = 8.49 Hz), 3.55 (s, 3H), 4.91 (s, 1H), 5.6 (s, 3H), 7.03 (d, 2H, *J* = 8.7 Hz), 7.20 (t, 1H, *J* = 7.47 Hz), 7.76 (t, 1H, *J* = 7.20 Hz), 7.96 (d, 2H, *J* = 9.75 Hz), 8.16 (m, 2H), 8.22 (s, 1H).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(4-methoxyphenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7f)***

Yield = 74.1 %; IR (KBr, cm^{-1}): 3413, 3018, 1751, 1697, 1604, 1583, 1552; ESI (*m/z*) 668.7 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.94 (m, 6H), 1.15 (s, 3H), 1.42 (s, 9H), 1.75 (m, 2H), 3.39 (m, 1H), 3.48 (s, 2H), 3.79 (t, 1H, *J* = 4.02 Hz), 3.88 (s, 3H), 4.95 (s, 1H), 5.56 (s, 2H), 5.65 (s, 2H), 7.47 (d, 2H, *J* = 8.3 Hz), 7.55 (t, 1H, *J* = 7.29 Hz), 7.75 (t, 1H, *J* = 7.23 Hz), 7.97 (t, 2H, *J* = 6.18 Hz), 8.13 (d, 2H, *J* = 8.9 Hz), 8.19 (d,

1H, *J* = 8.28 Hz).

(R)-Methyl 2-((R)-3-(4-((2-(4-(benzyloxy) phenyl) quinolin-4-yl) methoxy) phenyl)-3-((tert-butoxycarbonyl) amino)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7g)***

Yield = 63.6 %; IR (KBr, cm^{-1}): 2954, 1741, 1699, 1602, 1581, 1550, 1488; ESI (*m/z*) 744 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.97 (m, 6H), 1.25 (s, 9H), 1.75 (m, 2H), 2.79 (m, 2H), 3.39 (d, 2H, *J* = 7.72 Hz), 3.54 (s, 3H), 4.91 (s, 1H), 5.15 (s, 2H), 5.55 (s, 2H), 5.62 (s, 1H), 7.03 (d, 2H, *J* = 8.71 Hz), 7.11 (d, 1H, *J* = 8.65 Hz), 7.32 (d, 1H, *J* = 6.93 Hz), 7.41 (d, 2H, *J* = 6.96 Hz), 7.47 (d, 3H, *J* = 8.45 Hz), 7.55 (t, 1H, *J* = 7.36 Hz), 7.40 (t, 1H, *J* = 7.21 Hz), 7.96 (t, 2H, *J* = 8.33 Hz), 8.18 (q, 3H, *J* = 8.37 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-isopropoxyquinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7k)***

Yield = 65.25 %; IR (KBr, cm^{-1}): 3411.8, 1739.7, 1693; ESI (*m/z*) 534.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.97 (d, 6H, *J* = 6.34Hz), 1.23 (d, 6H *J* = 5.93 Hz), 1.76 (m, 2H), 2.10 (m, 1H), 2. 43 (m, 1H), 3.19 (m, 2H), 3.70 (s, 3H), 3.73 (m, 1H), 4.80 (s, 2H), 4.96 (t, 1H, *J* = 7.81Hz), 5.52 (s, 2H), 7.01 (d, 2H, *J* = 8.72 Hz), 7.46 (d, 2H, *J* = 8.64 Hz), 7.54 (t, 1H, *J* = 7.30 Hz), 7.70 (t, 1H, *J* = 7.34 Hz), 7.97 (s, 1H), 7.96 (d, 1H *J* = 7.91 Hz), 8.08 (d, 1H, *J* = 8.30 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(4-cyclopropylphenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7l)***

Yield = 50 %; ESI (*m/z*) 602.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.95 (m, 6H), 1.06 (m, 2H), 1.58, (m, 3H), 1.71 (s, 9H), 2.20 (s, 2H), 3.43 (m, 1H), 4.91 (s, 2H), 5.44 (s, 2H), 7.69 (d, *J* = 8.85 Hz), 7.44 (s, 1H), 7.64 (d, 2H, *J* = 5.52 Hz), 7.8 (m, 1H), 7.85 (d, 1H, *J* = 8.28 Hz), 8.0 (m, 1H).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(methoxymethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7o)***

Yield = 33 %; IR (KBr, cm^{-1}): 3417, 3325, 2956, 2929, 2871, 1174, 1701, 1606; ESI (*m/z*) 605.9 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.25 (m, 2H), 1.40 (s, 9H), 1.62 (m, 2H), 1.72 (m, 2H), 2.78 (m, 2H), 3.35 (m, 2H), 3.41 (s, 3H), 4.73 (s, 2H), 4.91 (m, 1H), 5.41 (s, 2H), 5.62 (s, 1H), 7.05 (d, 2H, *J* = 8.73 Hz), 7.44 (d, 2H, *J* = 8.73 Hz), 7.54 (t, 1H, *J* = 7.17 Hz), 7.76 (m, 2H), 7.98 (d, 1H, *J* = 8.25 Hz), 8.11 (d, 1H, *J* = 8.49 Hz).

(R)-Methyl 2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(methoxyethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(7p)***

Yield = 68.3 %; IR (KBr, cm^{-1}): 3018, 1697, 1608, 1215; ESI (*m/z*) 619.9 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.41 (s, 9H), 1.65 (m, 5H), 1.75 (m, 2H), 3.25 (t, 2H, *J* = 6.66 Hz), 3.55 (s, 3H), 3.85 (t, 2H, *J* = 6.63 Hz), 4.95 (m, 1H), 5.49 (s, 2H), 7.05 (d, 2H, *J* = 8.7 Hz), 7.45 (m, 2H), 7.75 (m, 1H), 7.95 (d, 2H, *J* = 8.25 Hz), 8.05 (d, 2H, *J* = 8.37 Hz).

General procedure for the synthesis of compound 8

The (R)-methyl-2-((R)-3-((tert-butoxycarbonyl) amino)-3-(4-((2-(methoxymethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate (**7o**; 1.65 mmol) was dissolved in MeOH (20 mL) and NH_2OH solution in MeOH (20 mL) was added to the reaction mixture at 0-5 ^{0}C. Mixture was stirred for 4 h at room temperature (25 ^{0}C) and quenched with ice-cold water (50 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude hydroxamic acid derivative (**8**), which was purified by column chromatography, using a mixture of chloroform and methanol (1:2) as an eluant to obtain pure hydroxamic acid derivative (**8**).

*Tert-butyl((R)-1-((R)-1-(hydroxyamino)-4-methyl-1-oxopentan-2-yl)-3-(4-((2-(methoxymethyl)quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-3-yl)carbamate **(8)***

Yield = 68 %; mp 118-120 °C; IR (KBr, cm^{-1}): 3419, 2958, 1695, 1606, 1512, 1244; ESI (*m/z*) 607.9 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.95 (m, 1H), 1.33 (s, 9H), 1.73 (m, 2H), 1.76 (m, 2H), 3.33 (s, 3H), 1.60 (m, 2H), 4.51 (m, 1H), 4.65 (s, 2H), 5.63 (s, 2H), 6.76 (s, 1H), 7.05 (d, 2H, *J* = 8.67 Hz), 7.42 (d, 2H, *J* = 7.86 Hz), 7.62 (m, 1H), 7.70 (s, 1H), 7.77 (m, 1H), 8.02 (d, 1H, *J* = 8.28 Hz), 8.12 (d, 2H, *J* = 8.26 Hz), 8.30 (s, 1H).

General procedure for the synthesis of compounds 9a-s

Boc protected ester derivatives (**7a-s**; 1.98 mmol) were dissolved in CH_2Cl_2 (25 mL), to this, TFA (3.9 mmol) was added at 0-5 ^{0}C under N_2. The reaction mixture was stirred at room temperature for 2h. Organic volatiles were evaporated under reduced pressure to get the deprotected ester derivatives (**9a-s**). Using above procedure, total 19 compounds (**9a**-**s**) were prepared and the physicochemical properties and spectral data of some of the representative compounds are listed below.

*(R)-Methyl 2-((R)-3-amino-2-oxo-3-(4-((2-phenylquinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-4-methylpentanoate **(9a)***

Yield = 66 %; mp 88-90°C; IR (KBr, cm^{-1}): 3369, 3018, 1739, 1691, 1510, 1215; ESI (*m/z*) 538 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.98 (m, 6H), 1.25 (m, 2H), 1.78 (m, 2H), 2.045 (m, 1H), 2.45 (m, 1H), 3.25 (m, 2H), 3.68 (s, 3H), 4.99 (t, 1H, *J* = 7.43 Hz), 5.58 (s, 2H), 7.05 (d, 2H, *J* = 8.79 Hz), 7.44-7.60 (m, 7H), 7.63 (t, 1H, *J* = 7.53 Hz), 7.98 (d, 1H, *J* = 8.1 Hz), 8.04 (s, 1H), 8.16 (d, 2H, *J* = 7.14 Hz), 8.23 (d, 1H, *J* = 8.04 Hz).

*(R)-2-((R)-3-Amino-2-oxo-3-(4-((2-(m-tolyl)quinolin-4-yl)methoxy)phenyl)pyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide **(9b)***

Yield = 67 %; mp 68-70 °C; IR (KBr, cm^{-1}): 3367, 2952, 2869, 1741, 1691, 1602, 1510; ESI (*m/z*) 552.3 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.97 (m, 6H), 1.50 (m, 2H), 1.63 (1H, m), 1.78 (m, 4H), 2.13 (m, 1H), 2.3 (m, 2H), 3.67 (s, 3H), 4.96 (t, 1H, *J* = 7.83 Hz), 5.57 (s, 2H), 7.03 (d, 2H, *J* = 8.46), 7.29 (m, 2H), 7.5 (m, 3H), 7.8 (m, 1H), 7.90 (m, 3H), 8.24 (d, 1H, *J* = 8.4 Hz).

(R)-Methyl 2-((R)-3-amino-2-oxo-3-(4-((2-(p-tolyl) quinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-4-methylpentanoate ***(9c)***

Yield = 65 %; IR ($CHCl_3$, cm^{-1}): 3392, 3018, 2927, 2871, 1735, 1678, 1608, 1560, 1512, 1425, 1348; ^{1}H NMR (DMSO-d_6): δ 0.93 (m, 6H), 1.54 (m, 3H), 1.51 (m, 2H), 2.17 (m, 1H), 2.32 (s, 3H), 2.42 (m, 2H), 2.71 (m, 2H), 3.36 (m, 2H), 3.62 (s, 3H), 4.90 (t, 1H, *J* = 8.25 Hz), 5.56 (s, 2H), 7.07 (d, 2H, *J* = 8.76 Hz), 7.32 (d, 2H, *J* = 7.8 Hz), 7.53 (d, 2H, *J* = 8.79 Hz), 7.60 (m, 1H), 7.78 (t, 1H, *J* = 7.23 Hz), 7.76 (d, 1H, *J* = 8.13 Hz), 8.05 (m, 3H), 8.30 (d, 1H, *J* = 8.4 Hz).

(R)-Methyl 2-((R)-3-amino-3-(4-((2-(4-chlorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(9d)***

Yield = 62 %; IR (KBr, cm^{-1}): 3066, 2956, 2869, 1741, 1689, 1602, 1492, 1425; ESI (*m/z*) 555.2 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 6H, *J* = 6.39 Hz), 1.78 (d, 2H, *J* = 7.38 Hz), 2.14 (m, 1H), 2.46 (m, 1H), 3.34 (m, 2H), 3.69 (s, 3H), 4.99 (t, 1H, *J* = 8.4 Hz), 5.75 (s, 2H), 7.03 (d, 2H, *J* = 8.73 Hz), 7.5 (d, 2H, *J* = 7.98 Hz), 7.58 (t, 1H, *J* = 7.20 Hz), 7.76 (t, 1H, *J* = 7.23 Hz), 7.90 (d, 1H, *J* = 8.49 Hz), 8.01 (s, 1H), 8.12 (d, 2H, *J* = 8.49 Hz), 8.21 (d, 1H, *J* = 8.19 Hz).

(R)-Methyl 2-((R)-3-amino-3-(4-((2-(4-fluorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(9e)***

Yield = 68 %; IR (KBr, cm^{-1}): 3369, 3018, 2958, 2873, 1739, 1693, 1604, 1556; ESI (*m/z*) 656 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 6H, *J* = 6.6 Hz), 1.78 (m, 2H), 2.12 (m, 2H), 2.45 (m, 1H), 3.35 (m, 2H), 3.69 (s, 3H), 4.99 (t, 1H, *J* = 7.98 Hz), 5.57 (s, 2H), 7.05 (d, 2H, *J* = 8.93 Hz), 7.20 (t, 1H, *J* = 8.64 Hz), 7.55 (d, 2H, *J* = 8.73 Hz), 7.57 (t, 1H, *J* = 7.47 Hz), 7.56 (t, 1H, *J* = 7.17 Hz), 7.98 (m, 2H), 8.16 (m, 2H), 8.22 (s, 1H).

(R)-Methyl 2-((R)-3-amino-3-(4-((2-(4-methoxyphenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(9f)***

Yield = 60 %; mp 165-167 °C; IR (KBr, cm^{-1}): 3379, 3004, 2960, 1739, 1674, 12604, 1583, 1552, 1427; ESI (*m/z*) 567 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 6H, *J* = 6.45 Hz), 3.33 (m, 6H), 3.68 (s, 1H), 3.88 (s, 3H), 5.99 (t, 1H, *J* = 8.9 Hz), 5.52 (s, 2H), 5.52 (s, 2H), 7.04 (d, 4H, *J* = 7.92 Hz), 7.53 (d, 2H, *J* = 8.7 Hz), 7.55 (d, 1H, *J* = 7.5 Hz), 7.74 (t, 1H, *J* = 7.47 Hz), 7.95 (d, 2H, *J* = 8.25 Hz), 7.99 (s, 1H), 8.13 (d, 2H, *J* = 8.7 Hz), 8.19 (d, 1H, *J* = 8.37 Hz).

(R)-Methyl 2-((R)-3-amino-3-(4-((2-(4-(benzyloxy) phenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(9g)***

Yield = 63 %; IR (KBr, cm^{-1}): 3367, 3008, 2958, 1739, 1674, 1604, 1427, 1406; ESI (*m/z*) 644 (M+H); ^{1}H NMR ($CDCl_3$): δ 0.99 (m, 2H), 1.99 (m, 2H), 2.15 (m, 4H), 3.35 (m, 5H), 3.68 (s, 3H), 4.88 (t, 1H), 5.01 (s, 2H), 5.15 (s, 2H), 7.04 (d, 4H, *J* = 6.6 Hz), 7.1 (d, 2H, *J* = 8.27 Hz), 7.38 (m, 4H), 7.52 (m, 2H), 7.59 (d, 1H, *J* = 8.28 Hz), 7.95 (t, 1H, *J* = 8.0 Hz), 8.13 (d, 2H, *J* = 8.7 Hz), 8.19 (d, 6H, *J* = 8.3 Hz).

(2R)-Methyl2-(3-amino-3-(4-((2-(methoxymethyl)quinolin-4-yl)methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate ***(9o)***

Yield = 67 %; IR (KBr, cm^{-1}) : 3367, 3292, 3065, 2823, 1732, 1681, 1606, 1568; ESI (m/z) 506.3 ($M+H^+$); ^{1}H NMR (DMSO-d_6): δ 0.97 (d, 6H, *J* = 6.45 Hz), 1.52 (m, 1H), 2.15 (m, 1H), 2.45 (m, 1H), 2.47 (m, 1H), 3.31 (m, 2H), 3.36 (s, 3H), 3.70 (s, 3H), 4.76 (s, 2H), 4.99 (m, 1H), 5.52 (s, 2H), 7.01 (d, 2H, *J* = 8.73 Hz), 7.50 (d, 2H, *J* = 8.73 Hz), 7.60 (m, 1H), 7.76 (m, 2H), 7.99 (d, 2H, *J* = 6.64 Hz), 8.14 (d, 1H, J = 8.45 Hz).

(2R)-Methyl 2-(3-amino-3-(4-((2-(2-methoxy ethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-4-methyl pentanoate ***(9p)***

Yield = 69 %; IR (KBr, cm^{-1}): 3449, 3018, 2929, 1739, 1691, 1608, 1510, 1215; ESI (m/z) 521.2 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.81 (m, 6H), 1.15 (m, 2H), 1.65 (m, 2H), 1.74 (m, 2H), 2.12 (m, 2H), 3.15 (t, 2H, *J* = 6.51 Hz), 3.2 (s, 3H), 3.6 (m, 3H), 3.7 (t, 2H, *J* = 6.58 Hz)

General procedure for the synthesis of compound 10

The (2R)-methyl 2-(3-amino-3-(4-((2-(methoxymethyl)quinolin-4-yl)methoxy)phenyl)-2-oxopyrrolidin-1-yl)-4-methylpentanoate (**9o**; 1.92 mmol) was dissolved in MeOH (20 mL) and NaOH solution (3.8 mmol) was added to the reaction mixture at 0-5 ^{0}C. The reaction mixture was stirred at room temperature for 4 h, quenched with ice-cold water (50 mL) and acidify with acetic acid (pH ~ 5).The aqueous layer was extracted with ethyl acetate (3 x 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get acid derivatives (**10**), which was purified by column chromatography, using a mixture of chloroform and methanol (1:2) as an eluant to obtain pure compound **10**.

(R)-3-((R)-3-((Tert-butoxycarbonyl) amino)-3-(4-((2-(methoxy methyl) quinolin-4-yl)methoxy) phenyl)-2-oxopyrrolidin-1-yl)-5-methyl-2-oxohexanoic acid ***(10)***

Yield = 69 %; mp 80-82 °C; Purity: 96 % by HPLC; IR (KBr, cm^{-1}): 3413, 2927, 1649, 1438, 1253, 1130; ESI (*m/z*) 506.6 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.89 (m, 6H), 1.51 (m, 3H), 1.61 (m, 2H), 2.13 (m, 3H), 3.15 (s, 3H), 4.59 (s, 2H), 5.64 (s, 2H), 7.04 (d, 2H, *J* = 8.63 Hz), 7.41 (d, 2H, *J* = 8.50 Hz), 7.63 (m, 1H), 7.71 (s, 1H), 7.77 (m, 1H), 8.00 (d, 2H, *J* = 8.34 Hz), 8.13 (d, 2H, *J* = 8.34 Hz), 8.30 (s, 1H).

General procedure for the synthesis of compound (11a-s)

The deprotected ester derivatives (**9a-s**; 1.85 mmol) was dissolved in MeOH (20 mL) and NH_2OH solution in MeOH (20 mL) was added to the reaction mixture at 0-5 ^{0}C. Mixture was stirred for 4 h at room temperature (25 ^{0}C) and quenched with ice-cold water (50 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude hydroxamic acid derivative (**11a**-**s**), which was purified by column chromatography, using a mixture of chloroform and methanol (1:2) as an eluant to obtain pure hydroxamic acid derivative (**11a**-**s**). Using above procedure, total 19 compounds (**11a**-**s**) were prepared and the physicochemical properties and spectral data of new compounds are listed below. Characterization of known compounds (**11h**-**j**, **m**-**n** and **q**) was carried out by melting point data and ESI MS and the obtained data was found to be comparable with the literature data.[4]

*(R)-2-((R)-3-Amino-2-oxo-3-(4-((2-phenylquinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide **(11a)***

Yield = 66 %; mp 88-90 °C; Purity: 96 % by HPLC; IR (KBr, cm^{-1}): 3466, 2925, 2856, 1670, 1604, 1510, 1431, 1242; ESI (*m*/*z*) 540 (M+H); ^{1}H NMR (DMSO-d$_6$): δ 0.84 (m, 6H), 1.49 (m, 3H), 1.64 (m, 2H), 1.75 (m, 2H), 4.55 (m, 1H), 5.67 (s, 2H), 7.11 (d, 2H, *J* = 8.64 Hz), 7.35 (d, 2H, *J* = 8.52 Hz), 7.45 (m, 3H), 7.64 (t, 1H, *J* = 7.35 Hz), 7.81 (t, 1H, *J* = 7.14 Hz), 8.16 (dd, 2H, *J* = 8.07 & 8.16 Hz), 8.27 (m, 3H), 8.91 (s 1H), 10.86 (s 1H).

*(R)-2-((R)-3-Amino-2-oxo-3-(4-((2-(m-tolyl) quinolin-4-yl) methoxy) phenyl) pyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide **(11b)***

Yield = 68 %; mp 120-122 °C; Purity: 97 % by HPLC; IR (KBr, cm^{-1}): 3619, 2954, 2925, 1670, 1604; ESI (*m*/*z*) 553.3 (M+H); ^{1}H NMR (DMSO-d$_6$): δ 0.89 (6H, m), 1.50 (2H, m), 1.63 (1H, m), 2.03 (2H, m), 2.43 (3H, s), 4.52 (1H, m), 5.66 (2H, s), 7.10 (2H, d, *J* = 8.46 Hz), 7.33 (3H, t, *J* = 7.75 Hz), 7.44 (1H, t, *J* = 7.82 Hz), 7.63 (1H, t, *J* = 8.46 Hz), 7.80 (1H, t, *J* = 7.92 Hz), 8.02 (1H, d, *J* = 8.46 Hz), 8.12 (3H,m), 8.25 (1H, s), 8.90 (1H, s), 10.85 (1H, s).

*(R)-2-((R)-3-Amino-2-oxo-3-(4-((2-(p-tolyl)quinolin-4-yl)methoxy)phenyl)pyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide **(11c)***

Yield = 64 %; mp 131-132 °C; Purity: 96 % by HPLC; IR (KBr, cm^1): 3423, 3267, 2956, 2923, 2869, 1654,1550, 1510, 1452, 1442; ESI (*m*/*z*) 553.3 (M+H); ^{1}H NMR (DMSO-d$_6$): δ 0.94 (m, 6H), 1.54 (m, 2H), 2.05 (m, 1H), 2.24 (m, 2H), 2.26 (m, 2H), 4.55 (t, 1H, *J* = 7.8 Hz), 5.66 (s, 2H), 7.15 (t, 1H, *J* = 7.5 Hz), 7.63 (t, 1H, *J* = 7 .59 Hz), 8.05 (m, 4H), 8.24 (s 1H), 8.90 (s, 1H).

*(R)-2-((R)-3-Amino-3-(4-((2-(4-chlorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide **(11d)***

Yield = 67 %; mp 102-104 °C; Purity: 96 % by HPLC; IR (KBr, cm^{-1}): 3197, 2923, 2868, 1666, 1602, 1510, 1423, 1242, 19091; ESI (*m/z*) 557.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.95 (d, 6H, *J* = 6.03 Hz), 1.17 (m 2H), 1.5 (m, 1H), 2.12 (m, 2H), 3.37 (s, 2H), 4.52 (m, 1H), 5.67 (s, 2H), 7.1 (d, 1H, *J* = 8.67 Hz), 7.35 (d, 2H, *J* = 8.64 Hz), 7.65 (m, 3H), 7.81 (t, 1H, *J* = 7.29, 15.15 Hz), 8.12 (d, 1H, *J* = 8.34 Hz), 8.20 (d, 1H, *J* = 8.28 Hz), 8.30 (m, 3H), 8.90 (s, 1H), 10.58 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(4-fluorophenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11e)***

Yield = 66 %; mp 100-102 °C; Purity: 98 % by HPLC; IR (KBr, cm^{-1}): 3230, 2869,1664, 1604, 1554, 1508, 1423, 1234; ESI (*m/z*) 573.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.95 (d, 6H, *J* = 6.00 Hz), 1.55 (m, 2H), 1.62 (m, 1H), 2.05 (m, 2H), 4.52 (m, 1H), 5.65 (s, 2H), 7.11 (d, 1H, *J* = 8.73 Hz), 7.37 (m, 4H), 7.64 (t, 1H, *J* = 7.44 Hz), 7.81 (t, 1H, *J* = 7.26 Hz), 8.10 (d, 1H, *J*= 8.43 Hz), 8.17 (d, 1H, *J*= 8.10 Hz), 8.32 (s, 4H), 8.91 (s, 1H), 10.86 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(4-methoxyphenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11f)***

Yield = 60 %; mp 165-167 °C; Purity: 99 % by HPLC; IR (KBr, cm^{1}): 3411, 3246, 2927, 1670, 1604, 1581, 1550, 1458, 1427, 1288; ESI (*m/z*) 568.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.90 (m, 6H), 1.6 (m, 4H), 2.13 (m, 3H), 2.6 (s, 1H), 3.84 (s, 3H), 4.52 (t, 1H, *J* = 6.21 Hz), 5.65 (s, 2H), 7.12 (t, 3 H, *J* = 4.83 Hz), 7.37 (d, 2H, *J* = 8.65 Hz), 7.61 (t, 1H, *J* = 7.56 Hz), 7.76 (t, 1H, *J* = 7.23 Hz), 8.13 (d, 1H, *J* = 11.2 Hz), 8.27 (d, 1H, *J* = 7.47 Hz), 8.92 (d, 3H, *J* = 7.12 Hz), 10.13 (s, 1H), 10.81 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(4-(benzyloxy) phenyl)quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11g)***

Yield = 67 %; mp 106-108 °C; Purity: 97 % by HPLC; IR (KBr, cm^{-1}): 3207, 2954, 1664, 1602, 1581, 1508, 1427, 1384, 1350, 1282, 1174; ESI (*m/z*) 645 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.90 (m, 6H), 1.32 (m, 2H), 1.64 (m, 1H), 2.08 (m, 6H), 3.84 (s, 3H), 4.52 (m, 1H), 5.20 (s, 2H), 5.64 (s, 2H), 7.09 (d, 2H, *J* = 8.32), 7.18 (d, 2 H, *J* = 4.83 Hz), 7.36 (m, 3H), 7.41(t, 2H, *J* = 6.92 Hz), 7.49 (d, 2H, *J* = 7.12 Hz), 7.59 (t, 1H, *J* = 7.32 Hz), 7.77 (t, 1H, *J* =7.0 Hz), 8.06 (d, 1H, *J* = 8.3 Hz), 8.14 (d, 1H, *J* = 8.21 Hz), 8.22 (d, 3H, *J* = 8.12 Hz), 8.89 (s, 1H), 10.84 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-isopropoxyquinolin-4-yl)methoxy)phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11k)***

Yield = 65 %; mp 42-44 °C; Purity: 97 % by HPLC; IR (KBr, cm^{-1}): 3429, 3426, 1664, 1608, 1510; ESI (*m/z*) 535.4 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.87 (m, 6H), 1.13 (d, 6H, *J* = 6.06 Hz), 1.62 (m, 2H), 2.06 (m, 2H), 2. 13 (m, 2H), 2.18 (m, 1H), 3.56 (m, 1H), 4.56 (m, 1H), 4.69 (s, 2H), 5.65 (s, 2H), 7.05 (d, 2H, *J* = 8.58 Hz), 7.34 (d, 2H, *J* = 8.61 Hz), 7.62 (t, 1H, *J* = 6.99 Hz), 7.73 (m, 1H), 7.99 (d, 1H, *J* = 8.22 Hz), 8.12 (d, 1H, *J* = 8.16 Hz), 8.90 (s, 1H), 10.86 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(4-cyclopropylphenyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11l)***

Yield = 67 %; mp 90-91 °C; Purity: 98 % by HPLC; IR (KBr, cm^{-1}): 3219.0, 2956.7, 1670.2, 1608.5, 1244.0, 833.2, 759.9; ESI (*m/z*) 503.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H, *J* = 5.94 Hz), 1.01 (m, 4H), 1.15, (m, 1H), 1.45 (m, 2H), 2.05 (m, 2H), 2.26 (m, 2H), 4.55 (q, 1H, *J* = 6.24 Hz), 5.52 (s, 2H), 7.05 (d, 2H, *J* = 8.73 Hz), 7.33 (d, 2H, *J* = 8.73 Hz), 7.45 (m, 2H, *J* = 7.08 Hz), 7.67 (d, 1H *J* = 8.1 Hz), 7.85 (d, 1H, *J* = 8.1 Hz) 8.01 (d, 1H, *J* = 8.16 Hz), 8.91 (s, 1H), 10.86 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(methoxymethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11o)***

Yield = 63 %; mp 80-82 °C; Purity: 99 % by HPLC; IR (KBr, cm^{-1}): 3419, 2980, 2970, 1695, 1608, 1514, 1384, 1249, 1190; ESI (*m/z*) 492.5 ($M+H^+$); ^{1}H NMR (DMSO-d_6) : δ 0.85 (m, 6H), 1.04 (d, 2H, *J* = 6.06 Hz), 1.25 (m, 1H), 1.46 (m, 1H), 1.33 (m, 2H), 4.52 (q, 1H, J = 6.27 Hz), 5.61 (s, 2H), 7.05 (d, 2H, *J* = 8.72 Hz), 7.38 (d, 2H, *J* = 8.67 Hz), 7.65 (m, 1H), 7.75 (m, 1H) 8.02 (d, 2H, *J* = 8.22 Hz), 8.11 (d, 2H, *J* = 8.37 Hz), 8.89 (s,1H), 10.01 (s,1H).

(R)-2-((R)-3-Amino-3-(4-((2-(2-methoxyethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11p)***

Yield = 69 %; mp 70-72 °C; Purity: 98 % by HPLC; IR (KBr, cm^{-1}): 3234, 2927, 2869, 2958, 1606, 1583, 1510, 1429; ESI (*m/z*) 521.3 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.41 (m, 2H), 1.65 (m, 1H), 2.05 (m, 2H), 2.25 (m, 2H), 3.15 (t, 2H, *J* = 6.54 Hz), 3.25 (s, 3H), 3.35 (m, 2H), 3.75 (t, 2H, *J* = 6.57 Hz), 4.55 (m, 1H), 5.57 (s, 2H), 7.05 (d, 2H, *J* = 8.67 Hz), 7.32 (d, 2H, *J* = 8.64 Hz), 7.65 (m, 2H), 7.75 (m, 2H), 7.95 (d, 2H, *J* = 8.25 Hz), 8.05 (d, 2H, *J* = 8.22 Hz), 8.90 (s, 1H), 10.86 (s, 1H).

(R)-2-((R)-3-Amino-3-(4-((2-(2-isopropoxyethyl) quinolin-4-yl) methoxy)phenyl)-2-oxopyrrolidin-1-yl)-N-hydroxy-4-methylpentanamide ***(11r)***

Yield = 60 %; Purity: 99 % by HPLC; IR (KBr, cm^{-1}): 3230, 2920, 2879, 2968, 1601, 1583, 1515, 1424; ESI (*m/z*) 549.7 (M+H); ^{1}H NMR (DMSO-d_6): δ 0.85 (m, 6H), 1.12 (d, 6H, *J* = 6.06 Hz), 1.42 (m, 2H), 1.65 (m, 1H), 2.05 (m, 2H), 2.25 (m, 2H), 3.15 (t, 2H, *J* = 6.54 Hz), 3.25 (m, 2H), 3.35 (m, 2H), 3.75 (t, 2H, *J* = 6.57 Hz), 3.56 (m, 1H), 4.55 (m, 1H), 5.57 (s, 2H), 7.05 (d, 2H, *J* = 8.67 Hz), 7.32 (d, 2H, *J* = 8.64 Hz), 7.65 (m, 2H), 7.75 (m, 2H), 7.95 (d, 2H, *J* = 8.25 Hz), 8.05 (d, 2H, *J* = 8.22 Hz), 8.91 (s, 1H), 10.85 (s, 1H).

(R)-3-((R)-3-Amino-3-(4-((2-(methoxymethyl) quinolin-4-yl) methoxy) phenyl)-2-oxopyrrolidin-1-yl)-2-oxobutanoic acid ***(11s)***

Yield = 63 %; mp 81-82 °C; Purity: 98 % by HPLC; IR (KBr, cm^{-1}): 3419, 2980, 2970, 1695, 1608, 1514, 1384, 1249, 1190; ESI (m/z) 492.5 (M+H); ^{1}H NMR (DMSO-d_6): δ 1.16 (t, 1H, *J* = 7.11 Hz), 1.28 (m, 3H), 1.21 (m, 1H), 1.45 (m, 1H), 1.35 (m, 2H), 4.55 (q, 1H, *J* = 6.27 Hz), 5.61 (s, 2H), 7.05 (d, 2H, *J* =

8.7 Hz), 7.32 (d, 2H, *J* = 8.67 Hz), 7.6 (m, 1H), 7.7 (m, 1H) 8.0 (d, 2H, *J* = 8.22 Hz), 8.1 (d, 2H, *J* = 8.37 Hz), 8.89 (s, 1H), 10.02 (s, 1H).

Inhibition of TNF-α in human whole blood assay (*Ex vivo*)

Fresh human blood (500 µl) drawn aseptically in the presence of heparin from healthy adult volunteers was incubated with the test compounds at the various concentrations for 1 h at 37 ^{0}C. At the end of the incubation period, lipopolysaccharide (LPS, Sigma; 100 ng/ml) was added to the blood and the samples were further incubated for 5h at 37 ^{0}C with constant rotation. The reactions were terminated by placing the samples over ice for 10 min. Finally, the plasma was separated by centrifugation at 3000 rpm for 10 min at 4 ^{0}C and stored at -70^{0}C until further analysis. Concentrations of TNF-α in the plasma were determined by an ELISA kit according to the manufacturer's instruction (BD Biosciences, USA) and concentration required for 50% TNF-α inhibition (IC_{50} values) were calculated and reported.[5]

TACE and MMP enzymatic assays (*In vitro*)

TACE FRET assay

Test compounds (**11o-p** and **1**) were assessed for their ability to inhibit the cleavage of the substrate by the purified enzyme in a fluorescence-based FRET assay as per modified literature procedure.[6,7] Briefly, the human catalytic domain of TACE (1 µg/ml) was pretreated with the test compounds at various concentration for 10 min at room temperature. The reaction was initiated by the addition of pro-TNF-α peptide (50 µM final concentration) to the TACE protein and the increase in fluorescence was monitored at excitation of 320 nm and emission of 420 nm, over a period of 10 min and the IC_{50} values (nM) were determined (n=3) and reported.

MMP FRET assays

The MMP-1,-2,-3,-7,-8,-9,-13 and -14 assays were carried as per modified literature procedure.[8] Briefly, the assays were carried out at room temperature in a buffer containing Hepes (50 mM; pH 7.4), NaCl (100 mM), $CaCl_2$ (5 mM) and Brij-35 (0.005%). The substrate used was Mca-PQGL-(3-[2,4-dinitrophenyl]-l-2,3-diaminopropionyl)-AR-OH (synthesized in-house) at a final concentration of 10 µM. The enzymatic reactions were initiated by adding the substrate to a final concentration of 20 µM. The initial rate of increase in fluorescence by the cleavage reaction was determined immediately after substrate addition and the IC_{50} values (nM) were determined (n=3) and reported.

ADAM-10 assay

ADAM-10 activity was assayed by a FRET assay in a buffer containing Tris-HCl (50 mM, pH 9 at 37 °C), $ZnCl_2$ (2.5 mM) Brij-35 (0.005%).[9] The final concentration of ADAM-10 enzyme (R&D Systems) was 1

ng/ml. The fluorescent substrate used was Mca-PQGL-(3-[2,4-dinitrophenyl]-l-2,3-diaminopropionyl)-AR-OH (synthesized in-house) at a final concentration of 10 μM. Test compounds were dissolved in DMSO and assayed at various concentrations following a 15-min pretreatment of the enzyme with inhibitors at room temperature. The reaction was monitored by a flourimeter (GeminiXS from Molecular Devices) for 15 min at 37 °C at excitation of 320 nm and emission of 420 nm. IC_{50} values (nM) were determined (n=3) by plotting % inhibition against inhibitor concentration and equation was fit to a sigmoidal curve with a Hill slope (B to 100) using the LSW software package on Excel (Microsoft) and the IC_{50} values (nM) are reported.

LPS induced acute TNF-α production in mouse (*in vivo*)

In vivo TNF-α inhibition was assessed using LPS induced acute TNF-α production in mouse.[9] Inhibition of the TNF-α production was taken as an indicator for inhibition of TACE activity. This study was conducted on Swiss Albino Mice (SAM) of either sex (age 8-12 weeks) weighing between 20 to 25g. The animals were divided into two groups (control and standard) and each experimental group consisted of six animals. All the animals were left for 2 days under laboratory conditions for acclimatisation and maintained on a standard pellet diet and water *ad libitum* before the day of the experiment. On the last day food was withdrawn and they were given water only. A 12 hours dark: light cycle was also maintained. All the animal experiments were conducted according to the internationally valid guidelines following approval by the 'Zydus Research Center Animal Ethical Committee'.

Vehicle (normal saline)/test/standard compounds were administered orally on a body weight basis, 30-min prior to the LPS (50 mg/kg/iv) injection. Blood samples were collected from each animal 60 min after the LPS injection, via retro-orbital plexus. Blood samples were centrifuged (3000 rpm, 15 min at 40 °C) and the separated serum was immediately subjected for TNF estimation. Concentrations of TNF-α in the serum were determined by an ELISA kit according to the manufacturer's instruction (BD Biosciences, USA). Mean values of duplicate samples were calculated using Microsoft excel and % TNF-α inhibition values (ED_{50}) values of test compounds (**11o**-**p** and **1**) are reported.

Pharmacokinetic study in wistar rats

The pharmacokinetic parameters of test compounds (**11o** and **1**) were determined in male wistar rats (n=6).[10] Briefly, test compounds were administered orally / iv on a body weight basis (5 mpk) to overnight fasted rats. Serial blood samples were collected in microcentrifuge tubes containing EDTA at pre-dose, 0.15, 0.3, 0.5, 0.75, 1, 2, 4, 6, 8, 24 and 30 h post-dose after compounds administration. Approximately 0.3 ml of blood was collected at each time point and centrifuged at 4 °C. The obtained plasma was frozen, stored at -70 °C and the concentrations of compounds in plasma were determined by the LC-MS/MS (Shimadzu LC10AD,

USA), using YMC hydrosphere C_{18} (2.0 x 50 mm, 3 µm) column (YMC Inc., USA). The pharmacokinetic parameters, such as Tmax, $t_{1/2}$, Kel, AUC and %F were calculated using a non-compartmental model of WinNonlin software version 5.2.1.

Repeated dose toxicity study (28 days) of compound 11o and 1 in wistar Rats (po)

Repeated dose toxicity studies (28 days) of compounds **11o** and **1** was carried out in male wistar rats (WR). Briefly, animals were divided into three groups (n=10), a control group and two separate groups for compounds **11o** and **1** respectively. To each of the test groups, daily oral dose of 100 mpk compounds (**11o / 1**) was administered, twice a day (bid), under fasted conditions for 28 days. After completion of treatment period (28 days), animals were sacrificed and subjected for complete necropsy examination and also changes in toxicological parameters, such as gross pathology, clinical signs, body weight, organ weights, and serum chemistry/ hematological changes were recorded.

Measurement of markers

Rats were anesthetized 24h post treatment and blood samples were collected. The whole blood was centrifuged at 3000 rpm using a centrifuge at 37 ^{o}C for 15 min and serum ALT, AST and ALP were assayed using diagnostic kit (Boehringer Mannheim).[11]

Docking

The molecules **11p** and DPC 333 were geometrically optimized by using Ligprep module of Schrodinger. The crystal structure 2FV5 was obtained from RCSB protein data bank and the protein was prepared by using protein preparation wizard of Schrodinger. The receptor grid files were generated using grid-receptor generation program. The grid box was generated at the centroid of the IK-682 ligand of the receptor. The ligands were docked using "xtra precision" Glide algorithm.[12-15]

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