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Synthesis of structural analogues of GGT1-DU40, a potent GGTase-1 inhibitor

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Abstract: A series of new substituted pyrazoles **2–12** have been synthesized. The synthesized compounds are structural analogues of GGT1-DU40 **1**, a highly potent and selective inhibitor of protein geranylgeranyltransferase I (GGTase-I) both in vitro and in vivo. The implications of GGTase-I in oncogenesis have highlighted its potential as a cancer therapeutic target. Accordingly, the development of GGTase-I inhibitors has been a subject of much interest. The synthesis of **2–12** stemmed from the acetylation or acylation of N-function of amino acids to produce suitably modified amino acids. Meanwhile, the substituted pyrazole subunit originated from the reaction of ethyl nicotinate with γ-butyrolactone followed by condensation of the resultant β-keto lactone with (3,4-dichlorophenyl) hydrazine. The operations of O-alkylation and thioetherification on the resultant intermediate eventually produced the substituted pyrazole fragment. The amidation of the latter with amino acid derivatives finally rendered **2–12** in good to excellent yields.

Keywords: geranylgeranyltransferase I; GGT1-DU40; oncogenesis; protein prenylation; pyrazole-based inhibitors.

1 Introduction

Protein prenylation by isoprenoid lipids plays an important role in biology [1, 2]. The majority of these prenylated proteins are termed "CaaX proteins", which are defined by a specific C-terminal motif that directs the lipid modification. The CaaX (C = cysteine, aa = aliphatic amino acids, and X = any amino acid) prenyltranferases, enzymes that catalyze the prenylation of substrate proteins, include protein farnesyltransferase (FTase), which adds the 15-carbon farnesyl group, and protein geranylgeranyltransferase type I (GGTase-I), which transfers the 20-carbon geranylgeranyl through a thioether linkage to a C terminus cysteine residue near the carboxyl terminus of a target substrate protein. The prenylation state of a protein, farnesylated or geranylgeranylated, is dictated by the nature of the terminal X-specificity residue, i.e. the substrate protein is farnesylated when "X" is methionine or serine or geranylgeranylated where the carboxyl terminal residue "X" is leucine or phenylalanine [3–5]. In addition to attachment of the isoprenoid, Ras and most other CaaX proteins undergo two subsequent prenylation-dependent processing steps, proteolytic removal of the -aaX tripeptide by the CaaX protease Rce1 and carboxymethylation of the now C-terminal prenylcysteine residue by an enzyme termed Icmt [6, 7]. This three-step modification process creates a mature form of the CaaX protein with increased hydrophobicity, facilitating its interaction with membranes. In addition, the modified C terminus can also be viewed as a motif for specific protein-protein recognition events [7, 8].

Prenylated CaaX proteins, most notably Ras family members, play critical role in a wide variety of cellular processes and have been implicated in pathologies such as cancer, inflammation, and viral infectivity. Accordingly, efforts have been devoted to develop inhibitors of CaaX processing as a rational approach to therapeutic development [8, 9].

Early studies were mostly focused on the development of FTase inhibitors (FTIs), given FTase importance in Ras maturation and oncogenic activity. FTIs showed efficacy in preclinical studies of malignancies, including those without Ras mutations [10]. However, unfortunately, clinical trials of FTIs in humans have not been particularly successful [11]. In FTI-treated cells, K-RAS and N-RAS are alternately prenylated by GGTase-I and continue to support tumorigenesis [12]. Meanwhile, GGTase-I inhibitors (GGTIs) have shown promise as therapeutic targets [4, 13–17]. In addition, the rationale for inhibiting GGTase-I is also supported by genetic studies in mice with K-RAS-induced lung cancer [18].

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In ongoing efforts toward the synthesis of molecules of medicinal value [19–22], we have synthesized a series of substituted pyrazoles **2–12**, which are structural analogues of GGTI-DU40 (**1**), a highly potent and selective inhibitor of GGTase-I both in vitro and in vivo (Fig. 1) [23]. Herein, we disclose the synthesis of compounds **2–12**.

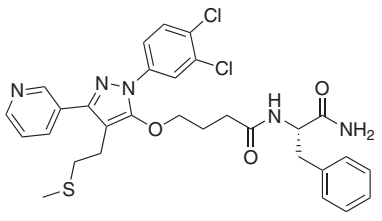
2 Results and discussion

The synthesis of compounds **2–12** required the preparation of suitably modified amino acids derivatives. To this end, L-phenylglycine was transformed to the known *N*-acetyl-L-phenylalanine **13** [24] and *N*-(methylsulfonyl)-L-phenylalanine **14** [25]. Likewise, amino acids **15–17** were first transformed to their corresponding methyl esters **18–20** by the action of thionyl chloride in methanol. The N-acetylation or N-acylation of **18–20** with acetyl chloride or methanesulfonyl chloride followed by basic hydrolysis with LiOH furnished the desired intermediates **21–26** (Scheme 1). Although this route provided straightforward access to the intermediates **21** and **22** in a moderate overall yield of 64 and 61 %, respectively, the transformation of **19** and **20** to their corresponding **23–26** was low yielding (36–41 %). In the latter case, the basic hydrolysis step resulted to fewer side products. In addition, the higher water affinity of **23–26** made their extraction difficult from the aqueous workup.

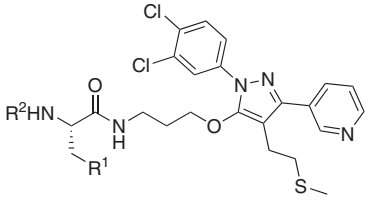
Consequently, a direct route for the preparation of intermediates **21–26** was envisioned (Scheme 2). The acetylation of **15** with acetic anhydride in MeOH under reflux followed by evaporation of the solvent and aging the obtained residues overnight in a refrigerator rendered **21** in high yield (86 %). Under identical conditions, the acetylation of **16** and **17** produced the corresponding **23** (73 %) and **25** (75 %) in good yields. Similarly, the acylation of **15** with methanesulfonyl chloride in a mixture of dichloromethane and 1 M aq. NaOH furnished **22** in good yield (80 %). By adopting a similar strategy, amino acids **16** and **17** were also transformed to the corresponding desired intermediates **24** and **26** in high yields.

Likewise, amino ester **27** was transformed to the known *N*-acetyl-(4-methoxyphenyl)alanine **28** by the operations of N-acetylation of the amine function with acetic anhydride, O-alkylation of phenolic hydroxyl group with iodomethane, and then basic hydrolysis of ester moiety with LiOH [26]. In addition, the *N*-Boc-protected analogue **29** was produced from **27** by N-acylation with di-*tert*-butyl dicarbonate followed by O-alkylation of the hydroxyl group with iodomethane and finally basic hydrolysis of the ester group [27]. Meanwhile, N-acylation of **27** with methanesulfonyl chloride in dichloromethane followed by O-alkylation of the phenolic hydroxyl moiety with iodomethane furnished intermediate **31** in a high yield (83 % for two steps). The basic hydrolysis of **31** with LiOH in a mixture of water, methanol, and THF finally produced the desired **32** in 68 % overall yield from **27** (Scheme 3).

With suitably modified amino acids on hand, we next moved to access the synthesis of key intermediate **40** (Scheme 4). To this end, ethyl nicotinate **33** was treated with γ-butyrolactone in ethanol using sodium ethoxide as a base to produce the known α-ketobutyrolactone **34** [28],

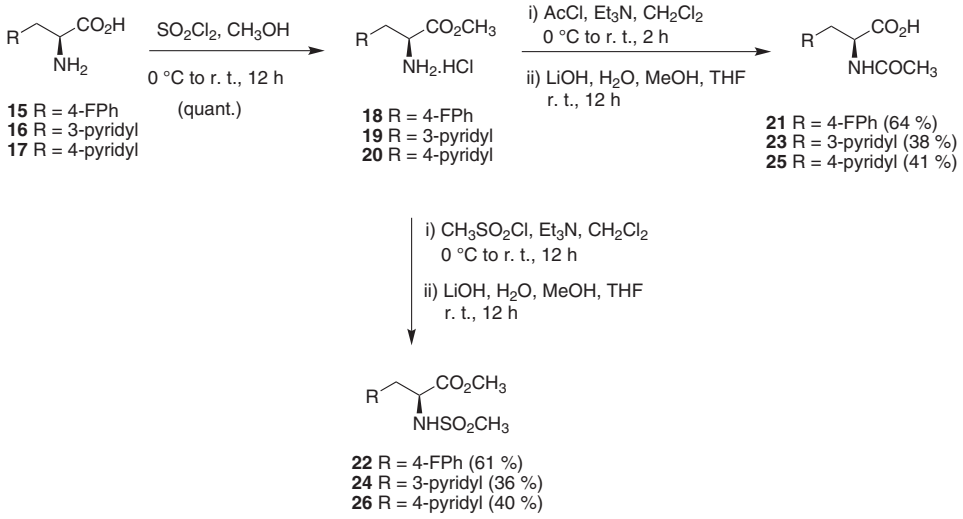


1 (GGTI-DU40)

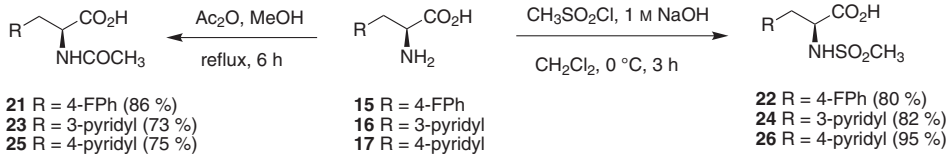


2 R^1 = Ph; R^2 = $COCH_3$
3 R^1 = Ph; R^2 = SO_2CH_3
4 R^1 = 4-FPh; R^2 = $COCH_3$
5 R^1 = 4-FPh; R^2 = SO_2CH_3
6 R^1 = 4-OMePh; R^2 = $COCH_3$
7 R^1 = 4-OMePh; R^2 = SO_2CH_3
8 R^1 = 4-OMePh; R^2 = $COO(CH_3)_3$
9 R^1 = 3-pyridyl; R^2 = $COCH_3$
10 R^1 = 3-pyridyl; R^2 = SO_2CH_3
11 R^1 = 4-pyridyl; R^2 = $COCH_3$
12 R^1 = 4-pyridy; R^2 = SO_2CH_3

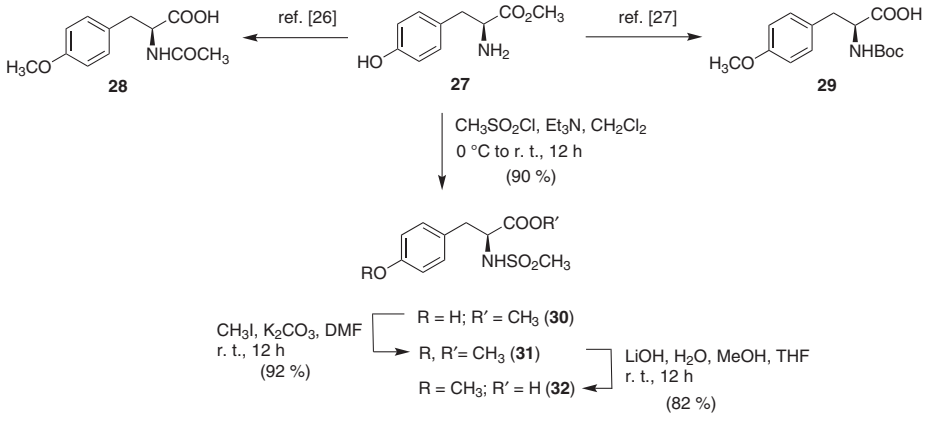
Fig. 1: Structural analogues of GGTI-DU40 (**1**).



Scheme 1: Synthesis of amino acid derivatives **21–26**.

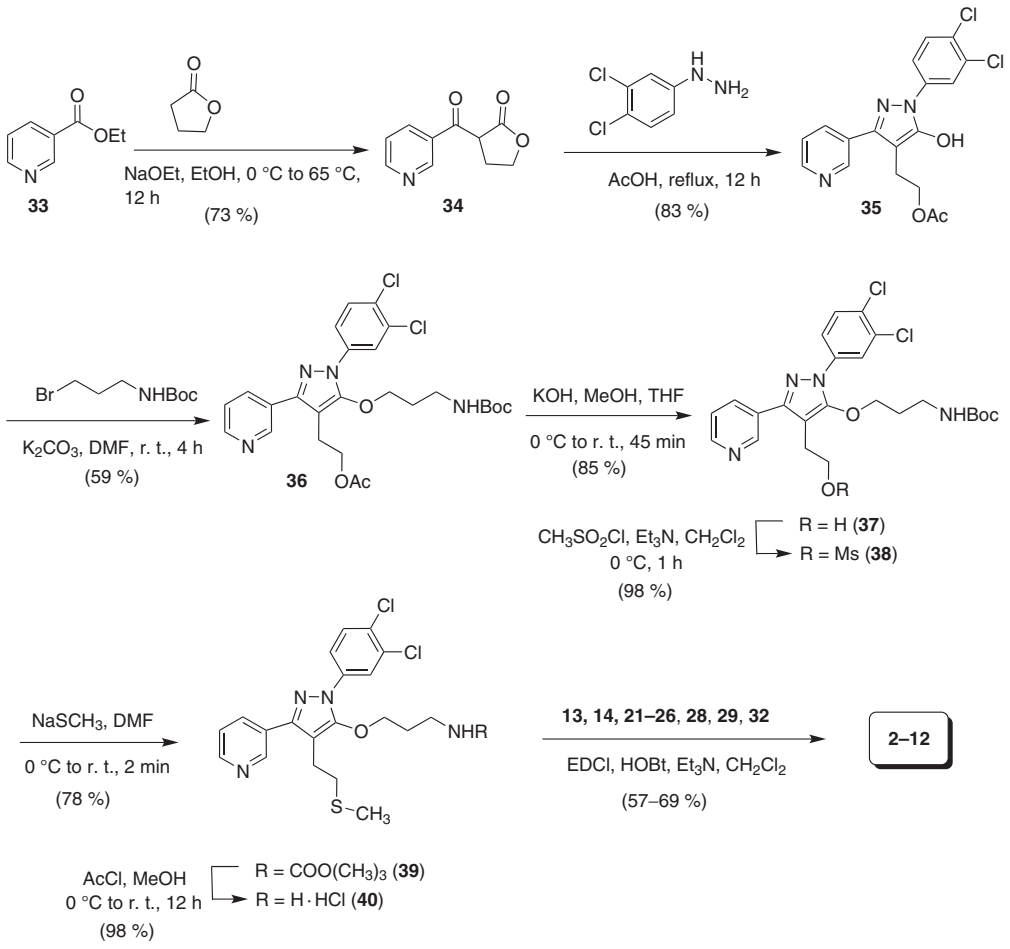


Scheme 2: Alternative synthesis of amino acid derivatives **21–26**.



Scheme 3: Synthesis of amino acid derivatives **28**, **29**, and **32**.

which in turn was heated with 3,4-dichlorophenylhydrazine hydrochloride in acetic acid to construct pyrazole **35** [29]. The O-alkylation of intermediate **35** with *tert*-butyl (3-bromopropyl)carbamate in DMF at room temperature, using K_2CO_3 as a base, gave the desired **36** in moderate yield (59 %). It is pertinent to mention that heating the reaction mixture at varied temperature ranging from 40 to 80 °C for different time periods resulted in sluggish reaction, leading to fewer side products. Base-induced removal of acetyl protection of **36** yielded alcohol **37**, which was subjected to acylation with methanesulfonyl chloride in dichloromethane to generate mesylate **38** in 83 % yield from **36**. Treatment of intermediate **38** with sodium methanethiolate in DMF furnished the thioether **39** in good yield (78 %), which was further transformed to the desired primary amine **40** by the action of acetyl chloride in MeOH



Scheme 4: Synthesis of compounds **2–12**.

(Scheme 4). Finally, to furnish the synthesis of final compounds **2–12**, the advanced intermediate **40** was coupled with intermediates **13**, **14**, **21–26**, **28**, **29**, and **32**, using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride and *N*-hydroxybenzotriazole as coupling agents to accomplish the synthesis of **2–12** in moderate to good yields (57–69 %) (Scheme 4). It is pertinent to mention that synthesis of **1** could also be realized from the O-alkylation of pyrazole **35** with ethyl 4-bromobutyrate followed by steps of basic hydrolysis and coupling of the resultant carboxylic acid with appropriate amino acid derivative. However, to the best of our knowledge, procedures for the synthesis of **1** are not known in the literature [30, 31].

3 Conclusion

We synthesized a series of substituted pyrazoles **2–12**, structural analogues of GGTI-DU40, in good to excellent yields.

4 Experimental section

4.1 (*S*)-2-acetamido-3-(4-fluorophenyl) propanoic acid (21)

To a solution of compound **15** (1.00 g, 5.46 mmol) in MeOH (7 mL) was added acetic anhydride (1.40 mL, 14.75 mmol), and the mixture was refluxed for 6 h. The reaction was cooled to room temperature, and all the volatiles were removed at reduced pressure. The residue was kept in a refrigerator overnight and then warmed up to the room temperature to allow the recrystallization of the title compound as a colorless crystalline solid (yield 86 %). M.p. 139–140 °C. – IR (neat): ν = 3367, 3025, 2953, 1720, 1625, 1581, 1451, 1360, 1028 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (s, 3 H, $COCH_3$), 2.92 (dd, J = 9.1, 14.0 Hz, 1 H, CH_2CH), 3.16 (dd, J = 5.5, 14.1 Hz, 1 H, CH_2CH), 4.61 (m, 1 H, CH_2CH), 6.98 (t, J = 8.5 Hz, 2 H, 3′-H, 5′-H), 7.22 (m, 2 H, 2′-H, 6′-H), 8.09 (d, J = 6.2 Hz, 1 H, NH) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.27 ($COCH_3$), 37.63 (CH_2CH), 55.10 (CH_2CH),

115.99 (d, J = 21.8 Hz, C-3′, C-5′), 131.95 (d, J = 8.3 Hz, C-2′, C-6′), 134.45 (C-1′), 162.60 (d, J = 247 Hz, C-4′), 173.10 (C=O), 174.54 (C=O) ppm. – $C_{11}H_{12}FNO_3$ (225.22): calcd. C 58.66, H 5.37, N 6.22; found C 58.61, H 5.41, N 6.14.

4.2 (*S*)-3-(4-fluorophenyl)-2-(methylsulfonamido)propanoic acid (22)

To a cold solution of compound **15** (0.50 g, 2.73 mmol) in 1 M aq. NaOH (10 mL) at 0 °C was added CH_2Cl_2 (2 mL) followed by the dropwise addition of methanesulfonyl chloride (0.25 mL, 3.28 mmol). The reaction mixture was stirred for 3 h at 0 °C, transferred into a separatory funnel, and washed with diethyl ether (10 mL). The aqueous layer was acidified to pH 3 with 1 N aq. HCl and extracted with EtOAc (2 × 10 mL). The organic layer was dried over Na_2SO_4 and evaporated to get compound **22** as a colorless gummy solid (yield 80 %). – IR (neat): ν = 3538, 3034, 2930, 1733, 1605, 1512, 1412, 1225 cm^{-1}. – ^{1}H NMR (500 MHz, CD_3OD): δ = 2.70 (s, 3 H, SO_2CH_3), 2.91 (dd, J = 8.5, 13.7 Hz, 1 H, CH_2CH), 3.13 (dd, J = 5.2, 13.7 Hz, 1 H, CH_2CH), 4.20 (m, 1 H, CH_2CH), 7.01 (m, 2 H, 3′-H, 5′-H), 7.28 (m, 2 H, 2′-H, 6′-H) ppm. – ^{13}C NMR (125.7 MHz, CD_3OD): δ = 39.11 (SO_2CH_3), 41.28 (CH_2CH), 58.90 (CH_2CH), 116.03 (d, J = 21.8 Hz, C-3′, C-5′), 132.40 (d, J = 8.3 Hz, C-2′, C-6′), 134.27 (C-1′), 162.56 (d, J = 247 Hz, C-4′), 174.59 (C=O) ppm. – $C_{10}H_{12}FNO_4S$ (261.27): calcd. C 45.97, H 4.63, N 5.36; found C 45.92, H 4.67, N 5.30.

4.3 (*S*)-2-acetamido-3-(pyridin-3-yl) propanoic acid (23)

Following the same procedure adopted for the synthesis of **21**, acetylation of compound **16** gave compound **23** as a colorless sticky solid (yield 73 %). – IR (neat): ν = 3428, 3050, 2946, 1732, 1668, 1606, 1512, 1370, 1226, 1060 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, $COCH_3$), 2.90 (dd, J = 8.5, 14.0 Hz, 1 H, CH_2CH), 3.17 (dd, J = 5.2, 14.0 Hz, 1 H, CH_2CH), 4.54 (m, 1 H, CH_2CH), 7.29 (m, 1 H, 5′-H), 7.67 (m, 1 H, 6′-H), 8.30 (m, 1 H, 4′-H), 8.41 (d, J = 1.1 Hz, 1 H, 2′-H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.39 ($COCH_3$), 35.91 (CH_2CH), 55.34 (CH_2CH), 125.10 (C-5′), 135.67 (C-6′), 139.26 (C-1′), 148.12 (C-4′), 150.68 (C-2′), 172.92 (C=O) ppm. – $C_{10}H_{12}N_2O_3$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.62, H 5.86, N 13.38.

4.4 (*S*)-2-(methylsulfonamido)-3-(pyridin-3-yl)propanoic acid (24)

Following the same procedure adopted for the synthesis of **22**, acylation of **16** produced compound **24** as a light yellow gum (yield 82 %). – IR (neat): ν = 3475, 3427, 3062, 2955, 1750, 1582, 1435, 1322, 1150 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.69 (s, 3 H, SO_2CH_3), 2.85 (dd, J = 7.3, 13.7 Hz, 1 H, CH_2CH), 3.05 (dd, J = 5.2, 13.7 Hz, 1 H, CH_2CH), 3.46 (m, 1 H, CH_2CH), 7.34 (m, 1 H, 5′-H), 7.76 (m, 1 H, 6′-H), 8.36 (m, 1 H, 4′-H), 8.43 (d, J = 1.3 Hz, 1 H, 2′-H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 39.42 (SO_2CH_3), 39.75 (CH_2CH), 58.71 (CH_2CH), 125.04 (C-5′), 136.77 (C-6′), 139.26 (C-1′), 147.86 (C-4′), 150.89 (C-2′), 181.15 (C=O) ppm. – $C_9H_{12}N_2O_4S$ (244.27): calcd. C 44.25, H 4.95, N 11.47; found C 44.20, H 4.99, N 11.40.

4.5 (*S*)-2-acetamido-3-(pyridin-4-yl) propanoic acid (25)

Following the same procedure adopted for the synthesis of **21**, acetylation of **17** gave compound **25** as a brown gum (yield 75 %). – IR (neat): ν = 3441, 3054, 2926, 1738, 1664, 1609, 1508, 1378, 1223, 1066 cm^{-1}. – ^{1}H NMR (500 MHz, CD_3OD): δ = 1.85 (s, 3 H, $COCH_3$), 3.01 (dd, J = 8.8, 13.7 Hz, 1 H, CH_2CH), 3.26 (dd, J = 5.5, 13.7 Hz, 1 H, CH_2CH), 4.72 (m, 1 H, CH_2CH), 7.35 (d, J = 6.1 Hz, 2 H, 2′-H, 6′-H), 8.44 (d, J = 6.1 Hz, 2 H, 3′-H, 5′-H) ppm. – ^{13}C NMR (125.7 MHz, CD_3OD): δ = 22.29 ($COCH_3$), 37.92 (CH_2CH), 54.21 (CH_2CH), 126.50 (C-2′, C-6′), 149.38 (C-1′), 150.29 (C-3′, C-5′), 173.11 (C=O), 175.27 (C=O) ppm. – $C_{10}H_{12}N_2O_3$ (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.63, H 5.86, N 13.39.

4.6 (*S*)-2-(methylsulfonamido)-3-(pyridin-4-yl)propanoic acid (26)

Following the same procedure adopted for the synthesis of **22**, acylation of **17** rendered compound **26** as a light yellow gum (yield, 85 %). – IR (neat): ν = 3500, 3073, 2923, 1702, 1607, 1393, 1297, 1153 cm^{-1}. – ^{1}H NMR (500 MHz, CD_3OD): δ = 2.85 (s, 3 H, SO_2CH_3), 2.98 (dd, J = 8.2, 13.7 Hz, 1 H, CH_2CH), 3.15 (dd, J = 5.2, 13.7 Hz, 1 H, CH_2CH), 4.02 (m, 1 H, CH_2CH), 7.36 (d, J = 6.8 Hz, 2 H, 2′-H, 6′-H), 8.43 (d, J = 6.8 Hz, 2 H, 3′-H, 5′-H) ppm. – ^{13}C NMR (125.7 MHz, CD_3OD): δ = 37.35 (CH_2CH), 40.29 (SO_2CH_3), 60.32 (CH_2CH), 126.96 (C-2′, C-6′), 149.47 (C-1′), 150.49 (C-3′, C-5′), 176.85 (C=O) ppm. – $C_9H_{12}N_2O_4S$ (244.27): calcd. C 44.25, H 4.95, N 11.47; found C 44.19, H 5.00, N 11.41.

4.7 (*S*)-methyl 3-(4-hydroxyphenyl)-2-(methylsulfonamido)propanoate (30)

To a cold suspension of compound **27** (0.50 g, 2.16 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.20 mL,

8.6 mmol) followed by the dropwise addition of a solution of methanesulfonyl chloride (0.25 mL, 3.24 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred overnight at room temperature and quenched with water (10 mL) followed by the addition of dilute hydrochloric acid to adjust pH 4–5. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure to get the title compound **30** as a white solid (yield 90 %). M.p. 102–103 °C. – IR (neat): ν = 3310, 3022, 2941, 1738, 1506, 1451, 1367, 973 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.76 (s, 3 H, SO_2CH_3), 3.06 (dd, J = 7.0, 14.0 Hz, 1 H, CH_2CH), 3.18 (dd, J = 5.5, 14.0 Hz, 1 H, CH_2CH), 3.79 (s, 3 H, OCH_3), 4.41 (m, 1 H, CH_2CH), 4.93 (d, J = 9.15 Hz, 1 H, NH), 6.70 (d, J = 8.5 Hz, 2 H, 3′-H, 5′-H), 6.96 (d, J = 8.5 Hz, 2 H, 2′-H, 6′-H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 38.80 (SO_2CH_3), 41.31 (CH_2CH), 52.95 (OCH_3), 56.84 (CH_2CH), 122.37 (C-3′, C-5′), 131.14 (C-1′), 134.80 (C-2′, C-6′), 148.40 (C-4′), 171.53 (C=O) ppm. – $C_{11}H_{15}NO_5S$ (271.31): calcd. C 48.34, H 5.53, N 5.12; found C 48.28, H 5.47, N 5.05.

4.8 (*S*)-methyl 3-(4-methoxyphenyl)-2-(methylsulfonamido)propanoate (31)

To a solution of compound **30** (0.70 g, 2.56 mmol) in DMF (15 mL) was added $NaHCO_3$ (0.43 g, 5.12 mmol) at room temperature, and after the mixture was stirred for 10 min, CH_3I (0.32 mL, 5.12 mmol) was added. The reaction mixture was stirred overnight at room temperature followed by the addition of H_2O (10 mL) and 1 M aq. HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to obtain the title compound **31** as a colorless thick gum (yield 92 %). – IR (neat): ν = 3033, 2971, 2936, 1738, 1660, 1506, 1362, 1146 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, SO_2CH_3), 3.00 (dd, J = 7.3, 13.9 Hz, 1 H, CH_2CH), 3.10 (dd, J = 5.8, 13.9 Hz, 1 H, CH_2CH), 3.78 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.37 (m, 1 H, CH_2CH), 6.85 (d, J = 8.5 Hz, 2 H, 3′-H, 5′-H), 7.10 (d, J = 8.5 Hz, 2 H, 2′-H, 6′-H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 38.57 (SO_2CH_3), 41.35 (CH_2CH), 52.72 (OCH_3), 55.23 (OCH_3), 57.15 (CH_2CH), 114.17 (C-3′, C-5′), 127.09 (C-1′), 130.49 (C-2′, C-6′), 158.94 (C-4′), 171.9 (C=O) ppm. – $C_{12}H_{17}NO_5S$ (287.33): calcd. C 50.16, H 5.96, N 4.87; found C 50.12, H 6.03, N 4.81.

4.9 (*S*)-3-(4-methoxyphenyl)-2-(methylsulfonamido)propanoic acid (32)

To a solution of **31** (0.86 g, 3 mmol) in a mixture of THF-MeOH-H_2O (6:2:1, 15 mL) was added $LiOH \cdot H_2O$ (0.38 g, 9 mmol), and the mixture was stirred overnight at room temperature followed by the addition of 1 M aq. HCl to adjust the pH of the reaction to 6. The mixture was extracted with EtOAc (20 mL), and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Column chromatography on silica gel, eluting with ethyl acetate-hexane (1:1) and then changing to (2:1), gave the title compound **32** as a thick brown gum (yield 86 %). – IR (neat): ν = 3541, 3281, 3025, 2936, 1735, 1609, 1513, 1307, 1149 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 12.67 (s, 3 H, SO_2CH_3), 2.96 (dd, J = 7.6, 14.0 Hz, 1 H, CH_2), 3.16 (dd, J = 4.5, 14.0 Hz, 1 H, CH_2), 3.78 (s, 3 H, OCH_3), 4.35 (m, 1 H, CH), 5.10 (br. s, 1 H, NH), 6.86 (d, J = 8.5 Hz, 2 H, aromatic H), 7.16 (d, J = 8.5 Hz, 2 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 38.07 (SO_2CH_3), 41.23 (CH_2CH), 55.28 (OCH_3), 57.48 (CH_2CH), 114.18, 127.74, 130.66, 158.85 (C_{arom}), 175.10 (C=O) ppm. – $C_{11}H_{15}NO_5S$ (273.31): calcd. C 48.34, H 5.53, N 5.12; found C 48.29, H 5.59, N 5.05.

4.10 2-(5-(3-((*tert*-Butoxycarbonyl)amino)propoxy)-1-(3,4-dichlorophenyl)-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)ethyl acetate (36)

To a solution of **35** (2.00 g, 5.11 mmol) in DMF (20 mL) was sequentially added K_2CO_3 (0.92 g, 6.66 mmol) followed by *tert*-butyl-(3-bromoropropyl)carbamate (1.45 g, 6.12 mmol), and the mixture was further stirred for 8 h at room temperature. The reaction was diluted with H_2O (15 mL) and extracted with EtOAc (50 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography of the dark orange oily material, eluting with EtOAc-hexane (3:1), yielded compound **36** as a light yellow oil (yield 59 %). – IR (neat): ν = 3361, 3040, 2973, 1740, 1710, 1675, 1592, 1481, 1386, 1234, 1029 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, J = 6.4 Hz, 9 H, $OC(CH_3)_3$), 1.96 (s, 3 H, $COCH_3$), 2.27 (pent, 2 H, $CH_2CH_2CH_2$), 2.98 (t, J = 7.3 Hz, 2 H, $ArCH_2$), 3.29 (m, 2 H, NCH_2), 4.04 (t, J = 6.1 Hz, 2 H, OCH_2), 4.22 (t, J = 7.0 Hz, 2 H, OCH_2), 7.39 (dd, J = 4.85, 7.9 Hz, 1 H, aromatic H), 7.66 (dd, J = 2.4, 8.5 Hz, 1 H, aromatic H), 7.94 (d, J = 2.4 Hz, 1 H, aromatic H), 8.00–8.03 (m, 2 H, aromatic H), 8.64 (dd, J = 2.1, 6.5 Hz, 1 H, aromatic H), 8.93 (*d*, J =1.8 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 20.84 ($COCH_3$), 21.25 ($Ar\text{-}CH_2$), 28.38 ($OC(CH_3)_3$), 30.30 ($CH_2CH_2CH_2$), 36.50 (NCH_2), 65.39 (OCH_2), 73.34 (OCH_2), 79.44 ($OC(CH_3)_3$), 103.27, 120.47, 123.62, 123.70, 129.58, 130.86, 133.23, 135.12, 137.62, 148.19, 148.46, 149.10, 152.06 (all C_{arom}), 155.97 (C=O), 170.97

(C=O) ppm. – $C_{26}H_{30}Cl_2N_4O_5$ (549.45): calcd. C 56.84, H 5.50, N 10.20; found C 56.78, H 5.55, N 10.14.

4.11 *tert*-Butyl (3-((1-(3,4-dichlorophenyl)-4-(2-hydroxyethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)-oxy)propyl)carbamate (37)

To a cold solution of compound **36** (0.83 g, 1.64 mmol) in a mixture of THF (10 mL) and MeOH (5 mL) at 0 °C was added a solution of KOH (0.34 g, 6.06 mmol) in H_2O (5 mL). After being stirred for 15 min at 0 °C, the reaction was further stirred for 45 min at room temperature. Upon completion of the reaction (TLC), the mixture was concentrated under reduced pressure and diluted with EtOAc (30 mL) and successively washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Column chromatography of the light orange oil material, eluting with EtOAc-hexane (6:4), gave the title compound **37** as a light yellow gum (yield 85 %). – IR (neat): ν = 3345, 3055, 2974, 1691, 1593, 1482, 1366, 1169 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, OC(CH_3)$_3$), 1.91 (pent, 2 H, $CH_2CH_2CH_2$), 2.86 (t, J = 6.7 Hz, 2 H, Ar-CH_2), 3.36 (m, 2 H, NCH_2), 3.77 (t, J = 5.8 Hz, 2 H, OCH_2), 4.02 (t, J = 5.8 Hz, 2 H, OCH_2), 4.81 (br. s, 1 H, NH/OH), 7.36 (dd, J = 4.8, 7.9 Hz, 1 H, aromatic H), 7.54 (d, J = 8.5 Hz, 1 H, aromatic H), 7.67 (dd, J = 2.4, 8.5 Hz, 1 H, aromatic H), 7.96 (d, J = 2.4 Hz, 1 H, aromatic H), 8.00 (dd, J = 5.8, 7.9 Hz, 1 H, aromatic H), 8.61 (dd, J = 1.5, 4.9 Hz, 1 H, aromatic H), 8.91 (d, J = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.30 (Ar-CH_2), 28.36 (OC(CH_3)$_3$), 30.28 ($CH_2CH_2CH_2$), 37.25 (NCH_2), 63.37 (OCH_2), 73.30 (OCH_2), 79.44 (O*C*(CH_3)$_3$), 102.68, 120.94, 123.54, 123.68, 129.46, 130.83, 133.21, 134.98, 137.58, 148.26, 148.59, 149.35, 152.26 (all C_{arom}), 155.97 (C=O) ppm. – $C_{24}H_{28}Cl_2N_4O_4$ (507.41): calcd. C 56.81, H 5.56, N 11.04; found C 56.76, H 5.50, N 11.97.

4.12 2-(5-(3-((*tert*-Butoxycarbonyl)amino) propoxy)-1-(3,4-dichlorophenyl)-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (38)

To an ice-cold solution of compound **37** (0.41 g, 0.81 mmol) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (0.34 mL, 2.44 mmol), and after being stirred for 15 min, methanesulfonyl chloride (0.094 mL, 1.212 mmol) was added to the mixture. The stirring was continued for 1 h at 0 °C, and the mixture then diluted with H_2O (5 mL) followed by the addition of 1 M aq. HCl (5 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure to obtain the target compound **38** as a crystalline white solid (yield 98 %). M.p. 94–95 °C. – IR (neat): ν = 3356, 3038, 3015, 2986, 1682, 1590, 1483, 1384, 1172 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, OC(CH_3)$_3$), 1.93 (pent, 2 H, $CH_2CH_2CH_2$), 3.00 (s, 3 H, SO_2CH_3), 3.14 (t, J = 6.4 Hz, 2 H, Ar-CH_2), 3.29 (m, 2 H, NCH_2), 4.02 (t, J = 6.1 Hz, 2 H, OCH_2), 4.37 (t, J = 6.7 Hz, 2 H, OCH_2), 4.72 (br. s, 1 H, NH), 7.59 (d, J = 8.5 Hz, 1 H, aromatic H), 7.65 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.86 (m, 1 H, aromatic H), 7.92 (d, J = 2.4 Hz 1 H, aromatic H), 8.63 (m, 1 H, aromatic H), 8.70 (d, J = 5.2 Hz, 1 H, aromatic H), 9.09 (d, J = 1.2 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 23.32 (Ar-CH_2), 28.38 (OC(CH_3)$_3$), 30.46 ($CH_2CH_2CH_2$), 37.70 (SCH_3), 38.35 (NCH_2), 68.43 (OCH_2), 73.78 (OCH_2), 79.59 (O*C*(CH_3)$_3$), 102.56, 121.15, 123.91, 126.23, 131.10, 131.89, 132.99, 133.52, 137.00, 141.11, 141.26, 141.55, 144.57, 152.92 (all C_{arom}), 156.03 (C=O) ppm.

4.13 *tert*-Butyl (3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl) carbamate (39)

To a solution of compound **38** (1.25 g, 2.14 mmol) in DMF (15 mL) at 0 °C was added $NaSCH_3$ (0.6 g, 8.57 mmol), and the mixture was stirred for 2 h at room temperature. The reaction was diluted with EtOAc (30 mL) and washed with H_2O (10 mL) and brine (10 mL × 2). The light yellow residue was resolved over column chromatography, eluting with EtOAc-hexane (6:4), to produce the title compound **39** as a light brown gum (yield 78 %). – IR (neat): ν = 3402, 3092, 2975, 1696, 1590, 1483, 1386, 1171 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, OC(CH_3)$_3$), 1.95 (pent, 2 H, $CH_2CH_2CH_2$), 2.10 (s, 3 H, SCH_3), 2.71 (t, J = 7.3 Hz, 2 H, SCH_2), 2.95 (t, J = 7.3 Hz, 2 H, Ar-CH_2), 3.28 (m, 2 H, NCH_2), 4.04 (t, J = 6.1 Hz, 2 H, OCH_2), 7.59 (d, J = 8.8 Hz, 1 H, aromatic H), 7.65 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.89 (m, 1 H, aromatic H), 7.93 (d, J = 2.4 Hz, 1 H, aromatic H), 8.65 (d, J = 7.9 Hz, 1 H, aromatic H), 8.71 (d, J = 4.6 Hz, 1 H, aromatic H), 9.12 (d, J = 2.4 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.90 (SCH_3), 23.21 (Ar-CH_2), 28.44 (OC(CH_3)$_3$), 30.96 ($CH_2CH_2CH_2$), 34.15 (SCH_2), 36.97 ((CH_2CH)), 38.49 (NCH_2), 73.54 (OCH_2), 79.33 (O*C*(CH_3)$_3$), 104.85, 120.89, 123.67, 125.66, 131.06, 131.61, 133.50, 137.17, 139.68, 142.50, 143.50, 144.82, 152.60 (all C_{arom}), 156.20 (C=O) ppm. – $C_{25}H_{30}Cl_2N_4O_3S$ (537.50): calcd. C 55.86, H 5.63, N 10.42; found C 55.80, H 5.68, N 10.36.

4.14 3-((1-(3,4-Dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)-propan-1-amine hydrochloride (40)

To a solution of compound **39** (0.37 g, 0.69 mmol) in anhydrous CH_3OH (10 mL) at 0 °C was added acetyl chloride (1 mL), and the reaction mixture was stirred overnight at room temperature. The volatiles were evaporated under reduced pressure and then triturated with diethyl ether to get a compound **40** as a hygroscopic light yellow solid (yield 98 %). – IR (neat): ν = 3419, 2962, 1624, 1586, 1481, 1140 cm^{-1}. – ^1H NMR (500 MHz, CD_3OD): δ = 1.98 (s, 3 H, SCH_3), 2.00 (m, 2 H, $CH_2CH_2CH_2$), 2.64 (t, J = 7.3 Hz 2 H, SCH_2), 2.95–3.00 (m, 4H, Ar-CH_2, NCH_2), 4.09 (t, J = 6.15 Hz, 2 H, OCH_2), 7.65 (m, 2 H, aromatic H), 7.90 (d, J = 2.2 Hz, 1 H, aromatic H), 8.07 (m, 1 H, aromatic H), 8.77 (d, J = 5.8 Hz, 1 H, aromatic H), 8.85 (d, J = 8.2 Hz, 1 H, aromatic H), 9.12 (*d*, J = 2.4 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, CD_3OD): δ = 15.66 (SCH_3), 23.65 (Ar-CH_2), 29.02 ($CH_2CH_2CH_2$), 35.05 (SCH_2), 38.01 (NCH_2), 74.02 (OCH_2), 108.02, 123.38, 125.60, 128.63, 131.18, 132.50, 132.78, 137.10, 141.73, 142.43, 145.02, 153.56, 156.13 (C_{arom}) ppm. – $C_{20}H_{23}Cl_3N_4OS$ (473.85): calcd. C 50.69, H 4.89, N 11.82; found C 50.63, H 4.95, N 11.74.

4.15 (*S*)-2-acetamido-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio) ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl) oxy)propyl)-3-phenylpropanamide (2)

To a solution of mixture of compounds **40** (0.15 g, 0.32 mmol) and **13** (0.068 g, 0.33 mmol) in CH_2Cl_2 (10 mL) was sequentially added hydroxybenzotriazole (0.050 g, 0.33 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.084 g, 0.44 mmol) and Et_3N (0.15 mL, 1.1 mmol), and the mixture was stirred overnight at room temperature. The reaction was diluted with ethyl acetate (20 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Column chromatography purifications of light yellow oily material, eluting with EtOAc-hexane (8:2), gave the product as a light green solid (yield 69 %). M.p. 125–126 °C. – $[\alpha]_D^{20}$ = –3.1 (c = 0.005, EtOH). – IR (neat): ν = 3255, 3072, 2952, 1670, 1639, 1592, 1563, 1480.7, 1368, 1139, 1082 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.83 (pent, 2 H, $CH_2CH_2CH_2$), 1.97 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, SCH_3), 2.67 (t, J = 7.1 Hz, 2 H, SCH_2), 2.91 (t, J = 7.9 Hz, 2 H, ArCH_2), 3.10 (dd, J = 8.2, 13.7 Hz, 1 H, CH_2CH), 3.11 (dd, J = 5.8, 13.7 Hz, 1 H, CH_2CH), 3.31 (m, 2 H, NCH_2), 3.87 (t, J = 6.2 Hz, 2 H, OCH_2), 4.58 (m, 1 H, CH_2CH), 6.23–6.29 (br. s, 2 H, 2NH), 7.18–7.22 (m, 2 H, aromatic H), 7.25–7.29 (m, 3 H, aromatic H), 7.57 (d, J = 8.8 Hz, 1 H, aromatic H), 7.63 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.76 (m, 1 H, aromatic H), 7.90 (d, J = 2.4 Hz, 1 H, aromatic H), 8.49 (d, J = 8.0 Hz, 1 H, aromatic H), 8.73 (d, J = 6.5 Hz, 1 H, aromatic H), 9.10 (s, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.89 (SCH_3), 23.05 ($COCH_3$), 23.21 (Ar-CH_2), 30.93 ($CH_2CH_2CH_2$), 34.19 (SCH_2), 36.15 (CH_2CH), 38.38 (NCH_2), 54.46 (CH_2CH), 73.21 (OCH_2), 106.19, 121.06, 123.72, 127.06, 128.68, 129.21, 129.42, 131.00, 131.33, 133.32, 136.62, 137.31, 152.12 (all C_{arom}), 170.10 (C=O), 171.10 (C=O) ppm. – $C_{31}H_{33}Cl_2N_5O_3S$ (626.60): calcd. C 59.42, H 5.31, N 11.18; found C 59.36, H 5.37, N 11.10.

4.16 (*S*)-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy) propyl)-2-(methylsulfonamido)-3-phenylpropanamide (3)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **14** gave the title compound **3** as a colorless solid (yield 57 %). M.p. 130–131 °C. – $[\alpha]_D^{20}$ = –38.4 (c = 0.003, EtOH). – IR (neat): ν = 3376, 3280, 3062, 2920, 1664. 1592, 1566, 1482, 1457, 1317, 1149 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.95 (pent, 2 H, $CH_2CH_2CH_2$), 2.08 (s, 3 H, SCH_3), 2.54 (s, 3 H, SO_2CH_3), 2.70 (t, J = 6.7 Hz, 2 H, SCH_2), 2.89 (dd, J = 7.2, 13.7 Hz, 1 H, CH_2CH), 2.97 (t, J = 7.6 Hz, 2 H, ArCH_2), 3.31 (m, 2 H, NCH_2), 3.41 (dd, J = 5.6, 13.7 Hz, 1 H, CH_2CH), 4.03 (t, J = 6.4 Hz, 2 H, OCH_2), 4.08 (m, 1 H, CH_2CH), 5.73 (br. s, 1 H, NH), 7.20–7.24 (m, 2 H, aromatic H), 7.25–7.30 (m, 3 H, aromatic H), 7.57 (d, J = 8.8 Hz, 1 H, aromatic H), 7.66 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.90 (m, 1 H, aromatic H), 7.95 (m, 1 H, aromatic H), 8.49 (d, J = 7.6 Hz, 1 H, aromatic H), 8.76 (d, J = 6.5 Hz, 1 H, aromatic H), 9.10 (s, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.66 (SCH_3), 23.17 (Ar-CH_2), 29.54 ($CH_2CH_2CH_2$), 33.98 (SCH_2), 36.45 (CH_2CH), 38.66 (NCH_2), 40.03 (SO_2CH_3), 59.12 (CH_2CH), 72.97 (OCH_2), 106.76, 121.03, 123.57, 123.69, 127.63, 129.13, 129.39, 129.62, 130.74, 130.89, 133.14, 134.92, 136.38, 137.66, 147.88, 148.52, 149.34, 151.73 (all C_{arom}), 170.46 (C=O) ppm. – $C_{30}H_{33}Cl_2N_5O_4S_2$ (662.65): calcd. C 54.38, H 5.02, N 10.57; found C 54.33, H 5.07, N 10.50.

4.17 (*S*)-2-acetamido-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio) ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-3-(4-fluorophenyl)-propanamide (4)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **21** gave the title compound **4** as a colorless solid (yield 67 %). M.p. 117–118 °C. – $[\alpha]_D^{20}$ = –5.6 (*c* = 0.005, EtOH). – IR (neat): ν = 3505, 3272, 3066, 2921, 1892, 1654, 1593.3, 1509, 1482, 1368, 1220, 1132 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, SCH_3), 2.08 (s, 3 H, $COCH_3$), 2.17 (pent, 2 H, $CH_2CH_2CH_2$), 2.70 (t, *J* = 7.2 Hz, 2 H, SCH_2), 2.89–2.95 (m, 4 H, $ArCH_2$, CH_2CH), 3.32 (t, *J* = 6.2 Hz, 2 H, NCH_2), 3.96 (t, *J* = 7.1 Hz, 2 H, OCH_2), 4.70 (m, 1 H, CH_2CH), 6.94 (m, 2 H, aromatic H), 7.20 (m, 2 H, aromatic H), 7.58 (d, *J* = 8.2 Hz, 1 H, aromatic H), 7.64 (d, *J* = 8.2 Hz, 1 H, aromatic H), 7.90 (m, 1 H, aromatic H), 7.99 (d, *J* = 2.6 Hz, 1 H, aromatic H), 8.74–8.79 (m, 2 H, aromatic H), 89.24 (d, *J* = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.69 (SCH_3), 23.17 ($COCH_3$, Ar-CH_2), 29.67 ($CH_2CH_2CH_2$), 34.04 (SCH_2), 36.31 (CH_2CH), 37.57 (NCH_2), 54.79 (CH_2CH), 72.98 (OCH_2) 105.72, 115.51 (d, *J* = 20.8 Hz), 120.98, 123.63, 129.63, 130.76, 130.89, 132.24, 133.17, 135.00, 137.63, 147.89, 148.45, 149.31, 151.73, 161.91 (d, *J* = 245.9 Hz) (all C_{arom}), 170.08 (C=O), 170.92 (C=O) ppm. – $C_{31}H_{32}Cl_2FN_5O_3S$ (644.59): calcd. C 57.76, H 5.00, N 10.86; found C 57.70, H 5.06, N 10.80.

4.18 (*S*)-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-3-(4-fluorophenyl)-2-(methylsulfonamido) propanamide (5)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **22** gave the title compound **5** as a white crystaline solid (yield 60 %). M.p. 126–127 °C. – $[\alpha]_D^{20}$ = –18.0 (*c* = 0.005, EtOH). – IR (neat): ν = 3663, 3282, 3066, 2921, 1664, 1593, 1511, 1482, 1319, 1223, 1150 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.92 (pent, 2 H, $CH_2CH_2CH_2$), 2.08 (s, 3 H, SCH_3), 2.54 (s, 3 H, SO_2CH_3), 2.64 (t, *J* = 7.3 Hz, 2 H, SCH_2), 2.89–2.93 (m, 3 H, $ArCH_2$, CH_2CH), 3.20 (dd, *J* = 5.1, 12.2 Hz, 1 H, -CH_2CH-), 3.44 (t, *J* = 6.4 Hz, 2 H, NCH_2), 3.96–3.99 (m, 3 H, OCH_2, CH_2CH), 4.93 (d, *J* = 5.6 Hz, 1 H, NH), 6.42 (br. s, 1 H, NH), 7.03 (m, 2 H, aromatic H), 7.19 (m, 2 H, aromatic H), 7.38 (dd, *J* = 2.7, 8.5 Hz, 1 H, aromatic H), 7.55 (d, *J* = 8.5 Hz, 1 H, aromatic H), 7.65 (dd, *J* = 2.4, 8.5 Hz, 1 H, aromatic H), 7.93 (d, *J* = 2.4 Hz, 1 H, aromatic H), 8.00 (m, 1 H, aromatic H), 8.63 (dd, *J* = 2.1, 7.6 Hz, 1 H, aromatic H), 8.90 (d, *J* = 2.1, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.69 (SCH_3), 23.22 (Ar-CH_2), 29.57 ($CH_2CH_2CH_2$), 34.03 (SCH_2), 36.56 (CH_2CH), 37.97 (NCH_2), 40.50 (SO_2CH_3), 58.94 (CH_2CH), 72.97 (OCH_2), 105.78, 116.00 (d, *J* = 20.8 Hz), 121.09, 123.58, 123.72, 129.63, 130.81, 130.93, 131.03, 133.17, 134.94, 137.69, 148.56, 149.41, 161.72 (d, *J* = 247.3 Hz) (all C_{arom}), 170.34 (C=O) ppm. – $C_{30}H_{32}Cl_2FN_5O_4S_2$ (680.64): calcd. C 52.94, H 4.74, N 10.29; found C 52.88, H 4.80, N 10.21.

4.19 (*S*)-2-acetamido-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio) ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl) oxy)propyl)-3-(4-methoxyphenyl)-propanamide (6)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **28** gave the title compound **6** as a colorless solid (yield 61 %). M.p. 131–132 °C. – $[\alpha]_D^{20}$ = –19.1 (*c* = 0.003, EtOH). – IR (neat): ν = 3275, 3039, 2917, 1652, 1591, 1483, 1368, 1284, 1030 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.82 (pent, 2 H, $CH_2CH_2CH_2$), 1.97 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, SCH_3), 2.62 (t, *J* = 7.1 Hz, 2 H, SCH_2), 2.84–2.93 (m, 3 H, $ArCH_2$, CH_2CH), 3.01 (dd, *J* = 5.5, 12.2 Hz, 1 H, CH_2CH), 3.32 (m, 2 H, NCH_2), 3.74 (s, 3 H, OCH_3), 3.88 (t, *J* = 6.2 Hz, 2 H, OCH_2), 4.49 (m, 1 H, CH_2CH), 6.05 (br. s, 1 H, NH), 6.18 (d, *J* = 6.7 Hz, 1 H, NH), 6.80 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.10 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.39 (m, 1 H, aromatic H), 7.54 (d, *J* = 8.8 Hz, 1 H, aromatic H), 7.65 (dd, *J* = 2.4, 8.8 Hz, 1 H, aromatic H), 7.91 (d, *J* = 2.4 Hz, 1 H, aromatic H), 8.00 (d, *J* = 7.9 Hz, 1 H, aromatic H), 8.63 (d, *J* = 4.9 Hz, 1 H, aromatic H), 8.90 (s, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.71 (SCH_3), 23.12 ($COCH_3$), 23.19 (Ar-CH_2), 32.75 ($CH_2CH_2CH_2$), 34.07 (SCH_2), 36.24 (CH_2CH), 37.57 (NCH_2), 54.97 (OCH_3), 55.22 (CH_2CH), 73.05 (OCH_2), 105.82, 114.07, 120.95, 123.63, 123.92, 128.48, 130.22, 130.90, 133.20, 135.80, 137.58, 147.37, 147.46, 148.20, 151.83, 158.65 (all C_{arom}), 170.00 (C=O), 171.17 (C=O) ppm. – $C_{32}H_{35}Cl_2N_5O_4S$ (656.62): calcd. C 58.53, H 5.37, N 10.67; found C 58.47, H 5.43, N 10.60.

4.20 (*S*)-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy) propyl)-3-(4-methoxyphenyl)-2-(methylsulfonamido)propanamide (7)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **32** gave the title compound **7** as a

yellow thick gum (yield 64 %). – $[\alpha]_D^{20}$ = –13.9 (*c* = 0.005, EtOH). – IR (neat): ν = 3403, 3066, 2925, 2835, 1667, 1592, 1514, 1482, 1321, 1248, 1150 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.92 (pent, 2 H, $CH_2CH_2CH_2$), 2.07 (s, 3 H, SCH_3), 2.50 (s, 3 H, SO_2CH_3), 2.64 (t, *J* = 7.3 Hz, 2 H, SCH_2), 2.82–2.90 (m, 3 H, $ArCH_2$, CH_2CH), 3.19 (dd, *J* = 6.4, 14.0 Hz, 1 H, CH_2CH), 3.40 (m, 2 H, NCH_2), 3.77 (s, 3 H, OCH_3), 3.96 (t, *J* = 6.4 Hz, 2 H, OCH_2), 4.48 (m, 1 H, CH_2CH), 5.04 (br. s, 1 H, NH), 6.22 (br. s, 1 H, NH), 6.86 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.14 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.38 (m, 1 H, aromatic H), 7.55 (d, *J* = 8.8 Hz, 1 H, aromatic H), 7.66 (dd, *J* = 2.4, 8.8 Hz, 1 H, aromatic-H), 7.92 (d, *J* = 2.45 Hz, 1 H, aromatic H), 8.00 (d, *J* = 7.9 Hz, 1 H, aromatic H), 8.63 (m, 1 H, aromatic H), 8.90 (d, *J* = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.67 (SCH_3), 23.19 (Ar-CH_2), 29.61 ($CH_2CH_2CH_2$), 34.02 (SCH_2), 36.48 (CH_2CH), 37.87 (NCH_2), 40.19 (SO_2CH_3), 55.33 (OCH_3), 59.18 (CH_2CH), 73.02 (OCH_2), 114.04, 114.48, 121.06, 123.58, 123.72, 128.10, 129.66, 130.44, 130.75, 130.91, 133.16, 134.96, 137.69, 147.92, 148.54, 149.34, 151.77, 159.09 (all C_{arom}), 170.65 (C=O) ppm. – $C_{31}H_{35}Cl_2N_5O_5S_2$ (692.68): calcd. C 53.75, H 5.09, N 10.11; found C 53.70, H 5.15, N 10.03.

4.21 (*S*)-*tert*-butyl (1-((3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamate (8)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **29** yielded compound **8** as a colorless crystalline solid (yield 55 %). M.p. 123–124 °C. – $[\alpha]_D^{20}$ = –8.9 (*c* = 0.003, EtOH). – IR (neat): ν = 3427, 3314, 3042, 2974, 2922, 1714, 1592, 1513, 1366, 1247, 1166 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, $OC(CH_3)_3$, 1.84 (pent, 2 H, $CH_2CH_2CH_2$), 2.06 (s, 3 H, SCH_3), 2.62 (t, *J* = 7.5 Hz, 2 H, SCH_2), 2.86 (t, *J* = 8.8 Hz, 2 H, $ArCH_2$), 2.93–3.02 (m, 2 H, CH_2CH), 3.34 (m, 2 H, NCH_2), 3.75 (s, 3 H, OCH_3), 3.91 (t, *J* = 6.4 Hz, 2 H, OCH_2), 4.42 (m, 1 H, CH_2CH), 5.04 (br. s, 1 H, NH), 6.01 (br. s, 1 H, NH), 6.80 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.10 (d, *J* =8.5 Hz, 2 H, aromatic H), 7.39 (m, 1 H, aromatic H), 7.55 (d, *J* = 8.5 Hz, 1 H, aromatic H), 7.65 (dd, *J* = 2.4, 8.5 Hz, 1 H, aromatic H), 7.91 (d, *J* = 2.4 Hz, aromatic H), 8.00 (dd, *J* = 2.1, 7.6 Hz, 1 H, aromatic H), 8.63 (d, *J* = 7.9 Hz, 1 H, aromatic H), 8.90 (d, *J* = 2.1, 7.6 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.66 (SCH_3), 23.12 (Ar-CH_2), 28.26 ($OC(CH_3)_3$), 29.70 ($CH_2CH_2CH_2$), 34.00 (SCH_2), 36.28 (CH_2CH), 37.59 (NCH_2), 55.20 (OCH_3), 55.24 (CH_2CH), 73.12 (OCH_2), 79. 92 ($OC(CH_3)_3$), 105.74, 114.06, 120.95, 123.58, 123.63, 129.60, 130.29, 130.76, 130.88, 133.17, 134.92, 137.62, 147.91, 148.52, 149.37, 151.76 (all C_{arom}), 158.60 (C=O), 171.54 (C=O) ppm. – $C_{35}H_{41}Cl_2N_5O_5S$ (387.52): calcd. C 58.82, H 5.78, N 9.80; found C 58.77, H 5.82, N 9.74.

4.22 (*S*)-2-acetamido-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-3-(pyridin-3-yl)propanamide (9)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **23** yielded compound **9** as a light brown gum (yield 58 %). – $[\alpha]_D^{20}$ = –17.5 (*c* = 0.004, EtOH). – IR (neat): ν = 3442, 3060, 2923, 1653, 1592, 1482, 1369, 1133 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.85 (pent, 2 H, $CH_2CH_2CH_2$), 1.96 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, SCH_3), 2.62 (t, *J* = 7.0 Hz, 2 H, SCH_2), 2.87 (t, *J* = 7.3 Hz, 2 H, $ArCH_2$), 3.01 (dd, *J* = 5.5, 12.7 Hz, 1 H, CH_2CH), 3.09 (dd, *J* = 7.3, 12.7 Hz, 1 H, CH_2CH), 3.35 (m, 2 H, NCH_2), 3.93 (t, *J* = 7.0 Hz, 2 H, OCH_2), 4.61 (m, 1 H, CH_2CH), 6.45 (br. s, 1 H, NH), 6.76 (br. s, 1 H, NH), 7.20 (m, 1 H, aromatic H), 7.38 (m, 1 H, aromatic H), 7.54 (d, *J* = 8.8 Hz, 1 H, aromatic H), 7.60 (m, 1 H, aromatic H), 7.64 (dd, *J* = 2.4, 8.8 Hz, 1 H, aromatic H), 7.91 (d, *J* = 2.5 Hz, 1 H, aromatic H), 8.00 (m, 1 H, aromatic H), 8.40 (d, *J* = 2.1 Hz, 1 H, aromatic H), 8.45 (dd, *J* = 2.1, 8.0 Hz, 1 H, aromatic H), 8.63 (dd, *J* = 2.1, 8.0 Hz, 1 H, aromatic H), 8.89 (d, *J* = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.68 (SCH_3), 23.11 ($COCH_3$), 23.18 (Ar-CH_2), 29.70 ($CH_2CH_2CH_2$), 34.04 (SCH_2), 35.58 (CH_2CH), 36.35 (NCH_2), 54.23 (CH_2CH), 73.06 (OCH_2), 105.72, 120.98, 123.48, 123.58, 129.59, 130.88, 132.31, 133.15, 134.92, 136.80, 137.66, 147.92, 148.36, 148.52, 149.73, 150.44, 151.75 (all C_{arom}), 170.18 (C=O), 170.69 (C=O) ppm. – $C_{30}H_{32}Cl_2N_6O_3S$ (627.58): calcd. C 57.41, H 5.14, N 13.39; found C 57.36, H 5.19, N 13.34.

4.23 (*S*)-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-2-(methylsulfonamido)-3-(pyridin-3-yl)propanamide (10)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **24** yielded compound **10** as a colorless gum (yield 65 %). – $[\alpha]_D^{20}$ = –28.3 (*c* = 0.004, EtOH). – IR (neat): ν = 3546, 3386, 3060, 2979, 1674, 1592, 1483, 1318, 1150 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.93 (pent, 2 H, $CH_2CH_2CH_2$), 2.08 (s, 3 H, SCH_3), 2.59 (s, 3 H, SO_2CH_3), 2.64 (t, *J* = 7.6 Hz, 2 H, SCH_2), 2.88 (t, *J* = 6.7 Hz, 2 H, $ArCH_2$),

2.97 (dd, J = 5.8, 14.0 Hz, 1 H, CH_2CH), 3.20 (dd, J= 6.1, 14.0 Hz, 1 H, CH_2CH), 3.45 (m, 2 H, NCH_2), 3.97 (t, J = 5.8 Hz, 2 H, OCH_2), 4.05 (m, 1 H, CH_2CH), 5.36 (d, J = 5.8 Hz, 1 H, NH), 6.60 (br. s, 1 H, NH), 7.29 (dd, J = 4.9, 7.9 Hz, 1 H, aromatic H), 7.38 (dd, J = 4.9, 7.8 Hz, 1 H, aromatic H), 7.55 (d, J = 7.9 Hz, 1 H, aromatic H), 7.61 (m, 1 H, aromatic H), 7.65 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.92 (d, J = 2.4 Hz, 1 H aromatic H), 8.00 (m, 1 H, aromatic H), 8.49 (d, J = 2.1 Hz, 1 H, aromatic H), 8.52 (dd, J = 2.1, 8.1 Hz, 1 H, aromatic H), 8.63 (dd, J = 2.1, 8.0 Hz, 1 H, aromatic H), 8.90 (d, J = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.69 (SCH_3), 23.20 (Ar-CH_2), 29.54 ($CH_2CH_2CH_2$), 34.02 (SCH_2), 36.06 (CH_2CH), 36.62 (NCH_2), 40.95 (SO_2CH_3), 58.45 (CH_2CH), 72.96 (OCH_2), 121.07, 123.60, 123.68, 123.75, 129.61, 130.78, 130.92, 132.15, 133.15, 134.94, 137.19, 137.66, 148.49, 148.77, 149.37, 150.57, 151.71 (all C_{arom}), 170.21 (C=O) ppm. – $C_{29}H_{32}Cl_2N_6O_4S_2$ (663.64): calcd. C 52.48, H 4.86, N 12.66; found C 52.42, H 4.90, N 12.60.

4.24 (*S*)-2-acetamido-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio) ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-3-(pyridin-4-yl)-propanamide (11)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **25** yielded compound **11** as a light brown gum (yield 59 %). – $[\alpha]_D^{20}$ = –14.6 (c = 0.003, EtOH). – IR (neat): ν = 3478, 3289, 3060, 2919, 1659, 1592, 1482, 1367, 1133 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.85 (pent, 2 H, $CH_2CH_2CH_2$), 1.96 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, SCH_3), 2.63 (t, J = 7.0 Hz, 2 H, SCH_2), 2.86 (t, J = 7.3 Hz, 2 H, ArCH_2), 3.02 (dd, J = 6.4, 12.7 Hz, 1 H, CH_2CH), 3.06 (dd, J = 5.3, 12.7 Hz, 1 H, CH_2CH), 3.36 (m, 2 H, NCH_2), 3.90 (t, J = 7.0 Hz, 2 H, OCH_2), 4.60 (m, 1 H, CH_2CH), 6.06 (br. s, 1 H, NH), 6.15 (br. s, 1 H, NH), 7.14 (d, J = 6.1 Hz, 1 H, aromatic H), 7.39 (d, J = 6.6 Hz, 2 H, aromatic H), 7.54 (d, J = 8.8 Hz, 1 H, aromatic H), 7.64 (dd, J = 2.4, 8.8 Hz, 1 H, aromatic H), 7.92 (d, J = 2.4 Hz, 1 H, aromatic H), 8.00 (m, 1 H, aromatic H), 8.51 (d, J = 6.6 Hz, 2 H, aromatic H), 8.62 (m, 1 H, aromatic H), 8.89 (d, J = 2.1 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.69 (SCH_3), 23.14 ($COCH_3$), 23.20 (Ar-CH_2), 29.54 ($CH_2CH_2CH_2$), 34.02 (SCH_2), 36.40 (CH_2CH), 37.38 (NCH_2), 53.82 (CH_2CH), 72.96 (OCH_2), 121.07, 123.60, 123.68, 123.75, 129.61, 130.78, 130.92, 132.15, 133.15, 134.94, 137.19, 137.66, 148.49, 148.77, 149.37, 150.57, 151.71 (all C_{arom}), 170.21 (C=O), 170.71 (C=O) ppm. – $C_{30}H_{32}Cl_2N_6O_3S$ (627.58): calcd. C 57.41, H 5.14, N 13.39; found C 57.35, H 5.19, N 13.32.

4.25 (*S*)-*N*-(3-((1-(3,4-dichlorophenyl)-4-(2-(methylthio)ethyl)-3-(pyridin-3-yl)-1*H*-pyrazol-5-yl)oxy)propyl)-2-(methylsulfonamido)-3-(pyridin-4-yl) propanamide (12)

Following the procedure adopted for the synthesis of **2**, the reaction of **40** with **26** yielded compound **12** as a colorless crystalline solid (yield 62 %). M.p. 136–137 °C. – $[\alpha]_D^{20}$ = –20.0 (c = 0.003, EtOH). – IR (neat): ν = 3373, 3281, 3062, 2919, 1675, 1592, 1482, 1415, 1319, 1183, 1150 cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (pent, 2 H, $CH_2CH_2CH_2$), 2.08 (s, 3 H, SCH_3), 2.59 (s, 3 H, SO_2CH_3), 2.65 (t, J = 7.7 Hz, 2 H, SCH_2), 2.88 (t, J = 6.7 Hz, 2 H, ArCH_2), 2.97 (dd, J = 5.2, 13.7 Hz, 1 H, CH_2CH), 3.20 (dd, J = 6.2, 13.7 Hz, 1 H, CH_2CH), 3.47 (m, 2 H, NCH_2), 3.97 (t, J = 5.9 Hz, 2 H, OCH_2), 4.08 (m, 1 H, CH_2CH), 5.11 (m, 1 H, NH), 6.44 (br. s, 1 H, NH), 7.19 (d, J = 5.8 Hz, 1 H, aromatic H), 7.38 (d, J = 6.8 Hz, 2 H, aromatic H), 7.56 (d, J = 8.2 Hz, 1 H, aromatic H), 7.64 (dd, J = 2.4, 8.2 Hz, 1 H, aromatic H), 7.92 (d, J = 2.4 Hz, 1 H, aromatic H), 8.00 (m, 1 H, aromatic H), 8.56 (d, J = 6.8 Hz, 2 H, aromatic H), 8.62 (m, 1 H, aromatic H), 8.90 (d, J = 1.5 Hz, 1 H, aromatic H) ppm. – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 15.71 (SCH_3), 23.23 (Ar-CH_2), 29.71 ($CH_2CH_2CH_2$), 34.02 (SCH_2), 36.65 (CH_2CH), 38.16 (NCH_2), 40.95 (SO_2CH_3), 58.02 (CH_2CH), 72.91 (OCH_2), 105.77, 121.10, 123.60, 123.70, 124.68, 130.94, 133.17, 134.92, 137.66, 145.44, 148.52, 149.42, 150.35, 151.68 (all C_{arom}), 169.98 (C=O) ppm. – $C_{29}H_{32}Cl_2N_6O_4S_2$ (663.64): calcd. C 52.48, H 4.86, N 12.66; found C 52.44, H 4.92, N 12.60.

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