SUPPORTING INFORMATION

Discovery of Novel Urea-based Hepatitis C Protease Inhibitors With High Potency Against PI-resistant Mutants.

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In vivo PK

The pharmacokinetics (PK) of selected inhibitors (7, 8 and 12) were evaluated in cannulated male Sprague Dawley (SD) rats following intravenous (IV) via tail vein and oral gavage (PO) administrations. Three animals having jugular vein (JV) cannula for IV group and three animals having both JV and portal vein (PV) cannula for PO group were used for each PK study of each inhibitor. The animals were administrated single dose of inhibitors, dissolved in 35/30/25/10 water/PEG400/PG/DMSO (pH 6.9 for inhibitor 7, pH 7.8 for inhibitor 12) or 33/31/26/10 water/PEG/PG/DMSO (pH 8.5 for inhibitor 8), at 1 and 5 mg/kg for IV and PO, respectively. Plasma samples were collected via JV and JV/PV at the following time points: 5, 15, 30 min, 1, 2, 4, 6, 8, and 24h post-dose for the IV group; 15, 30 min, 1, 2, 4, 6, 8 and 24 h post-dose for the PO group.

The plasma concentration-versus-time data of each inhibitor was analyzed with LC/MS/MS to determine the PK parameters with WinNonlin Pro 4.2. The clearance (CL), area under the curve (AUC), half-life ($t_{2/1}$), bioavailability (%) and estimated maximum absorption (%) were evaluated. The dose-corrected area under curve (AUC) of plasma samples from PV or JV in the orally dosed rats were divided by AUC of plasma samples from JV in the intravenously dosed rats for determination of the maximum oral absorption and absolute oral bioavailability.

Replicon Luciferase cell based assay

A 10 mM stock solution in DMSO of each test compound was further diluted in DMSO in the first row of a 384-well, V-bottom microplate, to give 100 times the top concentration of the required dilution series. Dilutions of compound were prepared in 1:3 serial dilutions from the

first row onwards robotically. A robot was also used to transfer 0.5 µL volumes from each dilution well into wells of white 384-well assay plates (Nunc #164610). Control wells received 0.5 µL of DMSO alone. Plates were made in duplicate for measuring HCV replication and cytotoxicity in the replicon cell lines.

Suspensions were prepared from cultures of Huh-7 cells stably transfected with sub-genomic HCV NS3-NS5B replicons of either genotype 1b (the ET subline described by Pietschmann,T., Lohmann, V., Kaul, A., Krieger, N., Rinck, G., Rutter, G., Strand, D. & Bartenschlager, R., *Journal of Virology*, 2002, **76**, 4008-4021) or genotype 1a linked to a firefly luciferase reporter gene. Monolayers nearing confluency were stripped from growth flasks with versene-trypsin solution and the cells re-suspended in assay medium comprising DMEM (Invitrogen #11965-092) supplemented with 5% v/v foetal calf serum, 1% v/v non-essential amino acids solution, 100 units/ml penicillin, 100 µg/ml streptomycin and 2 mM GlutaMAX-1. 50 µL of suspension containing 5,000 cells of either genotype 1b or genotype 1a luciferase replicon were added to all wells, except medium controls, of the assay plate with a Multidrop Combi (Thermo Scientific Corporation) and the plate incubated for 48 hours at 37 °C in a 5% CO_2 atmosphere. A solution of Steady-Glo cytolytic buffer/luciferase substrate (Promega #E2550) was prepared according to the manufacturer's instructions, and 20 µL were added to each well with a Multidrop Combi. To measure cytotoxicity, a solution of CellTiter-Glo Luminescent Cell Viability Assay reagent (Promega #G7573) was prepared according to the manufacturer's instructions, and 20 ul were added to each well with a Multidrop Combi. The plates were then read for luminescence on an Envision Multilabel Reader (Perkin Elmer)

HCV PI transient replicon assay protocol.

A model system for HCV RNA replication is a cell based assay using subgenomic or genomic HCV replicons containing HCV genes and possibly a selectable and/or screenable marker. The HCV replicon is a self-replicating RNA that does not produce infectious particles. The HCV PI transient replicons assay was derived from two publications (*Science 258, 110, 1999*; *J Virol 75, 12047, 2001*). In this assay, the target cells were "ET Cured cells", a cell line generated by treating ET replicons cells (RebliKon) with Interferon α for several passages until the HCV genome was cleared. Other modifications to the published protocol included 1) cells were transefected in PBS and 2) were treated for 72 hours with compounds. Data from dose responses was analyzed using BioAssay. EC50 values were generated by plotting percent inhibition against compound concentration. The various HCV mutant replicons were generated by standard molecular biology techniques and confirmed by sequencing.

HCV protease enzyme assay

Enzyme data was generated as described in reference 13 (Li, X. et al. *Bioorg. Med. Chem. Lett.*, **2011**, *21*, 2048-2054, see reference 21 quoted therein). Our assay utilized the protease domain (the first 180 amino acids of the full length NS3/4A protein) of NS3 genotype 1a and the NS4A cofactor peptide (KKGSVVIVGRIVLSGKPAIIPKK-OH). Based on Thibeault et al. (*Biochemistry* **2009**, *48*, 744-753), our assay system represents the protease activity of full length NS3/4A.

General Synthetic Procedures**.**

Unless stated otherwise, the reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. The reactions were carried out at ambient temperature unless otherwise

indicated. Silica gel (EM Science, 230-400 mesh) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal). ^{1}H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers; the chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b) broad, s) singlet, d) doublet, t) triplet, q) quartet, m) multiplet. Mass spectra (ms) were obtained using electrospray (positive or negative ion). All compounds were >95% pure as determined by LC/MS (equipped with UV and Evaporative Light Scattering Detectors) in both acid- and base-modified acetonitrile/water gradients and ^{1}H NMR.

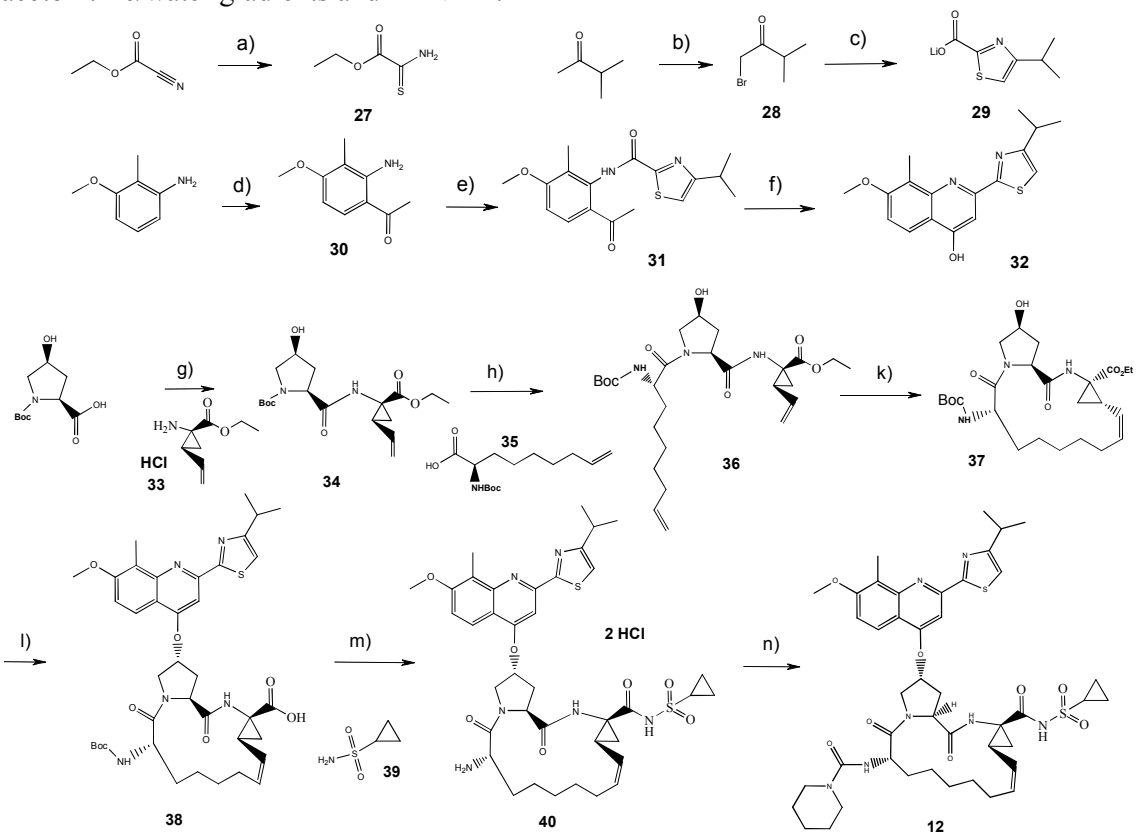

Figure 1. Reagents and Conditions: a) H_2S, ether, 95%; b) Br_2, methanol, - 30°C, 54%; c) i. **27**, ethanol, reflux; ii. LiOH, water/tetrahydrofuran/methanol, 50% two steps; d) BCl_3, $AlCl_3$, acetonitrile, 71%; e) **29**, HATU, DIEA, DMF, 40%; f) t-BuOH, KO^{t}Bu, 100°C, 99%; g) **33**, HATU, DIEA, dichloromethane, rt, 95%; h) i. HCl, dioxane, dichloromethane; ii.**35**, HATU, DIEA, dichloromethane; 88% two steps; k) Zhan 1B, DCE, c=0.01 M, 75°C, 62%; l) i. **32**, DIAD, Ph_3P, THF; ii. LiOH, tetrahydrofuran, 61%, two steps; m) i. **39**, CDI, DMF, DBU; ii. HCl, dioxane, 60% two steps; n) cyclohexylamine, triphosgene, dichloroethane

Compound **27**

Solution of [(cyanocarbonyl)oxy]ethane (25g,0.25mol) and triethylamine (1ml) in ether (200ml) cooled to 0°C was bubbled-in H_2S for 2 hours. The resulting mixture was stirred overnight at ambient temperature, followed by addition of 1N HCl (200ml). After stirring for 30 min, the product was extracted with ether and dried over $MgSO_4$, affording ethyl

amino(thioxo)acetate **27** (32g , 95%) as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.37 (t, *J*=7.14 Hz, 3 H), 4.34 (q, *J*=7.14 Hz, 2 H), 7.49 - 8.43(m, 2 H), LC-MS (ESI): *m/z* 134 $(M + H)^+$.

Compound **28**

To a solution of methyl isopropyl ketone (10.0 g, 114 mmol) in anhydrous methanol (110 mL) cooled to – 30^{0}C under a nitrogen atmosphere bromine (5.8 mL, 114 mmol) was added dropwise and the reaction was allowed to warm to room temperature and stirred for 3 h, then concentrated *in vacuo,* diluted with diethyl ether and washed with aqueous saturated $NaHCO_3$ solution followed by brine, dried ($MgSO_4$) and concentrated *in vacuo*. Following silica gel chromatography eluting with 0 – 60% hexanes/dichloromethane, **28** as a clear oil was obtained (12.46 g, 54% yield). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.07 - 1.20 (m, 6 H), 2.96 (m, 1 H), 3.96 (s, 2 H).

Compound **29**

To a solution of ethyl amino(thioxo)acetate **27** (4.16 g, 31.3 mmol) in ethanol (30 mL) was added 1-bromo-3-methyl-2-butanone **28** (5.16 g, 31.3 mmol) and the solution was heated to reflux for 1.5 h under a nitrogen atmosphere. The reaction was cooled to room temperature and solid $NaHCO_3$ was added until gas evolution ceased. Water (50 mL) was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The reaction was repeated in an identical fashion on a 27.6 mmol scale and combined to afford 7.46 g of an orange oil. The oil was dissolved in THF (70 mL), water (15 mL) and methanol (25 mL) followed by the addition of anhydrous lithium hydroxide (1.3 g, 54.3 mmol) and the solution was stirred at room temperature for 18 h. The reaction was concentrated *in vacuo* and the residue triturated in diethyl ether and filtered to afford intermediate **29** as a white solid (5.26 g, 50% yield). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.28 (d, *J*=7.0 Hz, 6 H), 3.08 (m, 1 H), 7.13 (s, 1 H). LC-MS (ESI): *m/z* 170.22 $(M - Li)^-$.

Compound **30**

To a solution of 2-methyl-3-(methyloxy)aniline (5.0 g, 36.5 mmol) in *p*-xylene (80 mL) cooled to 0^{0}C, BCl_3 (36.5 mL) was added as 1M solution in dichloromethane and stirred for 30 min at 0^{0}C under a nitrogen atmosphere. Acetonitrile (2.6 mL, 54.7 mmol) was added and the solution was stirred for an additional 30 min at 0^{0}C, and then added dropwise to $AlCl_3$ (4.87 g, 36.5 mmol) suspension in anhydrous dichloromethane (50 mL) at 0 ^{0} C. The reaction was stirred at 0^{0}C for 45 min, dichloromethane removed *in vacuo* and the xylene solution heated to 70^{0}C for 18 h. Water (80 mL) was added to the reaction colled off to room temperature and the solution was heated to 70 ^{0}C for 1 h, cooled to room temperature, diluted with ethyl acetate and the aqueous layer separated. The organic layer was washed with an equal volume of water, brine and dried ($MgSO_4$) and concentrated *in vacuo*. To the residue was added 5:1 hexanes:diethyl ether and the precipitate collected by filtration to afford **30** as a white solid (4.66 g, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.42 (s, 3 H) 3.77 (s, 3 H) 6.30 (d, *J*=9.04 Hz, 1 H) 7.03 (br. s., 2 H) 7.65 (d, *J*=9.0 Hz, 1 H). LC-MS (ESI): *m/z* 180.10 $(M + H)^+$.

Compound **31**

To a solution of **29** (2.86g, 0.016 mmol) in DMF (42 ml) was added HATU (11.03g, 0.029 mmol) and stirred for 20 min at ambient temperature before adding **30** (2.595 g, 0.0145 mmol) and stirred overnight. The reaction mixture was partitioned between water and ethyl acetate and combined organic phases were dried over $MgSO_4$ and purified by silica gel chromatography (ethyl acetate/hexane,0-50%) to afford **31** (1.92g, 40%). ^{1}H NMR (400 MHz, CHLOROFORM- d) δ ppm 1.39 (d, *J*=6.8 Hz, 6 H), 2.15(s, 3 H), 2.57 (s, 3 H), 3.21 (s, 1H), 3.91 (s, 3 H), 6.77 (d, *J*=8.6 Hz, 1 H), 7.15 (s, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 11.28 (s, 1 H) , LC-MS (ESI): *m/z* 333 $(M + H)^+$

Compound **32**

To a solution of **31** (3.22 g, 9.7 mmol) in anhydrous *tert*-butanol (90 mL) was added solid potassium *tert*-butoxide (2.3 g, 20.4 mmol) and the reaction was heated to reflux under a nitrogen atmosphere for 18 h. The reaction was cooled to room temperature, the *tert*-butanol removed *in vacuo* and the residue partitioned between ethyl acetate and an equal volume of 0.15 N aqueous HCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried ($MgSO_4$) and concentrated *in vacuo* to afford **32** (3.03 g, 99% yield) as a brown solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.31 - 1.41 (m, 6 H), 2.42 (s, 3 H), 3.17 (m, 1 H), 3.97 (s, 3 H) 6.83 (br. s., 1 H), 7.02 (d, *J*=9.0 Hz, 1 H), 7.09 (s, 1 H), 8.24 (d, *J*=8.8 Hz, 1 H), 9.63 (br. s., 1 H). LC-MS (ESI): *m/z* 315.14 $(M + H)^+$.

Compound **34**

To a solution of (4*S*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-4-hydroxy-L-proline (1.80 g, 7.8 mmol), ethyl (1*R*,2*S*)-1-amino-2-ethenylcyclopropanecarboxylate hydrochloride (1.49 g, 7.8 mmol) and HATU (3.26 g, 8.6 mmol) in dichloromethane (80 mL) which had been cooled to 0 ^{0}C was added diisopropylethylamine (2.9 mL, 16.4 mmol) and the solution was stirred at 0 ^{0}C for 30 min and them room temperature for 5 h under a nitrogen atmosphere. The reaction was concentrated *in vacuo* and purified by silica gel chromatography eluting with 70-100% hexanes/ethyl acetate. The eluent was concentrated to about 200 mL and washed with 10% aqueous potassium carbonate solution (50 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to afford **34** as a white foam (2.72 g, 95% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.19 (m, 3 H) 1.24 (dd, *J*=9.33, 5.12 Hz, 1 H) 1.28 - 1.45 (m, 9 H) 1.54 - 1.67 (m, 1 H) 1.67 - 1.81 (m, 1 H) 2.05 - 2.20 (m, 1 H) 2.20 - 2.41 (m, 1 H) 3.05 - 3.22 (m, 1 H) 3.41 - 3.57 (m, 1 H) 3.91 - 4.09 (m, 3 H) 4.07 - 4.23 (m, 1 H) 4.98 - 5.19 (m, 2 H) 5.19 - 5.32 (m, 1 H) 5.40 - 5.82 (m, 1 H) 8.55 - 8.87 (m, 1 H). LC-MS (APCI): *m/z* 369.19 $(M + H)^+$.

Compound **36**

To a solution of **34** (2.70 g, 7.3 mmol) in dichloromethane (75 mL) was added 4N HCl in dioxane (18 mL) and the solution was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The solution was concentrated *in vacuo* and the residue suspended in ethyl acetate and concentrated *in vacuo.* The residue was suspended in dichloromethane (50 mL)

and HATU (3.05 g, 8.0 mmol) was added followed by a solution of (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-8-nonenoic acid **35** (2.0 g, 7.3 mmol) in dichloromethane (25 mL). The reaction was cooled to 0 ^{0}C and diisopropylethylamine (4.1 mL, 23.4 mmol) was added dropwise. The reaction was stirred under an atmosphere of nitrogen at 0 ^{0}C for 30 min and room temperature for 3.5 h. The reaction was concentrated *in vacuo* and purified by silica gel chromatography eluting with 50-100% hexanes/ethyl acetate to afford intermediate **36** as an oil (3.37 g, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.18 (m, 3 H), 1.18 - 1.51 (m, 17 H), 1.50 - 1.65 (m, 2 H), 1.70 (m, 1 H), 1.89 - 2.13 (m, 3 H), 2.18 - 2.40 (m, 1 H), 3.91 - 4.11 (m, 4 H), 4.10 - 4.30 (m, 3 H), 4.80 - 5.13 (m, 3 H), 5.15 - 5.27 (m, 1 H), 5.31 (m, 1 H), 5.62 (m, 1 H), 5.69 - 5.89 (m, 1 H), 6.65 - 7.06 (m, 1 H), 8.48 - 8.76 (m, 1 H). LC-MS (APCI): *m/z* 522.36 $(M + H)^+$.

Compound **37**

To a solution of **36** (3.37 g, 6.5 mmol) in anhydrous 1,2-dichloroethane (700 mL) was added Zhan 1B catalyst (950 mg, 1.3 mmol) and the reaction was evacuated and purged with nitrogen several times. The reaction was heated to 75 ^{0}C under a nitrogen atmosphere with mechanical stirring for 21 h. The reaction was concentrated *in vacuo* and purified by silica gel chromatography eluting with 50-100% hexanes/ethyl acetate to afford **37** as a brown solid (1.98 g, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.22 (m, 3 H), 1.22 - 1.44 (m, 12 H), 1.44 - 1.50 (m, 1 H), 1.51 - 1.59 (m, 1 H), 1.58 - 1.72 (m, 1 H,) 1.78 (br. s., 2 H), 2.00 - 2.16 (m, 1 H), 2.21 - 2.44 (m, 4 H), 2.53 - 2.61 (m, 1 H), 3.34 - 3.46 (m, 1 H), 3.84 - 4.06 (m, 4 H), 4.07 - 4.17 (m, 1 H), 4.23 (br. s., 2 H), 5.19 - 5.32 (m, 1 H), 5.43 - 5.63 (m, 2 H), 6.76 - 7.03 (m, 1 H), 8.81 (s, 1 H). LC-MS (APCI): *m/z* 494.34 $(M + H)^+$.

Compound **38**

A solution of **37** (1.87 g, 3.8 mmol), 8-methyl-2-[4-(1-methylethyl)-1,3-thiazol-2-yl]-7-(methyloxy)-4-quinolinol **32** (1.43 g, 4.5 mmol) , and triphenylphosphine (1.19 g, 4.5 mmol) in anhydrous toluene (60 mL) was concentrated *in vacuo* to remove trace water. The residue was dissolved in anhydrous THF (20 mL) and cooled to 0 ^{0}C. Diisopropylazodicarboxylate (0.9 mL, 4.5 mmol) was added dropwise and the ice bath removed, and the reaction was stirred at room temperature for 18 h under an atmosphere of nitrogen. The reaction was quenched with water (20 mL) and partitioned between an equal volume of ethyl acetate and water. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 20-70% hexanes/ethyl acetate. The residue obtained was dissolved in a mixture of THF (12 mL), water (6 mL) and methanol (6 mL) to which was added lithium hydroxide (530 mg, 23 mmol) and the reaction stirred at room temperature for 18 h. The reaction was treated with 1N HCl (25 mL) and partitioned between an equal volume of ethyl acetate and water. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo* to afford intermediate **38** as tan solid (1.95 g, 61% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (s, 6 H) 1.25 - 1.42 (m, 15 H) 1.41 - 1.55 (m, 2 H) 1.73 (br. s., 2 H) 2.10 - 2.26 (m, 2 H) 2.30 - 2.43 (m, 2 H) 2.58 (s, 3 H) 3.06 - 3.23 (m, 1 H) 3.84 - 3.92 (m, 2 H) 3.93 (s, 3 H) 4.42 - 4.50 (m, 1 H) 4.53 - 4.64 (m, 1 H) 5.13 - 5.33 (m, 1 H) 5.45 - 5.58 (m, 1 H) 5.64 (br. s., 2 H) 7.05 (br. s., 1 H) 7.26 - 7.36 (m, 1 H) 7.46 (s, 1 H) 7.51 (s, 1 H) 8.05 (m, 1 H) 8.65 (s, 1 H) 12.18 (br. s., 1 H). LC-MS (ESI): *m/z* 762.58 $(M + H)^+$.

Compound **40**

To a solution of **38** (1.75 g, 2.3 mmol) in anhydrous DMF (15 mL) was added N,N'-carbonyldiimidazole (410 mg, 2.5 mmol) and the reaction heated to 40 ^{0}C for 1 h under an atmosphere of nitrogen. Cyclopropanesulfonamide (450 mg, 3.7 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.37 mL, 2.5 mmol) were added and the reaction stirred at 40 ^{0}C for 18 h under an atmosphere of nitrogen. The reaction was diluted with ethyl acetate (150 mL) and washed with 0.1 N HCl (150 mL). The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo.* The residue was dissolved in dry dichloromethane (20 mL) and treated with 4N HCl in dioxane (5 mL) and the reaction stirred at room temperature for 3 h under an atmosphere of nitrogen, concentrated *in vacuo*, triturated with ethyl acetate and filtered to afford **40** (1.2 g, 60 % yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 1.10 (m, 2 H), 1.30 - 1.37 (m, 6 H), 1.37 - 1.52 (m, 4 H), 1.51 - 1.64 (m, 4 H), 1.63 - 1.93 (m, 4 H), 2.14 - 2.28 (m, 1 H), 2.59 (s, 3 H), 2.65 - 2.78 (m, 2 H), 2.89 - 2.97 (m, 2 H) 3.07 - 3.22 (m, 1 H), 3.97 (s, 3 H), 3.99 - 4.11 (m, 2 H), 4.19 - 4.36 (m, 2 H), 4.43 - 4.57 (m, 1 H), 5.11 - 5.24 (m, 1 H), 5.57 - 5.66 (m, 1 H), 5.72 (br. s., 1 H), 7.44 (d, *J*=9.4 Hz, 1 H), 7.49 (s, 1 H), 7.55 (s, 1 H), 8.06 (d, *J*=9.0 Hz, 1 H), 8.23 (br. s., 3 H), 9.10 (s, 1 H), 11.10 (s, 1 H). LC-MS (ESI): *m/z* 765.35 $(M + H)^+$.

Compound **6**

To a stirred solution of **40** (50 mg, 0.06 mmol) in THF (5mL) were added N,N-diisopropylethylamine (34 mg, 0.3 mmol) and triphosgene (12 mg, 0.04mmol) at 0°C. The mixture was stirred at room temperature for 6 hours, diethyl amine (22 mg, 0.3 mmol) added, and the reaction allowed to proceed for 4 hours. The crude product was purified by RP HPLC (C-18, 20 to 90% acetonotrile/water (0.1% formic acid)) to give **6** as white foam (36 mg, yield 69%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.08 (d, *J*=9.0 Hz, 1 H), 7.60 (s, 1 H), 6.89 - 7.30 (m, 2 H), 5.59 - 5.75 (m, 1 H), 5.55 (br. s., 1 H), 5.06 (m, 1 H), 4.55 - 4.75 (m, 2 H), 4.40 (m, 1 H), 4.09 (m, 1 H), 3.92 (s, 3 H), 3.03 - 3.23 (m, 5 H), 2.88 (m, 1 H), 2.71 - 2.81 (m, 1 H), 2.57 (s, 5 H), 2.38 (m, 1 H), 1.78 - 2.04 (m, 2 H), 1.70 (m, 1 H), 1.39 - 1.62 (m, 6 H), 1.15 - 1.40 (m, 9 H), 1.03 - 1.15 (m, 2 H), 0.97 (m, 7 H) LC-MS (ESI): *m/z* 865.7 $(M + H)^+$.

Compounds **3-26** were synthesized analogously to **6**, using respective amines in triphosgene-mediated urea formation. In case of **23-26,** the cyclopropyl-substituted P2* intermediate was synthesized analogously to **32**.

Compound **3**: ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.05 (d, *J*=6.0 Hz, 3 H), 7.58 (s, 1 H), 7.19 - 7.38 (m, 3 H), 5.58 - 5.79 (m, 1 H), 5.47 - 5.58 (m, 1 H), 4.96 - 5.14 (m, 1 H), 4.59 (s, 3 H), 4.29 - 4.49 (m, 2 H), 4.03 - 4.26 (m, 2 H), 3.93 (s, 4 H), 3.06 - 3.24 (m, 2 H), 2.81 - 3.00 (m, 2 H), 2.65 - 2.81 (m, 2 H), 2.29 - 2.49 (m, 2 H), 1.74 - 1.98 (m, 2 H), 1.63 - 1.74 (m, 1 H), 1.36 (m, 15 H), 1.07 (br. s., 2 H), 0.96 (m, 1 H). LC-MS (ESI): *m/z* 808.6 $(M + H)^+$.

Compound **4**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 0.99 (m, 1 H), 1.05 - 1.19 (m, 2 H), 1.29 - 1.37 (m, 2 H), 1.40 (d, *J*=6.5 Hz, 6 H), 1.44 - 1.55 (m, 5 H), 1.62 (m, 2 H), 1.84 (br. s., 1 H), 1.89 - 1.95 (m, 2 H), 2.24 (d, *J*=8.5 Hz, 1 H), 2.64 (s, 3 H), 2.69 - 2.76 (m, 2 H), 2.86 - 2.94 (m, 6 H), 3.16 - 3.28 (m, 1 H), 3.49 (s, 1 H), 3.74 (s, 1 H), 3.88 (s, 2 H), 4.05 - 4.13 (m, 1 H), 4.41 (br. s., 1 H), 4.55 (d, *J*=11.5 Hz, 1 H), 4.63 (s, 1 H), 4.88 (d, *J*=6.5 Hz, 1 H), 5.03 (d, *J*=9.0 Hz, 1 H), 5.51 (d, *J*=1.0 Hz, 1 H), 5.75 (d, *J*=9.3 Hz, 1 H), 7.04 (s, 1 H) 7.08 (d, *J*=9.29 Hz, 1 H) 7.47 (s, 1 H) 7.94 - 8.03 (m, 2 H) 10.46 (br. s., 1 H). LCMS= 836 (M + H).

Compound **5**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.87 - 1.00 (m, 2 H), 1.05 - 1.13 (m, 3 H), 1.11 - 1.23 (m, 3 H), 1.40 (d, *J*=7.0 Hz, 6 H), 1.44 - 1.58 (m, 6 H), 1.61 - 1.72 (m, 2 H), 1.89 - 1.96 (m, 2 H), 2.20 - 2.33 (m, 2 H), 2.55 - 2.64 (m, 1 H), 2.68 (s, 3 H), 2.70 - 2.76 (m, 2 H), 2.84 (s, 3 H), 2.88 - 2.96 (m, 1 H), 3.18 - 3.34 (m, 3 H), 3.94 (s, 3 H), 3.95 - 4.02 (m, 1 H), 4.05 - 4.13 (m, 1 H), 4.42 - 4.53 (m, 1 H), 4.57 - 4.72 (m, 2 H), 4.80 - 4.92 (m, 1 H), 4.96 - 5.09 (m, 1 H), 5.51 - 5.59 (m, 1 H), 5.68 - 5.83 (m, 1 H), 7.02 - 7.05 (m, 1 H), 7.10 - 7.16 (m, 1 H), 7.49 - 7.51 (m, 1 H), 8.03 - 8.09 (m, 1 H). LCMS =850 (M + H)

Compound **7**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.82 - 1.02 (m, 1 H), 1.06 - 1.22 (m, 2 H), 1.24 - 1.37 (m, 5 H), 1.40 (d, *J*=6.8 Hz, 6 H), 1.45 - 1.55 (m, 6 H), 1.91 - 1.98 (m, 2 H), 2.20 - 2.32 (m, 2 H), 2.52 - 2.62 (m, 1 H), 2.69 (s, 3 H), 2.71 - 2.77 (m, 2 H), 2.87 - 2.95 (m, 2 H), 3.08 - 3.28 (m, 3 H), 3.90 - 3.96 (m, 2 H), 3.97 (s, 3 H), 4.08 - 4.17 (m, 1 H), 4.46 - 4.66 (m, 2 H), 4.70 - 4.76 (m, 1 H), 4.97 - 5.06 (m, 1 H), 5.51 - 5.58 (m, 1 H), 5.69 - 5.80 (m, 1 H), 6.90 (br. s., 1 H), 7.04 (br. s., 1 H), 7.15 - 7.19 (m, 1 H), 7.52 (s, 1 H), 8.00 - 8.05 (m, 1 H), 8.10 (br. s., 1 H). LCMS 848 (M + H).

Compound **8**
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.03 (d, 1H), 7.73 (bs, 1H), 7.45 (s, 1H), 7.23 (d, 1H), 6.11 (bs, 1H), 5.70 (m, 1H), 5.53 (s, 1H), 5.05 (bs, 1H), 5.02 (m, 1H), 4.76 (m, 1H), 4.56 (m, 1H), 4.41 (s, 1H), 4.25-3.90 (m, 7H), 3.29 (m, 1H), 2.88 (m, 1H), 2.80-2.64 (m, 4H), 2.54 (s, 3H), 2.26 (m, 1H), 1.94-1.76 (m, 3H), 1.68-1.53 (m, 2H), 1.54-0.85 (m, 15H). MS calcd for $(C_{42}H_{51}N_7O_8S_2+H)^+$ = 884.3; MS found (ESI positive): $(M+H)^+$ = 884.3
MS calcd for $(C_{42}H_{51}N_7O_8S_2-H)^-$ = 882.3; MS found (ESI negative): $(M-H)^-$ = 882.3

Compound **9**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 1.00 (m, 1 H), 1.10 (br. s., 2 H), 1.27 - 1.36 (m, 2 H), 1.41 (d, *J*=7.0 Hz, 6 H), 1.44 - 1.55 (m, 6 H), 1.62 (m, 3 H), 1.92 - 1.99 (m, 2 H), 2.25 (s, 1 H), 2.20 - 2.31 (m, 1 H), 2.52 - 2.63 (m, 1 H), 2.69 (s, 3 H), 2.71 - 2.77 (m, 2 H), 2.92 (br. s., 1 H), 3.17 - 3.35 (m, 4 H), 3.63 (m, 4 H), 3.97 (s, 3 H), 4.07 - 4.18 (m, 1 H), 4.41 - 4.51 (m, 1 H), 4.62 (t, *J*=7.3 Hz, 2 H), 4.93 (br. s., 1 H), 5.03 (br. s., 1 H), 5.57 (d, *J*=1.3 Hz, 1 H), 5.69 - 5.81 (m, 1 H), 6.75 - 6.84 (m, 1 H), 7.06 (s, 1 H), 7.15 (d, *J*=9.0 Hz, 1 H), 7.56 (br. s., 1 H), 8.03 (d, *J*=9.0 Hz, 1 H), 10.20 - 10.30 (m, 1 H). LCMS 878 (M + H).

Compound **10**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.87 - 1.01 (m, 1 H), 1.06 - 1.24 (m, 2 H), 1.29 - 1.38 (m, 2 H), 1.42 (d, *J*=6.8 Hz, 6 H), 1.45 - 1.60 (m, 6 H), 1.66 - 1.77 (m, 1 H), 1.82 - 1.98 (m, 6 H), 2.27 (d, *J*=9.0 Hz, 1 H), 2.52 - 2.63 (m, 1 H), 2.67 (s, 3 H), 2.73 (br. s., 2 H), 2.92 (s, 1 H), 3.30 (m, 4 H), 3.23 - 3.35 (m, 3 H), 3.93 (s, 3 H), 4.09 - 4.23 (m, 1 H), 4.47 - 4.56 (m, 1 H), 4.62 (br. s., 2 H), 4.66 - 4.74 (m, 1 H), 4.97 - 5.07 (m, 1 H), 5.54 - 5.61 (m, 1 H), 5.69 - 5.83 (m, 1 H), 7.06 (s, 1 H), 7.09 - 7.17 (m, 1 H), 7.61 (br. s., 1 H), 8.05 (d, *J*=8.78 Hz, 1 H), 10.30 - 10.42 (m, 1 H). LCMS 862 (M + H).

Compound **11**
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.10 (d, 1H), 7.83 (s, 1H), 7.40 (s, 1H), 7.22 (m, 1H), 5.73 (m, 1H), 5.56 (s, 1H), 5.05 (m, 1H), 4.81 (m, 1H), 4.62 (m, 1H), 4.45 (m, 1H), 4.09 (m, 1H), 3.89 (s, 3H), 3.40-3.15 (m, 3H), 3.0-2.45 (m, 9H), 2.28 (m, 1H), 1.90 (m, 3H), 1.63 (m, 4H), 1.55-1.20 (m, 14H), 1.24-0.90 (m, 10H). MS calcd for $(C_{45}H_{59}N_7O_8S_2+H)^+$ = 890.3; MS found (ESI positive): $(M+H)^+$ = 890.3
MS calcd for $(C_{45}H_{59}N_7O_8S_2-H)^-$ = 888.3; MS found (ESI negative): $(M-H)^-$ = 888.3

Compound **12**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.85 - 1.00 (m, 1 H), 1.04 - 1.22 (m, 2 H), 1.33 (br. s., 2 H), 1.41 (m, 6 H), 1.45 - 1.71 (m, 15 H), 1.91 - 1.99 (m, 2 H), 2.25 (m, 1 H), 2.54 - 2.63 (m, 1 H), 2.67 (s, 3 H), 2.70 - 2.77 (m, 2 H), 2.92 (s, 1 H), 3.18 - 3.28 (m, 2 H), 3.32 (d, *J*=4.8, 2 H), 3.93 (s, 3 H), 4.07 - 4.17 (m, 1 H), 4.38 - 4.51 (m, 1 H), 4.62 (br. s., 2 H), 4.88 (br. s., 1 H), 4.98 - 5.09 (m, 1 H), 5.55 (br. s., 1 H), 5.69 - 5.82 (m, 1 H), 6.90 - 7.02 (m, 1 H), 7.05 (s, 1 H), 7.09 - 7.15 (m, 1 H), 7.48 - 7.61 (m, 1 H), 8.08 (d, *J*=9.0 Hz, 1 H), 10.29 - 10.37 (m, 1 H). LCMS 876 (M + H).

Compound **13**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 1.00 (m, 1 H), 1.05 - 1.21 (m, 2 H), 1.30 - 1.37 (m, 2 H), 1.41 (d, *J*=6.78 Hz, 6 H), 1.44 - 1.55 (m, 6 H), 1.55 - 1.72 (m, 4 H), 1.79 - 1.89 (m, 4 H), 1.92 (m, 2 H), 2.17 - 2.28 (m, 1 H), 2.65 (br. s., 4 H), 2.70 - 2.77 (m, 2 H), 2.85 - 3.03 (m, 2 H), 3.04 - 3.15 (m, 1 H), 3.17 - 3.30 (m, 1 H), 3.55 - 3.67 (m, 1 H), 3.75 (s, 1 H), 3.85 - 3.91 (m, 3 H), 4.05 - 4.09 (m, 1 H), 4.40 (br. s., 1 H), 4.54 - 4.68 (m, 2 H), 4.93 (d, *J*=6.0 Hz, 1 H), 4.96 - 5.06 (m, 1 H), 5.53 (br. s., 1 H), 5.70 - 5.82 (m, 1 H), 7.05 (s, 1 H), 7.08 (d, *J*=8.8 Hz, 1 H), 7.31 - 7.43 (m, 1 H), 7.44 - 7.56 (m, 1 H), 8.02 (d, *J*=9.3 Hz, 1 H), 10.44 (br. s., 1 H). LCMS 892 (M + H)

Compound **14**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.88 - 1.00 (m, 1 H), 1.06 - 1.23 (m, 2 H), 1.25 - 1.38 (m, 2 H), 1.41 (d, *J*=7.0, 6 H), 1.45 - 1.54 (m, 6 H), 1.55 - 1.69 (m, 6 H), 1.69 - 1.76 (m, 4 H), 1.94 (br. s., 2 H), 2.19 - 2.28 (m, 1 H), 2.55 - 2.63 (m, 1 H), 2.65 (s, 3 H), 2.71 - 2.76 (m, 2 H), 2.76 - 2.83 (m, 1 H), 2.88 - 2.98 (m, 1 H), 3.19 - 3.30 (m, 1 H), 3.49 (m, 2 H), 3.79 - 3.88 (m, 1 H), 3.90 (s, 4 H), 4.07 - 4.17 (m, 1 H), 4.37 - 4.45 (m, 1 H), 4.63 (br. s., 2 H), 4.86 - 4.95 (m, 1 H), 4.97 - 5.07 (m, 1 H), 5.51 - 5.58 (m, 1 H), 5.67 - 5.81 (m, 1 H), 7.05 (s, 1 H), 7.07 - 7.13 (m, 1 H), 7.56 (br. s., 1 H), 8.00 - 8.10 (m, 1 H), 10.34 - 10.46 (m, 1 H). LCMS 906 (M + H).

Compound **15**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 1.02 (m, 1 H), 1.08 - 1.22 (m, 2 H), 1.24 - 1.38 (m, 2 H), 1.38 - 1.45 (m, 6 H), 1.45 - 1.57 (m, 6 H), 1.58 - 1.88 (m, 6 H), 1.87 - 2.02 (m, 2 H), 2.14 (d, *J*=7.0 Hz, 2 H), 2.20 - 2.34 (m, 1 H), 2.62 (br. s., 3 H), 2.66 - 2.84 (m, 2 H), 2.92 (br. s., 1 H), 3.18 - 3.31 (m, 1 H), 3.86 (br. s., 4 H), 4.06 - 4.17 (m, 1 H), 4.32 - 4.44 (m, 1 H), 4.55 - 4.73 (m, 2 H), 4.90 - 5.10 (m, 3 H), 4.90 - 5.09 (m, 1 H), 5.47 - 5.60 (m, 1 H), 5.53 (br. s., 1 H), 5.68 - 5.89 (m, 1H), 5.69 - 5.87 (m, 1 H), 7.01 - 7.11 (m, 2 H), 7.06 (br. s., 1 H), 7.40 - 7.63 (m, 1 H), 7.43 - 7.61 (m, 1 H), 7.95 - 8.09 (m, 1 H), 7.98 - 8.07 (m, 1 H), 10.49 - 10.60 (m, 1 H). LCMS 932 (M + H).

Compound **17**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.89 - 1.02 (m, 1 H), 1.08 - 1.22 (m, 2 H), 1.24 - 1.38 (m, 2 H), 1.38 - 1.45 (m, 6 H), 1.45 - 1.57 (m, 6 H), 1.58 - 1.88 (m, 4 H), 1.87 - 2.02 (m, 2 H), 2.14 (m, 2 H), 2.20 - 2.34 (m, 1 H), 2.62 (br. s., 3 H), 2.66 - 2.84 (m, 2 H), 2.92 (br. s., 1 H), 3.18 - 3.31 (m, 1 H), 3.86 (br. s., 5 H), 4.06 - 4.17 (m, 1 H), 4.32 - 4.44 (m, 1 H), 4.55 - 4.73 (m, 2 H), 4.90 - 5.10 (m, 3 H), 4.90 - 5.09 (m,1 H), 5.47 - 5.60 (m, 1 H), 5.53 (br. s., 1H), 5.68 - 5.89 (m, 1 H), 5.69 - 5.87 (m, 1 H), 7.01 - 7.11 (m, 2 H), 7.06 (br. s., 1 H), 7.40 - 7.63 (m, 1 H), 7.43 - 7.61 (m, 1 H), 7.95 - 8.09 (m, 1 H), 7.98 - 8.07 (m, 1 H), 10.49 - 10.60 (m, 1 H), LCMS 902 (M + H).

Compound **18**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.90 (s, 2 H), 1.05 - 1.24 (m, 2 H), 1.26 - 1.38 (m, 2 H), 1.41 (m, 6 H), 1.44 - 1.76 (m, 7 H), 1.80 - 1.89 (m, 2 H), 1.95 (m, 2 H), 2.21 - 2.32 (m, 1 H), 2.56 - 2.65 (m, 1 H), 2.67 (s, 3 H), 2.72 - 2.99 (m, 6 H), 3.19 - 3.32 (m, 1 H), 3.89 (s, 3 H), 3.91 - 3.96 (m, 1 H), 4.04 - 4.19 (m, 3 H), 4.40 - 4.50 (m, 1 H), 4.65 (d, *J*=7.5 Hz, 2 H), 4.94 - 5.00 (m, 1 H), 5.04 (s, 1 H), 5.52 - 5.61 (m, 1 H), 5.67 - 5.83 (m, 1 H), 7.05 (s, 1 H), 7.12 (d, *J*=9.3 Hz, 1 H), 7.17 - 7.21 (m, 3 H), 7.23 (d, *J*=7.3 Hz, 1 H), 7.29 - 7.34 (m, 3 H), 7.52 - 7.61 (m, 1 H), 8.09 (d, *J*=9.0 Hz, 1 H), 10.29 - 10.45 (m, 1 H). LCMS 904 (M + H).

Compound **19**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.88 - 1.00 (m, 1 H), 1.17 (m, 4 H), 1.39 - 1.46 (m, 6 H), 1.46 - 1.57 (m, 6 H), 1.87 - 2.01 (m, 3 H), 2.27 (m, 1 H), 2.37 - 2.54 (m, 3 H), 2.64 (s, 6 H), 2.69 (s, 3 H), 2.75 (m, 2 H), 2.87 - 2.97 (m, 1 H), 3.20 - 3.30 (m, 1 H), 3.46 - 3.58 (m, 2 H), 3.62 (m, 1 H), 3.97 (s, 3 H), 4.07 - 4.16 (m, 1 H), 4.46 (br. s., 1 H), 4.63 (s, 1 H), 4.68 - 4.75 (m, 1 H), 4.97 (d, *J*=7.5 Hz, 1 H), 5.02 (d, *J*=9.5 Hz, 1 H), 5.56 (br. s., 1 H), 5.75 (d, *J*=9.3 Hz, 1 H), 6.79 - 6.90 (m, 1 H), 7.05 (s, 1 H), 7.15 (d, *J*=9.0 Hz, 1 H), 7.53 - 7.60 (m, 1 H), 8.03 (s, 1 H), 8.07 (d, *J*=9.3 Hz, 1 H), 10.25 (br. s., 1 H). LCMS =906 (M + H).

Compound **20**
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.88 - 1.04 (m, 1 H), 1.07 - 1.24 (m, 2 H), 1.31 (m, 2 H), 1.38 - 1.47 (m, 5 H), 1.46 - 1.58 (m, 5 H), 1.58 - 1.73 (m, 2 H), 1.75 - 1.86 (m, 2 H), 1.97 (m, 2 H), 2.23 (m, 1 H), 2.53 - 2.65 (m, 1 H), 2.68 (s, 3 H), 2.72 - 2.97 (m, 8 H), 3.19 - 3.33 (m, 1 H), 3.64 (br. s., 3 H), 3.97 (s, 3 H), 4.02 - 4.14 (m, 1 H), 4.31 - 4.40 (m, 1 H), 4.61 - 4.74 (m, 2 H), 5.03 (br. s., 1 H), 5.32 (br. s., 1 H), 5.57 (br. s., 1 H), 5.74 (br. s., 1 H), 6.77 - 6.90 (m, 1 H), 7.07 (br. s., 1 H), 7.18 (d, *J*=9.3, 1 H), 7.47 - 7.60 (m, 1 H), 7.95 (d, *J*=8.5, 1 H), 8.01 (s, 1 H), 10.18 - 10.27 (m, 1 H). LCMS 926 (M + H).

Compound **21**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.88 - 0.99 (m, 1 H) 1.04 - 1.24 (m, 2 H), 1.33 (br. s., 2 H), 1.41 (d, *J*=7.0, 6 H), 1.44 - 1.65 (m, 17 H), 1.77 - 1.87 (m, 2 H), 1.90 - 1.99 (m, 2 H), 2.25 (d, *J*=8.5 Hz, 2 H), 2.55 - 2.63 (m, 1 H), 2.67 (s, 3 H), 2.71 - 2.79 (m, 2 H), 2.92 (s, 1 H), 3.18 - 3.28 (m, 3 H), 3.32 (m, 3 H), 3.93 (s, 3 H), 4.06 - 4.19 (m, 1 H), 4.39 - 4.49 (m, 1 H), 4.58 - 4.71 (m, 2 H), 4.88 (br. s., 1 H), 4.99 - 5.08 (m, 1 H), 5.55 (br. s., 1 H), 5.69 - 5.83 (m, 1 H), 6.90 - 7.01 (m, 1 H), 7.05 (s, 1 H), 7.09 - 7.18 (m, 1 H), 7.54 (br. s., 1 H), 8.08 (d, *J*=9.0`, 1 H), 10.25 - 10.40 (m, 1 H). LCMS 945 (M + H).

Compound **22**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.86 - 0.99 (m, 1 H), 1.04 - 1.21 (m, 2 H), 1.26 (d, *J*=6.0 Hz, 2 H), 1.40 (d, *J*=7.0 Hz, 6 H), 1.42 - 1.55 (m, 8 H), 1.57 - 1.77 (m, 6 H), 1.77 - 1.95 (m, 6 H), 2.23 (m, 1 H), 2.53 - 2.63 (m, 1 H), 2.66 (s, 4 H), 2.68 - 2.83 (m, 5 H), 2.85 - 2.96 (m, 1 H), 3.22 (m, 1 H), 3.46 (br. s., 4 H), 3.93 (s, 3 H), 4.08 (m, 1 H), 4.32 - 4.42 (m, 1 H), 4.61 - 4.72 (m, 1 H), 4.98 (t, *J*=9.4 Hz, 1 H), 5.51 (br. s., 2 H), 5.69 (m, 1 H), 7.03 (s, 1 H), 7.12 (d, *J*=9.0 Hz, 1 H), 7.48 (s, 1 H), 7.62 (br. s., 1 H), 8.02 (d, *J*=9.0 Hz, 1 H), 8.30 (s, 1 H). LCMS 945 (M + H).

Compound **23**

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.85 - 0.95 (m, 6 H), 0.94 - 1.14 (m, 6 H), 1.23 (br. s., 2 H), 1.36 (br. s., 6 H), 1.50 - 1.60 (m, 2 H), 1.69 (br. s., 1 H), 1.87 (br. s., 1 H), 2.12 - 2.27 (m, 1 H), 2.29 - 2.46 (m, 3 H), 2.55 (s, 3 H), 2.57 (s, 3 H), 2.61 - 2.77 (m, 2 H), 2.81 - 2.98 (m, 1 H), 3.84 - 3.91 (m, 1 H), 3.95 (s, 3 H), 4.02 - 4.24 (m, 2 H), 4.37 (m, 1 H), 4.76 - 4.88 (m, 1 H), 5.12 (m, 1 H), 5.54 - 5.71 (m, 2 H), 6.24 (d, *J*=6.6, 1 H), 7.27 (d, *J*=9.4, 1 H), 7.42 (s, 1 H), 7.50 (s, 1 H), 8.19 (d, *J*=9.2, 1 H), 8.79 (s, 1 H), 11.10 (s, 1 H). HRMS for $C_{43}H_{56}N_7O_8S_2$ $(M + H)^+$ calc: 862.3632, found: 862.3625.

Compound **24**

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 - 1.12 (m, 16 H), 1.17 - 1.30 (m, 2 H), 1.39 (br. s., 5 H), 1.55 (d, *J*=8.8, 2 H), 1.70 (br. s., 1 H), 1.88 (br. s., 1 H), 2.11 - 2.24 (m, 1 H), 2.28 - 2.46 (m, 2 H), 2.57 (s, 3 H), 2.61 - 2.77 (m, 2 H), 2.83 - 2.94 (m, 1 H), 2.94 - 3.11 (m, 2 H), 3.91 (d, *J*=2.7, 2 H) ,3.94 (s, 3 H), 4.06 (m, 1 H), 4.18 (br. s., 1 H), 4.39 (m, 1 H), 4.69 - 4.91 (m, 1 H), 5.05 - 5.20 (m, 1 H), 5.62 (br. s., 2 H), 6.11 (d, *J*=6.6, 1 H), 7.26 (d, *J*=9.4, 1 H), 7.42 (s, 1 H), 7.50 (s, 1 H), 8.14 (d, *J*=9.2, 1 H), 8.8 (br. s., 1 H), 11.11 (s, 1 H). HRMS for $C_{44}H_{58}N_7O_8S_2$ $(M + H)^+$ calc: 876.3788, found: 876.3783.

Compound **25**

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 1.14 (m, 10 H) 1.14 - 1.29 (m, 6 H), 1.39 (br. s., 6 H), 1.50 - 1.63 (m, 2 H), 1.70 (br. s., 1 H), 1.77 - 1.90 (m, 1 H), 2.12 - 2.28 (m, 1 H), 2.26 - 2.46 (m, 3 H), 2.57 (s, 3 H), 2.67 (s, 4 H), 2.91 (qd, 1 H), 3.82 - 4.00 (m, 5 H), 4.07 (br. s., 1 H), 4.40 (dd, *J*=10.0, 6.7, 1 H), 4.78 - 4.90 (m, 1 H), 5.04 - 5.20 (m, 1 H), 5.49 - 5.69 (m, 2 H), 6.15 - 6.27 (m, 1 H), 7.26 (d, *J*=9.2, 1H), 7.39 - 7.46 (m, 1 H), 7.50 (s, 1 H), 8.07 (d, *J*=9.2, 1 H), 8.86 (br. s., 1 H), 11.10 (s, 1 H). HRMS for $C_{44}H_{58}N_7O_8S_2$ $(M + H)^+$ calc: 876.3788, found: 876.3782.

Compound **26**

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 - 1.14 (m, 16 H), 1.14 - 1.31 (m, 3 H), 1.38 (br. s., 6 H), 1.56 (d, *J*=8.8, 2 H), 1.71 (br. s., 1 H), 1.83 (br. s., 1 H), 2.14 - 2.27 (m, 1 H) 2.28 - 2.47 (m, 3 H), 2.57 (s, 3 H), 2.61 - 2.77 (m, 2 H), 2.90 (br. s., 1 H), 3.49 - 3.68 (m, 2 H), 3.73 - 3.99 (m, 5 H), 4.11 (br. s., 1 H), 4.42 (m, 1 H), 4.80 - 4.94 (m, 1 H) 5.04 - 5.19 (m, 1 H), 5.62 (br. s., 2 H), 6.00 (br. s., 1 H), 7.26 (d, *J*=9.4, 1 H), 7.41 (s, 1 H) 7.49 (s, 1 H), 8.07 (d, *J*=9.2, 1 H), 8.87 (br. s., 1 H), 11.11 (br. s., 1 H). HRMS for $C_{45}H_{60}N_7O_8S_2$ $(M + H)^+$ calc: 890.3945, found: 890.3939.