Supporting Information

Heterodimerization of dibenzodiazepinone-type muscarinic acetylcholine receptor ligands leads to increased M_2R affinity and selectivity

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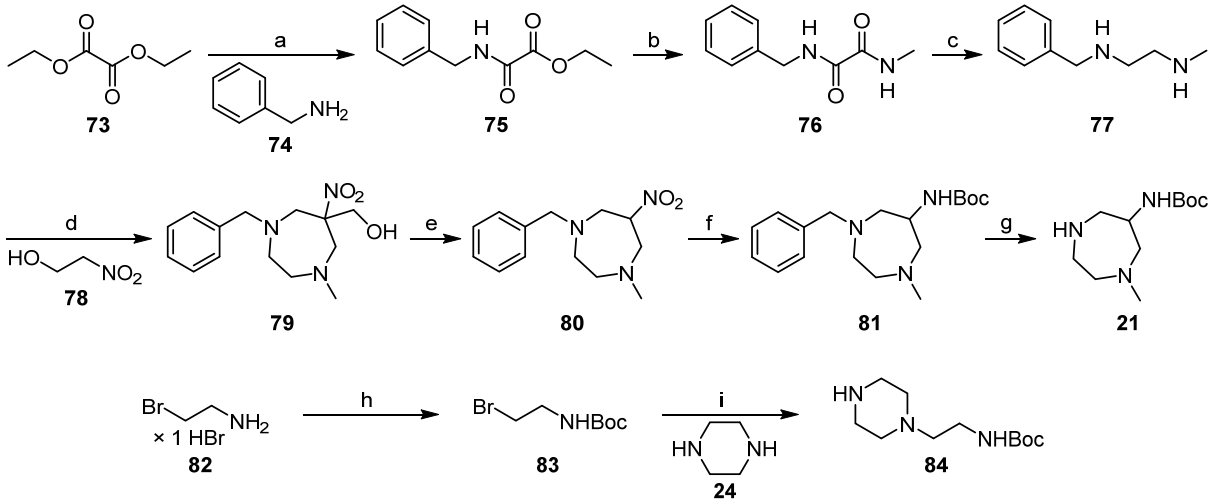
1. Preparation of the intermediates 20, 21, 23, 26, 30, 32, 33, 36, 37, 40, 42, 45, 47, 49, 53, 55-57, 62, 65, 68 and 71

The synthesis of diazepane derivative **21** started with diethyl oxalate (**73**), which was treated with one equivalent of benzylamine (**74**) to give the N-benzylated ethyl oxamate **75** (SI Scheme 1). The subsequent reaction with methylamine converted compound **75** to the unsymmetrically *N*,*N*'-disubstituted oxamide **76**. Reduction of **76**, using lithium aluminum hydride, resulted in compound **77** as reported (SI Scheme 1).[1] Homopiperazine **79** was obtained from **77** by nitro-Mannich reaction using nitroethanol and paraformaldehyde. Treatment of compound **79** with an excess of potassium *tert*-butanolate in methanol resulted in compound **80**.[2-4] Reduction of the nitro group in **80** to an amino group using Raney nickel, and subsequent N-Boc-protection gave compound **81**. Debenzylation of **81** applying palladium-catalyzed hydrogenolysis yielded compound **21** (SI Scheme 1).

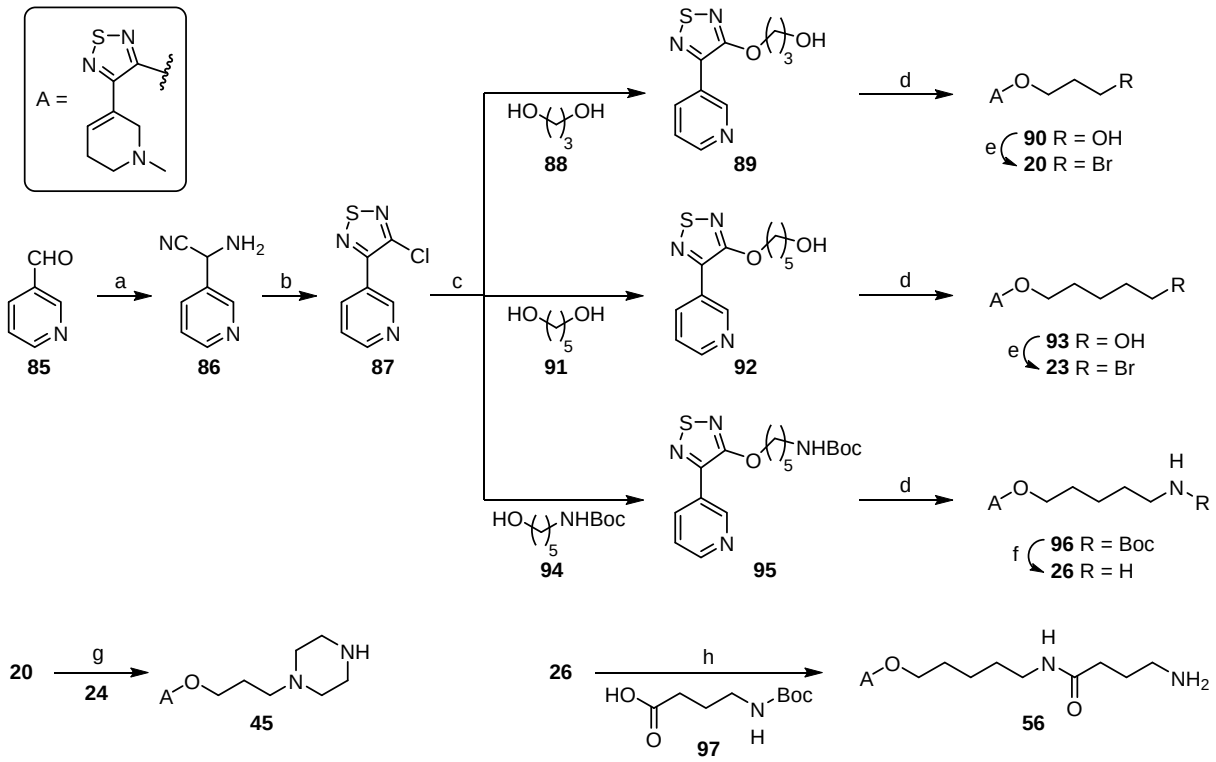


SI Scheme 1. Synthesis of diazepane derivative **21** and piperazine derivative **84**. Reagents and conditions: (a) chloroform, reflux, overnight, 65%; (b) methylamine (2 M in THF), EtOH, rt, 8 h, 97%; (c) $LiAlH_4$, THF, 0 °C/reflux, overnight, 60%; (d) paraformaldehyde, toluene/EtOH 1:1 v/v, reflux, 6 h, 88%; (e) potassium *tert*-butoxide, MeOH, 40 °C, 30 min, 67%; (f) (1) hydrogen, Raney-Ni, EtOH, rt, overnight; (2) di-*tert*-butyl dicarbonate, chloroform, rt, overnight, 53%; (g) 10% Pd/C, hydrogen, THF/H_2O 1:4 v/v, rt, overnight, 77%; (h) di-*tert*-butyl dicarbonate, triethylamine, CH_2Cl_2, rt, overnight, 80%; (i) K_2CO_3, MeCN, reflux, 3 h, 91%.

The preparation of the piperazine derivative **84** started with commercially available 2-bromoethan-1-amine hydrobromide (**82**), which was Boc-protected to obtain compound **83** (SI Scheme 1). This intermediate was treated with an excess of piperazine (**24**) to afford

building block **84** (SI Scheme 1).

For the synthesis of the bromo- or amino-functionalized xanomeline derivatives **20**, **23** and **26** aldehyde **85** was converted to **86** according to a described protocol of a slightly modified Strecker synthesis (SI Scheme 2).[5,6] The intermediate **86** was cyclized with disulfur dichloride in DMF to give the thiadiazole derivative **87**. Treatment of **87** with the alcoholates generated from the alcohols **88**, **91** or **94**, using sodium hydride, afforded compounds **89**, **92** and **95**, respectively (SI Scheme 2). **89**, **92** and **95** were quaternized by treatment with an excess of methyl iodide in acetone followed by reduction with sodium borohydride yielding the N-methylated tetrahydropyridine derivatives **90**, **93** and **96** (SI Scheme 2).

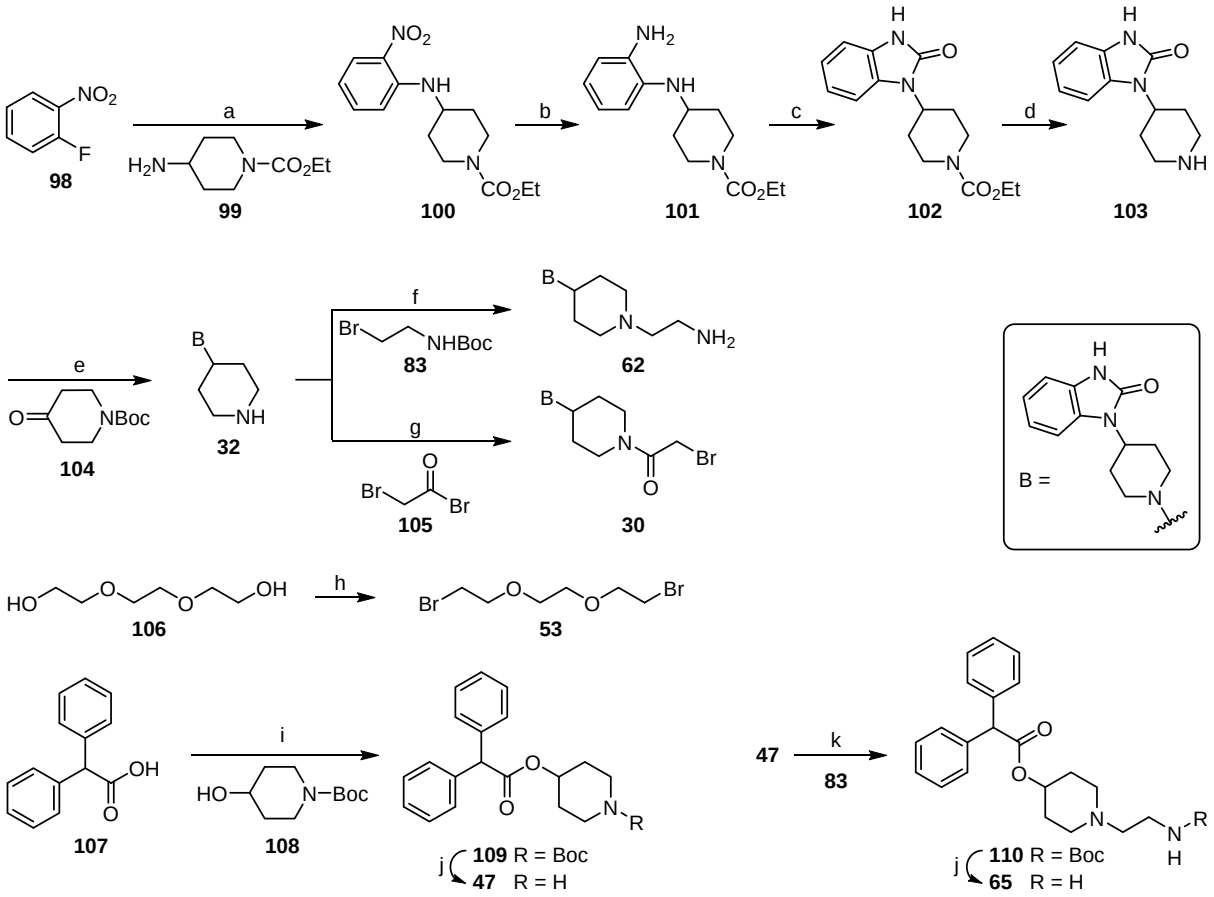


SI Scheme 2. Synthesis of the xanomeline derivatives **20**, **23**, **26**, **45** and **56**. Reagents and conditions: (a) (1) KCN, H_2O, AcOH, 5 °C/rt, 2 h; (2) NH_4Cl, 25% aq NH_3, rt, 20 h, 66%; (b) S_2Cl_2, DMF, 5-10 °C, 45 min, 69%; (c) NaH, THF, reflux, 2-8 h, 52% (**89**), 48% (**92**), 27% (**95**); (d) (1) methyl iodide, acetone, rt, 24-36 h; (2) $NaBH_4$, MeOH, 0 °C/rt, overnight, 33% (**90**), 88% (**93**), 79% (**96**); (e) CBr_4, PPh_3, CH_2Cl_2, −5 °C/rt, 24 h, 50% (**20**), 82% (**23**); (f) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 56%; (g) K_2CO_3, MeCN, reflux, 2 h, 66%; (h) (1) TBTU, HOBt, DIPEA, DMF, rt/60 °C, 3 h; (2) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 60%.

In order to convert the alcohols **90** and **93** to the respective bromides (**20** and **23**), an Appel reaction[7] was applied using tetrabromomethane and triphenylphosphine in dichloromethane. Cleavage of the Boc group in **96** using trifluoroacetic acid afforded compound **26**, which was isolated as the free base (SI Scheme 2). Alkylation of piperazine using bromide **20** gave the xanomeline derivative **45**, and acylation of **26** by N-Boc protected γ-aminobutyric acid (**97**), using the coupling reagents TBTU and HOBt, gave xanomeline derivative **56** after subsequent removal of the Boc group (SI Scheme 2).

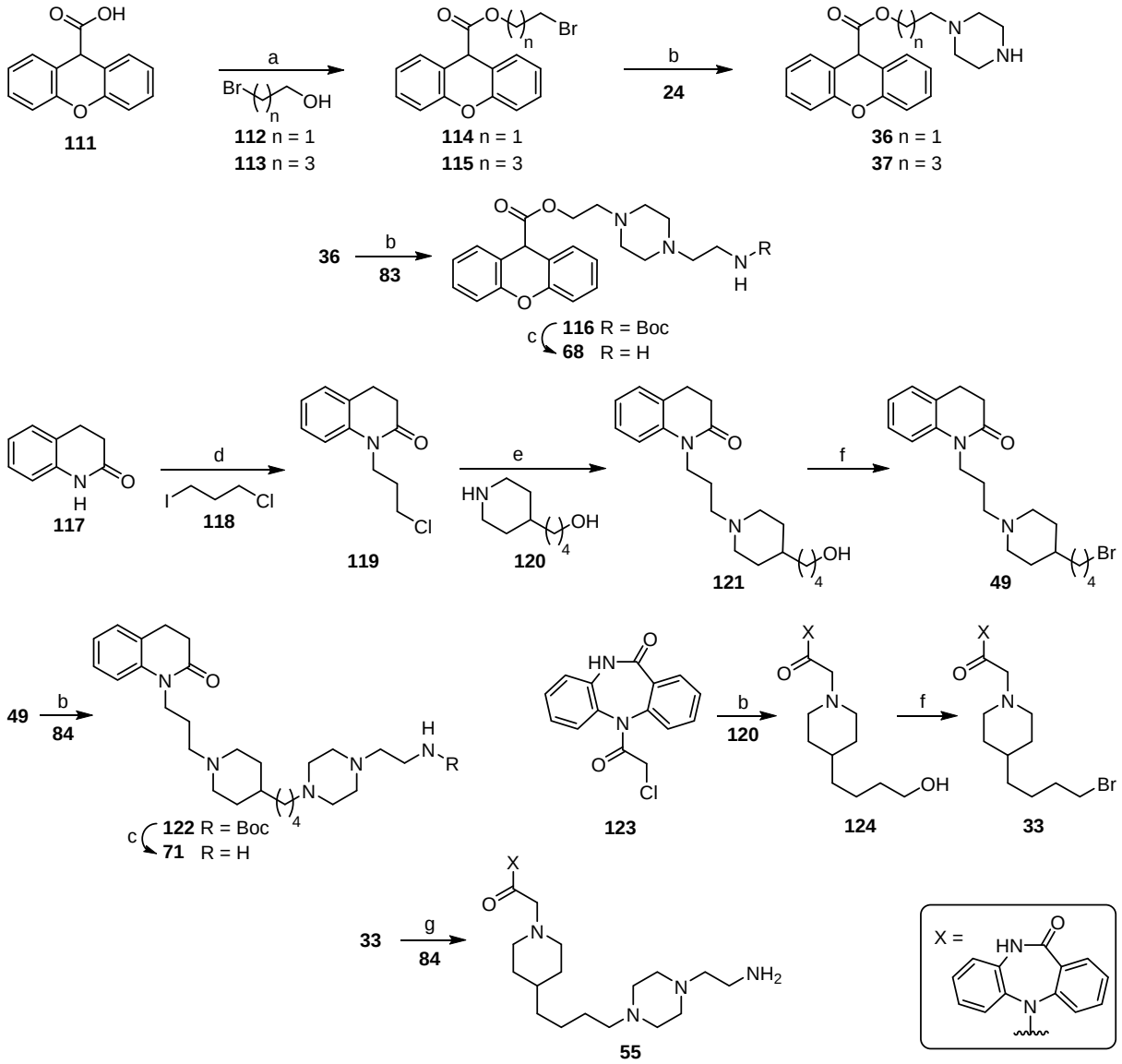
The synthesis of the TBPB derivatives **30**, **32** and **62** is outlined in SI Scheme 3. Beginning with commercially available 1-fluoro-2-nitrobenzene (**98**), an aromatic nucleophilic substitution with ethyl 4-aminopiperidine-1-carboxylate (**99**) under microwave irradiation yielded nitroaniline **100**, which was reduced by palladium-catalyzed hydrogenation to provide o-phenylendiamine derivative **101** (SI Scheme 3). The benzimidazolinone formation from **101** using triphosgene afforded **102**. Subsequent removal of the ethyl carbamate group by basic hydrolysis gave **103**.[8] Reductive amination of piperidinone **104** with the secondary amine **103**, using sodium cyanoborohydride, followed by removal of the Boc group afforded compound **32** (SI Scheme 3). Alkylation of **32**, using bromide **83**, and subsequent Boc-deprotection yielded **62**. Acylation of **32** using 2-bromoacetyl bromide (**105**) afforded amide **30**.

Bromide **53**, used for the preparation of the homodimeric ligand **54** (*cf*. Scheme 2, main article), was prepared from alcohol **106** by treatment with 48% HBr at 120 °C (SI Scheme 3). The synthesis of the building blocks **47** and **65** started from diphenylacetic acid (**107**) and Boc protected piperidin-4-ol (**108**). Unlike a reported procedure for the synthesis of the ester **109**, which was based on the conversion of carboxylic acid **107** into the corresponding acid chloride followed by treatment with alcohol **108**,[9] compound **109** was formed from **107** and **108** using DCC and 4-dimethylaminopyridine as coupling reagents. Treatment of **109** with TFA gave **47** as the bisdesmethyl analogue of 4-DAMP. Alkylation of **47** using bromide **83** afforded compound **110**, which was converted to **65** by removal of the Boc group (SI Scheme 3).



SI Scheme3. Synthesis of the TBPB derivatives **30**, **32**, **62**, bromide **53** and the 4-DAMP derivatives **47** and **65**. Reagents and conditions: (a) K_2CO_3, NaI, DMF, microwave 180 °C, 10 min, 72%; (b) 10% Pd/C, hydrogen, rt, overnight, 89%; (c) triphosgene, $NaHCO_3$, CH_2Cl_2, 0 °C/rt, 2 h, 73%; (d) 10% aq NaOH, reflux, 5 h, 81%; (e) (1) $NaBH_3CN$, acetic acid, MeOH, 0 °C/rt, overnight; (2) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 75%; (f) (1) K_2CO_3, MeCN, reflux, 8 h; (2) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 86%; (g) pyridine, chloroform, 0 °C/rt, overnight, 91%; (h) 48% aq HBr, 120 °C, 2.5 h, 6%; (i) DCC, DMAP, CH_2Cl_2, 0 °C/rt, overnight, 97%; (j) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 56% (**47**), 83% (**65**); (k) K_2CO_3, MeCN, reflux, 3 h, 67%.

The synthesis of the propantheline (**4**) building blocks **36**, **37** and **68**, which were used for the synthesis of the 'DIBA-propantheline'-type heterodimeric ligands (**38**, **39**, **69**, **70**), is shown in SI Scheme 4. Xanthene-9-carboxylic acid (**111**) was condensed with 2-bromoethan-1-ol (**112**) or 4-bromobutan-1-ol (**113**) to yield compounds **114** and **115**, respectively. Treatment of **114** and **115** with an excess of piperazine (**24**) afforded the alkylation products **36** and **37** in moderate yield (SI Scheme 4). Alkylation of **36** with bromide **83** gave compound **116**, which was converted to the propantheline-derived compound **68** by Boc-deprotection using TFA.

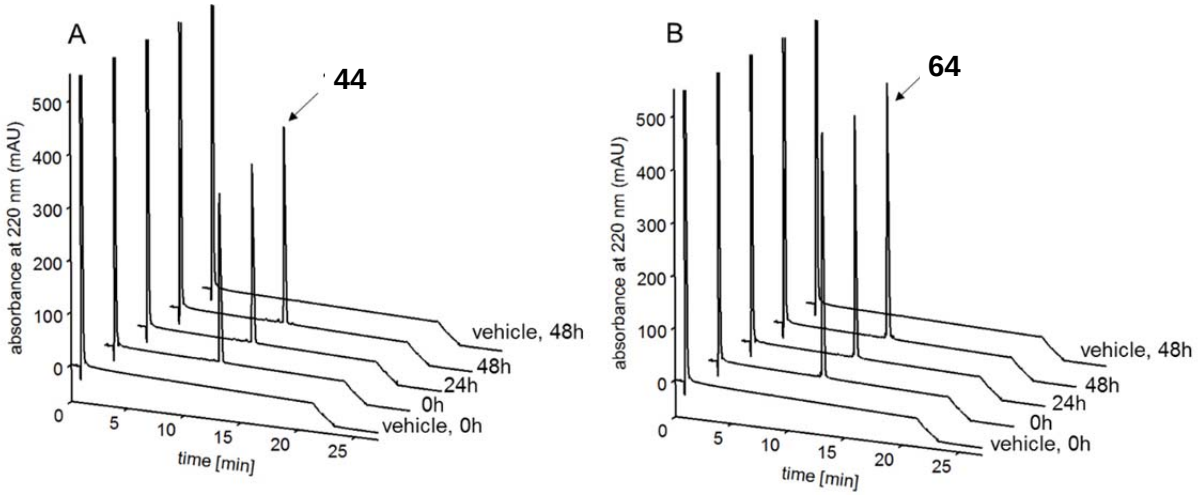


SI Scheme4. Synthesis of the dibenzodiazepinone derivatives **33** and **55**, the propantheline derivatives **36**, **37** and **68**, and the 77-LH-28-1 derivatives **49** and **71**. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C/rt, overnight, 68% (**114**), 56% (**115**); (b) K_2CO_3, MeCN, reflux, 1.5 h, 2 h, 8 h or 16 h, 59% (**36**), 46% (**37**), 57% (**116**), 62% (**122**), 62% (**124**); (c) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h or overnight, 88% (**68**), 97% (**71**); (d) Cs_2CO_3, MeCN, 50 °C, 12 h, 69%; (e) K_2CO_3, NaI, MeCN, 50 °C, 24 h, 53%; (f) CBr_4, PPh_3, CH_2Cl_2, −5°C/rt, overnight, 78% (**33**), 31% (**49**); (g) (1) K_2CO_3, MeCN, reflux, 3 h; (2) TFA/CH_2Cl_2 1:4 v/v, rt, 8 h, 48%.

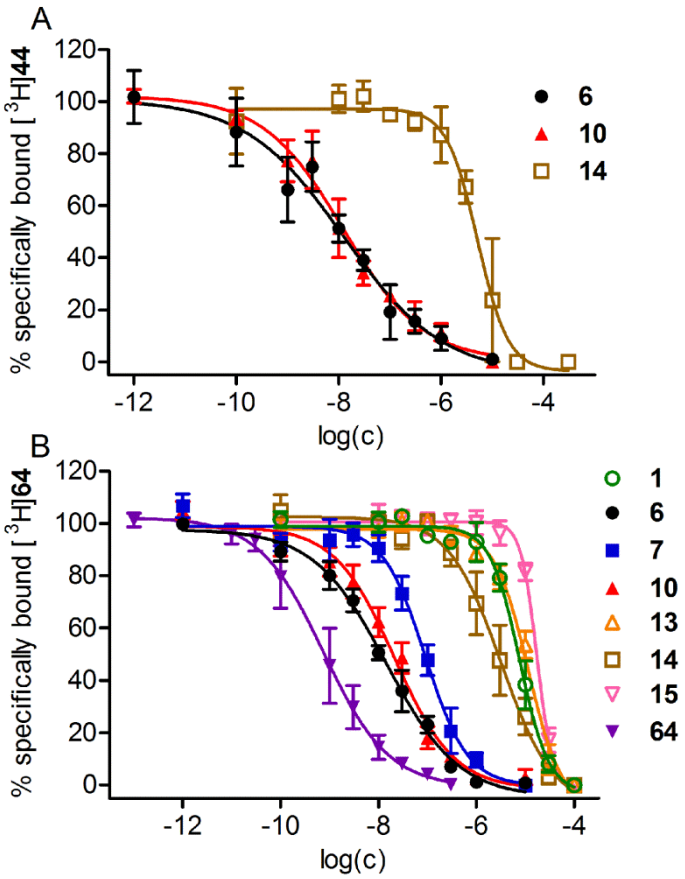
The synthesis of the 77-LH-28-1-derived intermediates **49** and **71** started with 3,4-dihydro-2(1*H*)-quinolinone (**117**), which was treated with 1-chloro-3-iodopropane (**118**) in the presence of caesium carbonate in acetonitrile to give compound **119** according to a described procedure (SI Scheme 4).[10] N-Alkylation of piperidine **120** using chloride **119** in the presence of potassium carbonate and sodium iodide yielded compound **121**. The alcohol

121 was converted to the corresponding bromide (**49**) under Appel reaction conditions using tetrabromomethane and triphenylphosphine. Compound **49** was treated with piperazine **84** to afford the alkylation product **122**, which was Boc-deprotected to yield the 77-LH-28-1 derivative **71** (SI Scheme 4). N-Alkylation of piperidine **120** using chloride **123** gave the dibenzodiazepinone derivative **124**, which was converted via Appel reaction to bromide **33** (SI Scheme 4), a building block used for the synthesis of various heterodimeric ligands (see Scheme 3, main article). Alkylation of piperazine derivative **84** using bromide **33**, followed by Boc-deprotection with TFA, resulted in building block **55**.

2. SI Figures 1 and 2



SI Figure 1. HPLC analysis of **44** (A) and **64** (B) after incubation in PBS (pH 7.4) at 23 °C for up to 48 h. **44** and **64** showed no decomposition. HPLC conditions see methods (section 4.3).



SI Figure 2. A: Concentration-dependent effects of the orthosteric MR ligand **1**, the dualsteric MR ligand **10** and the allosteric M_2R modulator **14** on M_2R equilibrium binding of [^{3}H]**44** (c = 2.0 nM, K_d = 1.0 nM) determined at CHO-hM_2R cell homogenates at 22 °C. B: Concentration-dependent effects of various reported orthosteric (**1**, **6**), dualsteric (**7**, **10**), allosteric (**13-15**) MR ligands and **64** on M_2R equilibrium binding of [^{3}H]**64** (c = 0.3 nM, K_d = 0.081 nM) determined at CHO-hM_2R cell homogenates at 22 °C. Data represent mean values ± SEM from at least three independent experiments (performed in triplicate).

3. Experimental protocols for the synthesis and analytical data of compounds 20-23, 25, 26-39, 43-57, 58-72, 75-77, 79-81, 83, 84, 86, 87, 89, 90, 92, 93, 95-97, 100-104, 108-110, 114-116, 119, 121, 122 and 124

3-(3-Bromopropoxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (20)[7]

Compound **90** (400 mg, 1.57 mmol) and PPh_3 (1.2 g, 4.57 mmol) were dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to -5 °C under an atmosphere of argon. A solution of CBr_4 (3.4 g, 10.25 mmol) in CH_2Cl_2 (20 mL) was slowly dropped into the stirred mixture, thereby keeping the temperature of the mixture below 5 °C. After completed addition, stirring

was continued at room temperature for 24 h. The solvent was removed under reduced pressure to give a brown residue, which was subjected to flash chromatography (eluent: light petroleum/acetone/25% aq NH_3 85:15:1 v/v/v) to afford compound **20** as a brown oil (300 mg, 50%). R_f = 0.6 (light petroleum/acetone/25% aq NH_3 65:35:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.26-2.36 (m, 2H), 2.41-2.49 (m, 5H), 2.58 (t, *J* 5.8 Hz, 2H), 3.45 (dd, *J* 4.4, 2.5 Hz, 2H), 3.71 (t, *J* 6.4 Hz, 2H), 4.61 (t, *J* 6.0, 2H), 6.91-7.08 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 26.5, 29.4, 31.8, 45.8, 51.1, 54.9, 68.4, 128.4, 129.1, 146.7, 161.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{11}H_{17}BrN_3OS]^+$ 318.0270, found: 318.0271. $C_{11}H_{16}BrN_3OS$ (318.23).

***tert*-Butyl (1-methyl-1,4-diazepan-6-yl)carbamate (21)**

Compound **81** (200 mg, 0.626 mmol) was suspended in THF/H_2O (1:4 v/v) (5 mL) followed by the addition of 10% Pd/C (40 mg). The mixture was stirred in an autoclave (1 L) under an atmosphere of hydrogen at 10 atm at room temperature overnight. Filtered the reaction mixture through a pad of celite, the filtrate was concentrated under reduced pressure to give compound **21** as colorless oil (110 mg, 77%), which was used without further purification. R_f = 0.2 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D_6]DMSO): δ (ppm) 1.36 (s, 9H), 2.27 (s, 3H), 2.35-2.49 (m, 4H), 2.58-2.69 (m, 2H), 2.59-2.68 (m, 2H), 2.85-2.91 (m, 1H), 3.49-3.66 (m, 1H), 6.58 (brs, 1H). ^{13}C-NMR (75 MHz, [D_6]DMSO): δ (ppm) 28.3, 47.2, 49.1, 50.7, 52.7, 60.4, 61.3, 77.7, 154.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{11}H_{24}N_3O_2]^+$ 230.1863, found: 230.1868. $C_{11}H_{23}N_3O_2$ (229.32).

1-Methyl-4-(3-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propyl)-1,4-diazepan-6-amine tetrakis(hydrotrifluoroacetate) (22)

Compound **20** (490 mg, 1.52 mmol) and compound **21** (354 mg, 1.54 mmol) were suspended in MeCN (20 mL) followed by the addition of potassium carbonate (427 mg, 3.09 mmol). The mixture was stirred at 110 ^{o}C under microwave irradiation for 30 min. Solids were separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The combined filtrate and washings were concentrated under reduced pressure yielding a yellow oily residue, which was dissolved in CH_2Cl_2 (10 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2

(3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure yielded the Boc-protected intermediate as yellow oily residue, which was dissolved in CH_2Cl_2/TFA (4:1 v/v) (5 mL). The mixture was stirred at room temperature overnight. CH_2Cl_2 (10 mL) was added, the volatiles were evaporated and the residue was subjected to purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:38, t_R = 11 min), which afforded compound **22** as white fluffy solid (830 mg, 66%). ^{1}H-NMR (400 MHz, [D$_4$]MeOH): δ (ppm) 2.09-2.16 (m, 2H), 2.66-2.86 (m, 2H), 2.93 (t, *J* 7.3 Hz, 2H), 2.97 (s, 3H), 2.96-3.02 (m, 1H), 3.05 (s, 3H), 3.09-3.14 (m, 1H), 3.15-3.29 (m, 2H), 3.32-3.39 (m, 1H), 3.47 (t, *J* 5.5 Hz, 2H), 3.52-3.68 (m, 3H), 3.83-3.93 (m, 1H), 4.00-4.05 (m, 1H), 4.49-4.54 (m, 1H), 4.57 (t, *J* 6.4 Hz, 2H), 7.22 (t, *J* 4.1 Hz, 1H). ^{13}C-NMR (100 MHz, [D$_4$]MeOH): δ (ppm) 23.8, 27.1, 43.3, 46.5, 48.7, 50.9, 51.7, 53.1, 55.3, 56.2, 57.8, 58.8, 70.2, 114.6 (TFA), 116.3 (TFA), 117.4 (TFA), 119.3 (TFA), 125.3, 128.3, 145.6, 162.1 (TFA), 162.4 (TFA), 163.8 (TFA), 163.1 (TFA), 163.6. RP-HPLC (220 nm): 97% (t_R = 10.7 min, k = 2.7). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{17}H_{31}N_6OS]^+$ 367.2275, found: 367.2273. $C_{17}H_{30}N_6OS \cdot C_8H_4F_{12}O_8$ (366.53 + 456.09).

3-((5-Bromopentyl)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (23)

Compound **93** (850 mg, 3.0 mmol) and PPh_3 (2.4 g, 9.15 mmol) were dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to -5 °C under an atmosphere of argon. A solution of CBr_4 (6.5 g, 19.59 mmol) in CH_2Cl_2 (15 mL) was slowly dropped into the stirred mixture, thereby keeping the temperature of the mixture below 5 °C. Stirring was continued at room temperature for 24 h. The solvent was removed under reduced pressure and the residue subjected to column chromatography (eluent: light petroleum/acetone/25% aq NH_3 65:35:1 v/v/v) to afford compound **23** as brown oil (740 mg, 71%). R_f = 0.4 (light petroleum/acetone/25% aq NH_3 65:35:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.56-1.71 (m, 2H), 1.81-2.01 (m, 4H), 2.39-2.50 (m, 5H), 2.57 (t, *J* 5.5 Hz, 2H), 3.36-3.52 (m, 4H), 4.46 (t, *J* 6.4 Hz, 2H), 6.97-7.13 (m, 1H). ^{13}C-NMR (75 MHz, CDCl3): δ (ppm) 24.7, 26.7, 28.0, 32.2, 33.5, 45.9, 51.2, 55.0, 70.4, 128.5, 129.3, 146.8, 162.3. HRMS (ESI): m/z

$[M+H]^+$ calcd. for $[C_{13}H_{21}BrN_3OS]^+$ 346.0583, found: 346.0585. $C_{13}H_{20}BrN_3OS$ (346.29).

1,4-Bis(5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)piperazine (25)

Compound **23** (730 mg, 2.11 mmol), potassium carbonate (193 mg, 1.39 mmol), and piperazine (60 mg, 0.70 mmol) were added to MeCN (5 mL). The mixture was stirred at 110 ^oC under microwave irradiation for 30 min, and cooled to room temperature. Insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure to give the crude product, which was dissolved in CH_2Cl_2 (10 mL) followed by washing with H_2O (3 x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:3:1 v/v/v) to afford compound **25** as white solid (96 mg, 22%), m.p. 41-42 ^oC. R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.31-1.61 (m, 8H), 1.71-1.90 (m, 4H), 2.26-2.33 (m, 5H), 2.34-2.38 (m, 4H), 2.39 (s, 6H), 2.41-2.52 (m, 11H), 3.38 (dd, *J* 4.3, 2.4 Hz, 4H), 4.38 (t, *J* 6.5 Hz, 4H), 6.85-7.15 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 24.0, 26.5, 26.6, 28.8, 45.9, 51.1, 53.1, 55.0, 58.5, 70.7, 128.3, 129.3, 146.8, 162.5. RP-HPLC (220 nm): 97% (t_R = 13.9 min, k = 3.8). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{30}H_{49}N_8O_2S_2]^+$ 617.3414, found: 617.3407. $C_{30}H_{48}N_8O_2S_2$ (616.89).

5-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentan-1-amine (26)

Compound **96** (50 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (4 mL) and TFA (1 mL) was added. The mixture was stirred at room temperature overnight and cooled to 0 °C followed by the addition of 25% aq NH_3 to adjust the pH to 10. The product was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to afford compound **26** as colorless oil (20 mg, 56%), which was used without further purification. R_f = 0.3 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.34-1.55 (m, 4H), 1.73-1.87 (m, 4H), 2.32-2.43 (m, 5H), 2.50 (t, *J* 5.5 Hz, 2H), 2.66 (t, *J* 6.7 Hz, 2H), 3.36-3.38 (m, 2H), 4.38 (t, *J* 6.6 Hz, 2H), 6.92-7.05 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.3, 26.6, 28.7, 33.1, 41.9, 45.9, 51.2, 55.0, 70.7,

128.4, 129.3, 146.7, 162.3. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{13}H_{23}N_4OS]^+$ 283.1587, found: 283.1586. $C_{13}H_{22}N_4OS$ (282.41).

N[1],*N*[8]-Bis(5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl) oxy)pentyl)octanediamide (27)

To a cooled (0 °C) solution of compound **26** (300 mg, 1.06 mmol) and triethylamine (322 mg, 3.18 mmol) in abs. THF (2 mL) was added dropwise octanedioyl dichloride (76 µL, 0.43 mmol) dissolved in abs. THF (1 mL) under an atmosphere of argon. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was dissolved in ethyl acetate (5 mL) followed by washing with water. The aqueous phase was treated with ethyl acetate (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:3:1 v/v/v) to afford compound **27** as white solid (118 mg, 39%), m.p. 55-57 °C. R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.26-1.37 (m, 4H), 1.48-1.65 (m, 10H), 1.78-1.96 (m, 6H), 2.14 (t, *J* 7.5 Hz, 4H), 2.40-2.50 (m, 10H), 2.57-2.61 (m, 4H), 3.23-3.29 (m, 4H), 3.42-3.49 (m, 4H), 4.44 (t, *J* 6.5 Hz, 4H), 5.58 (brs, 2H), 7.02-7.05 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.4, 25.8, 26.6, 28.5, 28.7, 29.4, 36.6, 39.3, 45.9, 51.2, 55.0, 70.6, 128.4, 129.3, 146.8, 162.4, 173.0. RP-HPLC (220 nm): 96% (t_R = 18.1 min, *k* = 5.3). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{34}H_{55}N_8O_4S_2]^+$ 703.3782, found: 703.3786. $C_{34}H_{54}N_8O_4S_2$ (702.98).

N[1],*N*[10]-Bis(5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)decanediamide (28)

To a cooled (0 °C) solution of compound **26** (400 mg, 1.42 mmol) and triethylamine (430 mg, 4.25 mmol) in abs. THF (5 mL) was added dropwise decanedioyl dichloride (92 µL, 0.57 mmol) dissolved in abs. THF (1 mL) under an atmosphere of argon. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was dissolved in ethyl acetate (5 mL) followed by washing with brine. The aqueous phase was treated with ethyl acetate (3 × 10 mL) and the organic extracts were collected. All organic phases were

combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:3:1 v/v/v) to afford compound **28** as white solid (270 mg, 65%), m.p. 45-49 °C. R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25-1.33 (m, 8H), 1.41-1.63 (m, 10H), 1.81-1.94 (m, 4H), 2.06 -2.23 (m, 4H), 2.12-2.17 (m, 4H), 2.46-2.53 (m, 8H), 2.63-2.67 (m, 4H), 3.27 (dd, *J* 13, 6.8 Hz, 4H), 3.49-3.54 (m, 4H), 4.44 (t, *J* 6.5 Hz, 4H), 5.54 (brs, 2H), 7.03-7.07 (m, 2H). ^{13}C-NMR (75 MHz, CDCl3): δ (ppm) 23.4, 25.7, 26.6, 28.5, 29.1, 29.2, 29.4, 36.8, 39.3, 45.9, 51.2, 55.0, 70.6, 128.4, 129.3, 146.8, 162.4, 173.1. RP-HPLC (220 nm): 98% (t_R = 19.5 min, k = 5.8). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{36}H_{59}N_8O_4S_2]^+$ 731.4095, found: 731.4097. $C_{36}H_{58}N_8O_4S_2$ (731.0320).

N^1,N^4-Bis(5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)terephthalamide (29)

To a solution of terephthalic acid (117 mg, 0.71 mmol) in DMF (3 mL) were added EDC (271 mg, 1.41 mmol), HOBt (216 mg, 1.41 mmol) and DIPEA (183 mg, 1.42 mmol) and the mixture was stirred at room temperature for 30 min. Compound **26** (400 mg, 1.42 mmol) in DMF (2 mL) was added and stirring was continued at room temperature overnight. H_2O (10 mL) was added followed by extraction with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 95:5:1 v/v/v) to afford compound **29** as white solid (130 mg, 26%), m.p. 50-53 °C. R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 95:5:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.52-1.61 (m, 4H), 1.67-1.78 (m, 4H), 1.83-1.96 (m, 4H), 2.42-2.52 (m, 4H), 2.62 (s, 6H), 2.78 (t, *J* 5.8 Hz, 4H), 3.46-3.54 (m, 4H), 3.65-3.70 (m, 4H), 4.47 (t, *J* 6.2 Hz, 4H), 6.94 (brs, 2H), 7.01-7.09 (m, 2H), 7.85 (s, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.6, 25.0, 28.5, 29.3, 39.9, 44.9, 50.7, 53.8, 70.9, 127.0, 127.3, 127.8, 137.2, 145.7, 162.4, 166.9. RP-HPLC (220 nm): 96% (t_R = 18.3 min, k = 5.4). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{34}H_{47}N_8O_4S_2]^+$ 695.3156, found: 695.3158. $C_{34}H_{46}N_8O_4S_2$ (694.91).

1-(1'-(2-Bromoacetyl)-[1,4'-bipiperidin]-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (30)

To a solution of compound **32** (630 mg, 2.09 mmol) in chloroform (50 mL) was added pyridine (762 μL, 9.45 mmol) and the mixture was cooled in an ice bath. 2-Bromoacetyl bromide (compound **105**) (820 μL, 9.45 mmol) was added dropwise and stirring was continued at room temperature overnight. H_2O (10 mL) was added and the phases were separated. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent was evaporated to obtain the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to yield compound **30** as colorless oil (800 mg, 91%). R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 95:5:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.35-1.73 (m, 2H), 1.78-1.92 (m, 2H), 2.01 (t, *J* 11 Hz, 2H), 2.36-2.61 (m, 4H), 2.72 (t, *J* 13 Hz, 2H), 3.14-3.22 (m, 3H), 3.99-4.10 (m, 3H), 4.26-4.33 (m, 1H), 4.55-4.57 (m, 1H), 7.02-7.09 (m, 3H), 7.33-7.48 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 28.8, 29.5, 29.9, 42.9, 47.4, 52.0, 62.7, 110.6, 110.8, 122.2, 122.6, 129.7, 130.4, 156.3, 167.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{19}H_{26}BrN_4O_2]^+$ 421.1234, found: 421.1244. $C_{19}H_{25}BrN_4O_2$ (421.34).

1-(1'-(2-(6-Amino-4-methyl-1,4-diazepan-1-yl)acetyl)-[1,4'-bipiperidin]-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one tetrakis(hydrotrifluoroacetate) (31)

Potassium carbonate (53 mg, 0.38 mmol) was added to a suspension of compound **30** (80 mg, 0.19 mmol) and compound **21** (48 mg, 0.21 mmol) in MeCN (2 mL). The mixture was stirred at 110 °C under microwave irradiation for 30 min and cooled to room temperature. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The combined filtrate and washings were concentrated under reduced pressure yielding a yellow residue, which was dissolved in CH_2Cl_2 (5 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the Boc-protected intermediate (50 mg), which was dissolved in CH_2Cl_2/TFA (4:1 v/v) (5 mL). The mixture was stirred at room temperature for 8 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex

XB-C18 5 μm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:38, t_R = 12 min) afforded compound **31** as white fluffy solid (35 mg, 20%). ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.63-1.90 (m, 2H), 2.09-2.11 (m, 2H), 2.21-2.22 (m, 2H), 2.68-2.72 (m, 1H), 2.82-2.91 (m, 2H), 3.02 (s, 3H), 3.05-3.21 (m, 4H), 3.25-3.29 (m, 1H), 3.32-3.37 (m, 2H), 3.47-3.58 (m, 3H), 3.59-3.66 (m, 2H), 3.65-3.74 (m, 4H), 3.77-3.82 (m, 1H), 3.96-3.97 (m, 1H), 4.57-4.63 (m, 1H), 4.72-4.75 (m, 1H), 7.03-7.09 (m, 3H), 7.32 (d, *J* 3.4 Hz, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 27.3, 27.5, 27.9, 41.6, 43.9, 46.7, 50.2, 50.4, 51.9, 58.5, 58.6, 60.6, 64.7, 110.0, 110.7, 115.1 (TFA), 117.0 (TFA), 118.9 (TFA), 120.9 (TFA), 122.4, 122.9, 129.7, 130.1, 156.1, 162.3 (TFA), 162.6 (TFA), 162.8 (TFA), 163.0 (TFA), 170.8. RP-HPLC (220 nm): 98% (t_R = 11.6 min, k = 3.0). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{25}H_{40}N_7O_2]^+$ 470.3238, found: 470.3241. $C_{25}H_{39}N_7O_2 \cdot C_8H_4F_{12}O_8$ (469.63 + 456.09).

1-([1,4'-Bipiperidin]-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (32)

Compound **104** (1.6 g, 8.03 mmol) and acetic acid (0.16 mL, 2.74 mmol) were added to a stirred and cooled (0 °C) solution of compound **103** (1.2 g, 5.53 mmol) in MeOH (50 mL) and the mixture was stirred at 0 °C for 15 min. Sodium cyanoborohydride (688 mg, 10.95 mmol) was added and the stirred mixture was allowed to warm up to room temperature, followed by stirring overnight. 5% aq $KHCO_3$ (16 mL) was added prior to extraction with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the product was purified by flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:2:1 to 95:4:1 v/v/v; R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v) to yield the Boc-protected intermediate *tert*-butyl 4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)-[1,4'-bipiperidine]-1'-carboxylate (1.15 g), which was dissolved in TFA/CH_2Cl_2 (1:4 v/v) (15 mL) followed by stirring of the mixture at room temperature overnight. The pH was carefully adjusted to 11 by adding 25% aq NH_3. The two phases were separated and the aqueous phase was treated with CH_2Cl_2 (5 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash chromatography with (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v) to afford compound **32** as white solid (620 mg, 75%), m.p. 180-182 ^{o}C. R_f= 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm)

1.63-1.88 (m, 4H), 2.05-2.09 (m, 2H), 2.36-2.58 (m, 4H), 2.65-2.74 (m, 1H), 2.84-3.02 (m, 2H), 3.12-3.15 (m, 2H), 3.34-3.42 (m, 2H), 4.24-4.33 (m, 1H), 6.95-7.17 (m, 3H), 7.33-7.39 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 27.1, 29.9, 45.1, 49.9, 52.0, 60.7, 110.5, 110.6, 122.2, 122.5, 129.6, 130.3, 156.2. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{17}H_{25}N_4O]^+$ 301.2023, found: 301.2025. $C_{17}H_{24}N_4O$ (300.41).

5-(2-(4-(4-Bromobutyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (33)

Under an atmosphere of argon compound **124** (200 mg, 0.49 mmol) and PPh_3 (386 mg, 1.47 mmol) were dissolved in CH_2Cl_2 (5 mL) in a three-necked round bottom flask and the solution was cooled to -5 °C. A solution of CBr_4 (1.06 g, 3.20 mmol) in CH_2Cl_2 (10 mL) was added dropwise, thereby keeping the temperature of the mixture below 5 °C. Stirring was continued at room temperature overnight. The solvent was evaporated and the residue subjected to column chromatography to column chromatography (eluent: light petroleum/acetone/25% aq NH_3 83:16:1 v/v/v) to afford compound **33** as white solid (180 mg, 78%). R_f = 0.5 (light petroleum/acetone/25% aq NH_3 66:33:1 v/v/v), m.p. 68-70 °C. Ratio of configurational isomers evident in the NMR spectra: ca 1.2:1. ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.03-1.27 (m, 5H), 1.31-1.46 (m, 2H), 1.46-1.62 (m, 2H), 1.73-1.82 (m, 2H), 1.82-2.03 (m, 2H), 2.47-2.64 (m, 1H), 2.77-2.85 (m, 1H), 3.01 (d, *J* 18 Hz, 0.55H), 3.10-3.18 (m, 1H), 3.21 (d, *J* 18 Hz, 0.45H), 3.41 (t, *J* 6.7 Hz, 2H), 7.17-7.40 (m, 3H), 7.40-7.59 (m, 3H), 7.61-7.66 (m, 1H), 7.84-7.90 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 26.3, 32.8, 34.1, 34.4, 36.3, 36.6, 54.8, 54.9, 61.0, 122.9, 126.6, 126.9, 127.8, 128.9, 129.0, 129.5, 129.9, 130.1, 130.6, 133.0, 132.1, 134.3, 134.7, 135.9, 143.9, 169.3, 171.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{29}BrN_3O_2]^+$ 470.1438, found: 470.1437. $C_{24}H_{28}BrN_3O_2$ (470.41).

5-(2-(4-(4-(4-(2-Oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)-[1,4'-bipiperidin]-1'-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one tris(hydrotrifluoroacetate) (34)

Compound **34** was prepared from **33** (80 mg, 0.17 mmol), potassium carbonate (71 mg, 0.51

mmol) and **32** (56 mg, 0.19 mmol) according to the procedure for the synthesis of **46**, but the reflux period was 3 h instead of 6 h. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 20:80-62:38, t_R = 11 min) afforded **34** as white fluffy solid (100 mg, 57%). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.24-1.45 (m, 6H), 1.44-1.58 (m, 4H), 1.69-1.77 (m, 2H), 1.88-1.98 (m, 3H), 2.09-2.26 (m, 3H), 2.44-2.48 (m, 1H), 2.80-2.99 (m, 3H), 3.02-3.14 (m, 4H), 3.34-3.48 (m, 2H), 3.54 (t, *J* 6.3 Hz, 1H), 3.62-3.82 (m, 6H), 4.38-4.40 (m, 0.4H), 4.42-4.45 (m, 0.6H), 4.58-4.67(m, 1H), 7.02-7.07 (m, 2H), 7.24-7.34 (m, 2H), 7.34-7.38 (m, 1H), 7.44-7.55 (m, 3H), 7.60-7.78 (m, 3H), 7.89-7.91 (m, 0.6H), 7.96-7.98 (m, 0.4H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 25.8, 27.8, 28.5, 29.8, 32.9, 36.4, 37.4, 52.0, 54.1, 54.9, 59.5, 61.0, 61.3, 62.8, 68.8, 110.6, 110.8, 122.2, 122.5, 123.0, 126.6, 127.0, 127.7, 128.9, 129.0, 129.4, 129.6, 129.9, 130.2, 130.5, 131.1, 132.1, 132.2, 134.3, 134.7, 136.0, 136.9, 143.7, 143.8, 156.2, 169.1, 169.3, 171.2, 171.4. RP-HPLC (220 nm): 99% (t_R = 14.9 min, k = 4.2). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{41}H_{52}N_7O_3]^+$ 690.4126, found: 690.4128. $C_{41}H_{51}N_7O_3 \cdot C_6H_3F_9O_6$ (689.91 + 342.07).

5-(2-(4-(4-(6-Amino-4-methyl-1,4-diazepan-1-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one tetrakis(hydrotrifluoroacetate) (35)

Potassium carbonate (70 mg, 0.51 mmol) was added to a solution of compound **33** (120 mg, 0.26 mmol) and compound **21** (65 mg, 0.28 mmol) in MeCN (5 mL), and the mixture was kept under reflux for 3 h. Insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to yield a yellow oil, which was dissolved in CH_2Cl_2 (5 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the Boc-protected intermediate as yellow oil (110 mg), which was dissolved in CH_2Cl_2/TFA/H_2O (10:10:1 v/v/v) (5 mL). The mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:38, t_R = 14 min) afforded compound **35** as white fluffy solid (30 mg, 12%). Ratio of configurational isomers evident in the NMR

spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.27-1.37 (m, 4H), 1.40-1.55 (m, 3H), 1.56-1.66 (m, 2H), 1.87-1.95 (m, 2H), 2.83 (s, 3H), 2.88 (t, *J* 7.9 Hz, 2H), 2.90-2.96 (m, 1H), 3.01-3.05 (m, 1H), 3.08-3.15 (m, 1H), 3.21-3.24 (m, 1H), 3.26-3.28 (m, 2H), 3.32-3.39 (m, 3H), 3.43-3.48 (m, 2H), 3.69-3.79 (m, 2H), 3.82-3.86 (m, 1H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 7.23-7.29 (m, 1H), 7.31-7.40 (m, 2H), 7.45-7.52 (m, 2H), 7.60-7.75 (m, 2H), 7.89 (d, *J* 8.0 Hz, 0.6H), 7.96 (d, *J* 8.0 Hz, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 24.8, 26.7, 30.4, 34.3, 36.4, 46.5, 52.7, 54.9, 55.3, 55.6, 56.4, 57.9, 58.0, 58.2, 59.6, 123.1, 123.7, 126.9, 127.5, 127.9, 128.5, 128.9, 129.4, 130.1, 130.5, 130.9, 131.2, 131.7, 131.9, 132.3, 132.9, 133.4, 134.6, 134.9, 135.5, 135.7, 136.9, 140.9, 142.7, 164.9, 165.5, 168.9, 168.8. RP-HPLC (220 nm): 99% (t_R = 13.7 min, *k* = 3.8). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{30}H_{43}N_6O_2$]$^+$ 519.3442, found: 519.3441. $C_{30}H_{42}N_6O_2 \cdot C_8H_4F_{12}O_8$ (518.71 + 456.09).

2-(Piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate (36)

Compound **114** (500 mg, 1.50 mmol), piperazine (1.04 g, 12.08 mmol) and potassium carbonate (416 mg, 3.01 mmol) were added to MeCN (18 mL) and the mixture was refluxed overnight. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The combined filtrate and washings were concentrated under reduced pressure yielding a yellow oil, which was dissolved in CH_2Cl_2 (10 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 15 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 96:3:1 v/v/v) to yield compound **36** as yellow solid (300 mg, 59%). R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v), m.p. 77-79 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36-2.54 (m, 6H), 2.82-2.92 (m, 4H), 4.61 (brs, 1H), 4.13 (t, *J* 10 Hz, 2H), 5.00 (s, 1H), 7.05-7.17 (m, 4H), 7.27-7.35 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 44.2, 45.6, 50.9, 56.3, 62.7, 117.0, 118.4, 123.3, 128.9, 129.2, 151.4, 171.5. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{20}H_{23}N_2O_3$]$^+$ 339.1703, found: 339.1707. $C_{20}H_{22}N_2O_3$ (338.41).

4-(Piperazin-1-yl)butyl 9*H*-xanthene-9-carboxylate (37)

Compound **115** (1.0 g, 2.77 mmol), piperazine (1.9 g, 22.07 mmol) and potassium carbonate (1.2 g, 8.70 mmol) were added to MeCN (50 mL) and the stirred mixture was kept under reflux for 1.5 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 20 mL). The combined filtrate and washings were concentrated under reduced pressure to give a yellow oil, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 30 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 94:5:1 v/v/v) to afford compound **37** as colorless oil (470 mg, 46%). R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.19-1.42 (m, 2H), 1.43-1.60 (m, 2H), 2.12-2.26 (m, 4H), 2.26-2.32 (m, 2H), 2.36 (brs, 1H), 2.81-2.94 (m, 4H), 4.04 (t, *J* 6.3 Hz, 2H), 4.98 (s, 1H), 7.00-7.17 (m, 4H), 7.23-7.35 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 22.6, 26.5, 45.6, 45.8, 54.1, 58.4, 65.3, 116.9, 118.5, 123.3, 128.9, 129.1, 151.3, 171.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{27}N_2O_3]^+$ 367.2016, found: 367.2027. $C_{22}H_{26}N_2O_3$ (366.46).

2-(4-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate tris(hydrotrifluoroacetate) (38)

Compound **38** was prepared from **33** (80 mg, 0.17 mmol) and **36** (58 mg, 0.17 mmol) according to the procedure for the synthesis of **46**, but the reflux period was 3 h instead of 6 h. Potassium carbonate: 94 mg, 0.68 mmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 20:80-64:36, t_R = 16 min) afforded compound **38** as white fluffy solid (93 mg, 51%). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 1.25-1.42 (m, 4H), 1.44-1.56 (m, 3H), 1.63-1.70 (m, 2H), 1.87-2.04 (m, 2H), 2.57-2.75 (m, 5H), 2.86-3.19 (m, 8H), 3.33-3.61 (m, 2H), 3.71-3.84 (m, 2H), 4.20 (t, *J* 5.1 Hz, 2H), 4.41 (d, *J* 12 Hz, 0.6H), 4.47 (d, *J* 12 Hz, 0.4H), 5.10 (s, 1H), 7.07-7.17 (m, 4H), 7/25-7.46 (m, 7H), 7.47-7.55 (m, 2H), 7.61-7.79 (m, 2H), 7.89-7.92 (m, 0.6 H), 7.96-7.98 (m, 0.4H). ^{13}C-NMR

(75 MHz, [D_4]MeOH): δ (ppm) 19.1, 24.6, 25.1, 30.5, 34.4, 36.2, 46.6, 50.9, 42.7, 55.3, 56.7, 57.7, 58.1, 63.3, 117.9, 120.2, 122.2, 123.7, 124.6, 126.9, 127.6, 127.9, 128.6, 128.9, 130.2, 130.4, 130.5, 130.9, 131.8, 132.4, 133.5, 134.6, 136.5, 137.1, 152.9, 162.8, 165.0, 165.5, 172.9. RP-HPLC (220 nm): 99% (t_R = 20.3 min, k = 6.1). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{44}H_{50}N_5O_5$]$^+$ 728.3806, found: 728.3805. $C_{44}H_{49}N_5O_5 \cdot C_6H_3F_9O_6$ (727.91 + 342.07).

4-(4-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)butyl 9*H*-xanthene-9-carboxylate (39)

Compound **39** was prepared from **33** (50 mg, 0.11 mmol) and **37** (39 mg, 0.11 mmol) according to the procedure for the synthesis of **46**, but the reflux period was 5 h instead of 6 h. Potassium carbonate: 59 mg, 0.43 mmol. Purification by column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) yielded compound **39** as white solid (32 mg, 38%), m.p. 43-45 ^{o}C. R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 0.98-1.11 (m, 2H), 1.24-1.37 (m, 8H), 1.41-1.64 (m, 6H), 1.84-2.00 (m, 2H), 2.15-2.25 (m, 3H), 2.26-2.38 (m, 4H), 2.38-2.51 (m, 4H), 2.61-2.65 (m, 1H), 2.78-2.85 (m, 1H), 2.99-3.04 (m, 0.6H), 3.12-3.26 (m, 1.4H), 4.04 (t, *J* 6.0 Hz, 2H), 5.05 (s, 1H), 7.07-7.13 (m, 4H), 7.19-7.26 (m, 2H), 7.27 (d, *J* 1.5 Hz, 1H), 7.30-7.38 (m, 4H), 7.41-7.49 (m, 1.6H), 7.50-7.58 (m, 1.4H), 7.62-7.67 (m, 1H), 7.84-7.91 (m, 1H). ^{13}C-NMR (75 MHz, [D_4]MeOH): δ (ppm) 23.6, 25.8, 27.6, 32.9, 33.1, 36.5, 37.5, 46.7, 53.7, 53.8, 54.9, 55.0, 58.9, 59.8, 61.1, 66.2, 117.9, 120.2, 123.1, 124.6, 126.6, 127.0, 127.8, 129.0, 129.5, 129.9, 130.2, 130.3, 132.1, 134.3, 134.7, 136.0, 136.9, 143.8, 152.8, 169.2, 169.4, 171.3, 171.5, 173.4. RP-HPLC (220 nm): 95% (t_R = 19.4 min, k = 5.8). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{46}H_{54}N_5O_5$]$^+$ 756.4119, found: 756.4117. $C_{46}H_{53}N_5O_5$ (755.96).

5-(2-(4-(4-(6-Amino-4-(3-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propyl)-1,4-diazepan-1-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one pentakis(hydrotrifluoroacetate) (43)

Compound **33** (196 mg, 0.42 mmol), *tert*-butyl (1,4-diazepan-6-yl)carbamate (compound **40**) (90 mg, 0.42 mmol) and compound **20** (134 mg, 0.42 mmol) were added to MeCN (10 mL),

followed by the addition of potassium carbonate (116 mg, 0.84 mmol). The mixture was stirred under reflux overnight. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the solvent was evaporated to yield a yellow residue, which was dissolved in CH_2Cl_2 (5 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined, dried over Na_2SO_4, and the volatiles were removed under reduced pressure. The residue was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1) to afford the Boc-protected intermediate as colorless oil, which was dissolved in CH_2Cl_2/TFA/H_2O (10:10:1 v/v/v) (5 mL). The mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:48, t_R = 15 min) afforded compound **43** as white fluffy solid (92 mg, 17%). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.27-1.41 (m, 4H), 1.41-1.47 (m, 1H), 1.49-1.58 (m, 2H), 1.65-1.79 (m, 2H), 1.84-2.01 (m, 2H), 2.07-2.20 (m, 2H), 2.64-2.85 (m, 2H), 2.92 (t, *J* 7.4 Hz, 3H), 3.05 (s, 3H), 2.98-3.09 (m, 3H), 3.14 (t, *J* 16 Hz, 2H), 3.17-3.19 (m, 1H), 3.23-3.28 (m, 1H), 3.31-3.33 (m, 1H), 3.34-3.40 (m, 1H), 3.40-3.48 (m, 2H), 3.48-3.56 (m, 2H), 3.59-3.66 (m, 1H), 3.69-3.80 (m, 2H), 3.82-3.89 (m, 1H), 3.97-4.09 (m, 1H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.46-4.54 (m, 1H), 4.57 (t, *J* 6.5 Hz, 2H), 7.20-7.23 (m, 1H), 7.23-7.30 (m, 1H), 7.29-7.42 (m, 2H), 7.44-7.56 (m, 2H), 7.61-7.76 (m, 2H), 7.89-7.90 (m, 0.6H), 7.96-7.97 (m, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 23.9, 24.6, 25.5, 27.1, 30.4, 34.3, 36.2, 43.3, 49.6, 50.9, 52.1, 53.1, 54.9, 55.3, 55.6, 56.2, 56.5, 57.9, 58.0, 59.9, 70.3, 117.0 (TFA), 118.9 (TFA), 123.1, 123.6, 125.4, 126.8, 127.5, 127.9, 128.3, 128.5, 128.9, 129.4, 130.1, 130.6, 130.9, 131.2, 131.7, 131.9, 132.4, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 137.0, 141.0, 142.7, 145.6, 162.4 (TFA), 162.6 (TFA), 163.6, 164.9, 165.4, 168.6, 168.8. RP-HPLC (220 nm): 98% (t_R = 14.3 min, k = 4.0). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{40}H_{56}N_9O_3S]^+$ 742.4221, found: 742.42210. $C_{40}H_{55}N_9O_3S \cdot C_{10}H_5F_{15}O_{10}$ (742.00 + 570.12).

***N*-(1-(3-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propyl)-4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)-1,4-diazepan-6-yl)propionamide tetrakis(hydrotrifluoroacetate) (44)**

Compound **105** (12.5 mg, 9.53 μmol) was dissolved in DMF (100 μL) in a 1.5-mL polypropylene reaction vessel, followed by the addition of DIPEA (17 μL, 98 μmol) and a solution of succinimidyl propionate (compound **42**) (2.5 mg, 14.6 μmol) in DMF (20 μL). Stirring of the mixture was continued at room temperature for 2 h. 10% aq TFA (100 μL) was added. Purification by preparative HPLC (column: Kinetex XB-C18 5 μm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:48, t_R = 16 min) afforded compound **44** as white fluffy solid (11.4 mg, 95%). IR (KBr): 3430, 3050, 2605, 1680, 1455, 1365, 1210, 1135, 840, 725. Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.10 (t, *J* 7.6 Hz, 3H), 1.26-1.42 (m, 4H), 1.43-1.59 (m, 3H), 1.64-1.76 (m, 2H), 1.88-1.96 (m, 2H), 2.13-2.17 (m, 2H), 2.23 (q, *J* 7.6 Hz, 2H), 2.65-2.83 (m, 2H), 2.89-2.95 (m, 1H), 3.05 (s, 3H), 2.98-3.08 (m, 3H), 3.12-3.15 (m, 2H), 3.16-3.28 (m, 5H), 3.41-3.44 (m, 5H), 3.63 (d, *J* 4.5 Hz, 1H), 3.70-3.74 (m, 1.5H), 3.79 (d, *J* 17 Hz, 0.5H), 4.03 (d, *J* 15 Hz, 1H), 4.25- 4.32(m, 1H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.46-4.55 (m, 1H), 4.60 (t, *J* 6.4 Hz, 2H), 7.21-7.23 (m, 1H), 7.24-7.30 (m, 1H), 7.30-7.39 (m, 2H), 7.46-7.49 (m, 1H), 7.51-7.53 (m, 1H), 7.60-7.76 (m, 2H), 7.88-7.92 (m, 0.6H), 7.96-7.97 (m, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.1, 23.9, 24.5, 25.6, 26.9, 29.9, 30.4, 34.3, 36.2, 43.2, 46.9, 49.6, 50.9, 52.4, 53.1, 54.9, 55.2, 56.2, 57.5, 58.0, 58.4, 59.2, 70.1, 116.9, 123.1, 123.6, 125.4, 126.9, 127.5, 127.9, 128.4, 128.5, 128.9, 129.4, 130.1, 130.6, 130.9, 131.2, 131.7, 132.4, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 137.1, 141.0, 142.7, 145.6, 162.1 (TFA), 162.3 (TFA), 163.6, 164.9, 165.4, 168.6, 168.8, 176.9. RP-HPLC (220 nm): 98% (t_R = 14.8 min, *k* = 4.2). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{43}H_{60}N_9O_4S$]$^+$ 798.4483, found: 798.4487. $C_{43}H_{59}N_9O_4S \cdot C_8H_4F_{12}O_8$ (798.06 + 456.09).

3-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-4-(3-(piperazin-1-yl)propoxy)-1,2,5 thiadiazole (45)

Compound **20** (600 mg, 1.89 mmol) and piperazine (1.3 g, 15.09 mmol) were suspended in MeCN (12 mL) followed by the addition of potassium carbonate (523 mg, 3.78 mmol). The

mixture was refluxed for 2 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the volatiles were evaporated to yield a brown oil-like residue, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:6:1 v/v/v) to obtain compound **45** as yellow oil (405 mg, 66%). R_f = 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.92-2.13 (m, 2H), 2.30-2.43 (m, 4H), 2.44 (s, 3H), 2.45-2.52 (m, 4H), 2.55 (t, *J* 5.7 Hz, 2H), 2.90 (t, *J* 4.7 Hz, 4H), 3.43 (s, 2H), 4.49 (t, *J* 6.4 Hz, 2H), 7.02-7.04 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 26.2, 26.6, 45.90, 45.92, 51.2, 54.3, 55.0, 55.7, 69.2, 128.3, 129.3, 146.8, 162.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{15}H_{26}N_5OS]^+$ 324.1853, found: 324.1854. $C_{15}H_{25}N_5OS$ (323.46).

5-(2-(4-(4-(4-(3-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propyl)piperazin-1-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one tetrakis(hydrotrifluoroacetate) (46)

Compound **33** (100 mg, 0.21 mmol), compound **45** (76 mg, 0.23 mmol) and potassium carbonate (88 mg, 0.64 mmol) were added to MeCN (5 mL) and the mixture was refluxed for 6 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the solvent was evaporated yielding a yellow oil, which was dissolved in CH_2Cl_2 (5 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined, dried over Na_2SO_4, and the volatiles were removed under reduced pressure. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 20:80-62:38, t_R = 8 min) afforded **46** as white fluffy solid (100 mg, 41%). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.29-1.36 (m, 2H), 1.38-1.43 (m, 2H), 1.44-1.59 (m, 3H), 1.69-1.75 (m, 2H), 1.89-1.97 (m, 2H), 2.20-2.28 (m, 2H), 2.68-2.78 (m, 2H), 2.92-2.96 (m, 1H), 3.06 (s, 3H), 2.98-3.09 (m, 3H), 3.09-3.14 (m, 2H), 3.17-3.30 (m, 5H),

3.42-3.45 (m, 5H), 3.63 (brs, 1H), 3.71-3.81 (m, 2H), 4.04 (d, *J* 14.3 Hz, 1H), 4.40 (d, *J* 17 Hz, 0.6H), 4.44 (d, *J* 17 Hz, 0.4H), 4.48-4.58 (m, 1H), 4.61 (t, *J* 6.2 Hz, 2H), 7.22-7.24 (m, 1H), 7.26-7.32 (m, 1H), 7.34-7.39 (m, 1H), 7.46-7.51 (m, 1H), 7.52-7.54 (m, 1H), 7.62-7.77 (m, 3H), 7.89-7.91 (m, 0.6H), 7.95-8.00 (m, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 23.9, 24.5, 25.1, 25.8, 30.4, 34.3, 36.1, 43.3, 50.6, 50.9, 51.4, 53.1, 54.9, 55.3, 57.8, 57.9, 58.0, 69.7, 115.1, 116.9, 123.1, 123.6, 125.3, 126.9, 127.5, 127.9, 128.4, 128.5, 128.9, 129.4, 130.1, 130.5, 130.9, 131.2, 131.9, 132.3, 132.9, 133.4, 134.6, 134.9, 135.5, 135.7, 137.0, 142.7, 145.6, 158.8, 159.1, 163.4, 164.9, 165.4. RP-HPLC (220 nm): 99% (t_R = 14.2 min, k = 3.9). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{39}H_{53}N_8O_3S$]$^+$ 713.3956, found: 713.3951. $C_{39}H_{52}N_8O_3S \cdot C_8H_4F_{12}O_8$ (712.96 + 456.09).

Piperidin-4-yl 2, 2-diphenylacetate (47)[11]

Compound **109** (860 mg, 2.17 mmol) was dissolved in CH_2Cl_2 (40 mL) and the solution was cooled to 0 °C. TFA (10 mL) was added dropwise, the mixture was allowed to warm up to room temperature and stirring was continued for 8 h. Ice water (10 mL) was added followed by the slow addition of 25% aq NH_3 to adjust the pH value to 11. The product was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give compound **47** as white solid (360 mg, 56%), m.p. 75-77 °C. R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v/). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.45-1.65 (m, 2H), 1.82 (brs, 1H), 1.84-1.93 (m, 2H), 2.64-2.73 (m, 2H), 2.89-3.03 (m, 2H), 4.90-4.99 (m, 1H), 5.01 (s, 1H), 7.21-7.35 (m, 10H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 31.9, 43.9, 57.4, 71.4, 127.3, 128.6, 128.7, 138.9, 171.9. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{19}H_{22}NO_2$]$^+$ 296.1645, found: 296.1666. $C_{19}H_{21}NO_2$ (295.38).

1-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperidin-4-yl 2,2-diphenylacetate (48)

Compound **48** was prepared from **33** (100 mg, 0.21 mmol) and **47** (69 mg, 0.23 mmol) according to the procedure for the synthesis of **46**, but the reflux period was 5 h instead of 6 h. Potassium carbonate: 88 mg, 0.64 mmol. Purification by column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) afforded compound **48** as white solid (40 mg, 27%),

m. p. 47-49 °C. R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 0.97-1.31 (m, 8H), 1.39-1.42 (m, 2H), 1.48-1.58 (m, 1H), 1.61-1.71 (m, 2H), 1.79-2.01 (m, 4H), 2.20-2.36 (m, 4H), 2.36-2.51 (m, 2H), 2.55-2.70 (m, 1H), 2.78-2.85 (m, 1H), 2.99-3.04 (m, 0.6H), 3.11-3.26 (m, 1.4H), 4.84-4.87 (m, 1H), 5.07 (s, 1H), 7.21-7.25 (m, 3H), 7.28-7.32 (m, 9H), 7.36-7.40 (m, 1H), 7.41-7.51 (m, 2H), 7.53-7.56 (m, 1H), 7.61-7.66 (m, 1H), 7.84-7.90 (m, 1H). ^{13}C-NMR (75 MHz, [D_4]MeOH): δ (ppm) 25.8, 27.7, 31.0, 32.9, 33.0, 36.4, 37.4, 51.2, 54.8, 55.0, 58.4, 59.6, 71.5, 123.0, 126.6, 126.9, 127.8, 128.3, 128.9, 129.0, 129.6, 129.7, 129.9, 130.6, 132.0, 132.2, 134.3, 134.7, 136.0, 136.9, 140.3, 143.8, 143.9, 169.4, 171.2, 171.5, 173.5. RP-HPLC (220 nm): 99% (t_R = 21.1 min, k = 6.4). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{43}H_{49}N_4O_4$]$^+$ 685.3748, found: 685.3752. $C_{43}H_{48}N_4O_4$ (684.88).

1-(3-(4-(4-Bromobutyl)piperidin-1-yl)propyl)-3,4-dihydroquinolin-2(1*H*)-one (49)

Compound **121** (900 mg, 2.61 mmol) and PPh_3 (2.06 g, 7.86 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) and the solution was cooled to -5 °C. A solution of CBr_4 (3.03 g, 9.14 mmol) in anhydrous CH_2Cl_2 (15 mL) was slowly dropped into the stirred mixture, thereby keeping the temperature of the mixture below 5 °C. Stirring was continued at room temperature overnight. The solvent was evaporated yielding a yellow residue, which was subjected to column chromatography (eluent: light petroleum/acetone/25% aq NH_3 80:20:1 v/v/v) to yield compound **49** as colorless oil (330 mg, 31%). R_f = 0.3 (light petroleum/acetone/25% aq NH_3 80:20:1 v/v/v). ^{1}H-NMR (300 MHz, CDCl3): δ (ppm) 1.26-1.31 (m, 5H), 1.35-1.52 (m, 2H), 1.68 (d, *J* 9.3 Hz, 2H), 1.76-2.03 (m, 6H), 2.42 (t, *J* 6.1 Hz, 2H), 2.60-2.65 (m, 2H), 2.80-3.01 (m, 4H), 3.40 (t, *J* 6.8 Hz, 2H), 3.96 (t, *J* 7.5Hz, 2H), 6.96-7.01 (m, 1H), 7.08 (d, *J* 8.1 Hz, 1H), 7.15 (dd, *J* 7.3, 1.1 Hz, 1H), 7.22 (dd, *J* 11, 4.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 24.8, 25.5, 25.7, 32.0, 32.2, 33.0, 34.1, 35.6, 35.7, 40.7, 54.1, 56.1, 115.1, 122.9, 126.6, 127.6, 128.1, 139.7, 170.4. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{21}H_{32}BrN_2O$]$^+$ 407.1693, found: 407.1695. $C_{21}H_{31}BrN_2O$ (407.40).

5-(2-(4-(4-((4-(1-(3-(2-Oxo-3,4-dihydroquinolin-1(2*H*)-yl)propyl)piperidin-4-yl)butyl)amino)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (50)

Compound **49** (50 mg, 0.12 mmol), compound **10** (50 mg, 0.12 mmol), potassium carbonate (71 mg, 0.51 mmol) and sodium iodide (9 mg, 0.06 mmol) were added to MeCN (5 mL) and the mixture was kept under reflux for 3 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the solvent was removed under reduced pressure yielding a yellow oily residue, which was dissolved in CH_2Cl_2 (5 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined, dried over Na_2SO_4, and the volatiles were removed under reduced pressure. Purification by column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) afforded compound **50** as yellow solid (46 mg, 52%), m.p. 141-143 °C. R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 0.98-1.17 (m, 3H), 1.17-1.35 (m, 12H), 1.42-1.51 (m, 5H), 1.55-1.58 (m, 1H), 1.63-1.69 (m, 2H), 1.78-1.86 (m, 2H), 1.87-2.02 (m, 4H), 2.32-2.43 (m, 2H), 2.48-2.58 (m, 5H), 2.58-2.66 (m, 2H), 2.78-2.81 (m, 0.6H), 2.83-2.95 (m, 4H), 2.99-3.04 (m, 0.4H), 3.10-3.25 (m, 1H), 3.99 (t, *J* 7.3 Hz, 2H), 7.00-7.05 (m, 1H), 7.13-7.28 (m, 5H), 7.28-7.38 (m, 1H), 7.39-7.51 (m, 2H), 7.54-7.57 (m, 1H), 7.62-7.67 (m, 1H), 7.84-7.90 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 25.1, 25.4, 25.5, 26.2, 30.4, 30.7, 32.7, 32.8, 32.9, 33.0, 34.0, 36.4, 36.8, 37.4, 37.5, 41.3, 50.5, 50.6, 54.8, 55.0, 57.1, 116.4, 123.0, 124.4, 126.6, 127.0, 127.8, 128.2, 128.6, 129.0, 129.1, 129.5, 129.9, 130.6, 131.1, 131.9, 132.0, 132.2, 134.3, 135.9, 140.2, 143.8, 144.9, 169.1, 169.3, 171.2, 171.4, 172.7. RP-HPLC (220 nm): 95% (t_R = 16.7 min, k = 4.8). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{45}H_{61}N_6O_3]^+$ 733.4800, found: 733.4805. $C_{45}H_{60}N_6O_3$ (733.01).

5-(2-(4-(4-(6-Amino-4-(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)-[1,4'-bipiperidin]-1'-yl)ethyl)-1,4-diazepan-1-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one pentakis(hydrotrifluoroacetate) (51)

Potassium carbonate (44 mg, 0.32 mmol) was added to a mixture of compound **30** (45 mg, 0.11 mmol), compound **33** (50 mg, 0.11 mmol), *tert*-butyl (1,4-diazepan-6-yl)carbamate

(compound **40**) (23 mg, 0.11 mmol) in MeCN (2 mL). The mixture was stirred at 110 °C under microwave irradiation for 30 min, and cooled to room temperature. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 5 mL). The filtrate and the washings were combined and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (5 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 5 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the Boc-protected intermediate, which was dissolved in CH_2Cl_2/TFA/H_2O (10:10:1 v/v/v) (4 mL). The mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:38, t_R = 16 min) afforded compound **51** as white fluffy solid (19 mg, 12%). ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.36-1.42 (m, 4H), 1.42-1.59 (m, 3H), 1.64-1.72 (m, 1H), 1.73-1.87 (m, 3H), 1.89-1.97 (m, 2H), 2.09-2.22 (m, 4H), 2.69 (t, *J* 13 Hz, 1H), 2.80-2.89 (m, 2H), 2.91-2.97 (m, 1H), 3.00-3.07 (m, 2H), 3.07-3.22 (m, 4H), 3.24-3.27 (m, 3H), 3.33-3.41 (m, 1H), 3.41-3.49 (m, 2H), 3.50-3.68 (m, 4H), 3.69-3.76 (m, 5H), 3.76-3.83 (m, 2H), 3.96-3.98 (m, 1H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.57-4.62 (m, 1H), 4.72-4.74 (m, 1H), 7.04-7.07 (m, 3H), 7.22-7.30 (m, 1H), 7.29-7.38 (m, 3H), 7.46-7.49 (m, 1H), 7.50-7.54 (m, 1H), 7.61-7.64 (m, 1H), 7.66-7.76 (m, 1H), 7.89 (d, *J* 7.7 Hz 0.6H), 7.96 (d, *J* 7.7 Hz, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 24.5, 25.0, 27.3, 27.5, 27.8, 27.9, 30.4, 34.3, 36.1, 41.6, 43.9, 50.2, 50.4, 51.8, 54.9, 55.3, 56.1, 58.0, 58.5, 59.9, 64.7, 109.9, 110.7, 115.0 (TFA), 116.9 (TFA), 118.9 (TFA), 120.9 (TFA), 122.4, 122.9, 123.1, 123.6, 126.8, 127.5, 127.9, 128.5, 128.9, 129.4, 129.7, 130.1, 130.5, 130.9, 131.2, 131.7, 131.9, 132.3, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 137.0, 141.0, 142.7, 156.1, 162.3 (TFA), 162.5 (TFA), 162.8 (TFA), 162.9 (TFA), 164.9, 165.4, 168.6, 168.8, 170.8. RP-HPLC (220 nm): 99% (t_R = 14.9 min, *k* = 4.2). HRMS (ESI): *m/z* $[M+2H]^{2+}$ calcd. for $[C_{48}H_{66}N_{10}O_4]^{2+}$ 423.2629, found: 423.2613. $C_{48}H_{64}N_{10}O_4 \cdot C_{10}H_5F_{15}O_{10}$ (845.11 + 570.12).

_N_-(1-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5_H_-dibenzo[_b,e_][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)-4-(2-oxo-2-(4-(2-oxo-2,3-dihydro-1_H_-benzo[_d_]imidazol-1-yl)-[1,4'-bipiperidin]-1'-yl)ethyl)-1,4-diazepan-6-yl)propionamide tetrakis(hydrotrifluoroacetate) (52)

Compound **52** was prepared from **51** (7.6 mg, 5.37 µmol) and **42** (1.4 mg, 8.18 µmol) according to the procedure for the synthesis of **44**. DIPEA: 10 µL, 58 µmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 5:95-62:48, t_R = 16 min) yielded compound **52** as hygroscopic white fluffy solid (7 mg, 96%). Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.14 (t, *J* 7.6 Hz, 3H), 1.32-1.45 (m, 4H), 1.45-1.59 (m, 3H), 1.60-1.80 (m, 4H), 1.80-1.89 (m, 1H), 1.91-1.99 (m, 2H), 2.09-2.12 (m, 2H), 2.19-2.24 (m, 2H), 2.27 (q, *J* 12 Hz, 2H), 2.68-2.76 (m, 1H), 2.81-2.89 (m, 2H), 2.89-3.00 (m, 2H), 3.03-3.17 (m, 4H), 3.16-3.23 (m, 3H), 3.33-3.51 (m, 5H), 3.51-3.60 (m, 2H), 3.69-3.85 (m, 6H), 3.98-4.06 (m, 1H), 4.12-4.19 (m, 1H), 4.41 (d, *J* 17 Hz, 0.6H), 4.45 (d, *J* 17 Hz, 0.4H), 4.58-4.62 (m, 1H), 4.74-4.76 (m, 1H), 7.05-7.08 (m, 3H), 7.19-7.40 (m, 4H), 7.47-7.51 (m, 1H), 7.51-7.53 (m, 1H), 7.63 (dd, *J* 15, 7.1 Hz, 1H), 7.66-7.76 (m, 1H), 7.90 (d, *J* 8.0 Hz, 0.6H), 7.97 (d, *J* 8.0 Hz, 0.4H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.2, 24.5, 25.4, 27.3, 27.5, 27.9, 30.1, 30.4, 34.3, 36.2, 41.7, 44.1, 50.2, 50.4, 54.9, 55.3, 56.7, 57.2, 58.0, 59.2, 59.6, 61.0, 64.8, 109.9, 110.7, 116.9 (TFA), 118.9 (TFA), 122.4, 122.9, 123.1, 123.6, 126.9, 127.5, 127.9, 128.5, 128.9, 129.4, 129.7, 130.1, 130.6, 130.9, 131.2, 131.7, 131.9, 132.4, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 137.0, 141.0, 142.7, 156.1, 162.6 (TFA), 162.8 (TFA), 164.9, 165.5, 168.6, 168.8, 177.1. RP-HPLC (220 nm): 99% (t_R = 15.6 min, *k* = 4.4). HRMS (ESI): *m/z* $[M+2H]^{2+}$ calcd. for $[C_{51}H_{70}N_{10}O_5]^{2+}$ 451.2760, found: 451.2764. $C_{51}H_{68}N_{10}O_5 \cdot C_8H_4F_{12}O_8$ (901.17 + 456.09).

1,2-bis(2-Bromoethoxy)ethane (53)[12]

Triethylene glycol (1.79 mL, 13.3 mmol) was dissolved in 48% aq HBr (15 mL, 133 mmol). The mixture was stirred at 120 °C for 2.5 h and then cooled to rt. The pH was adjusted to 8 by the addition of NH_3 (32% in water). The product was extracted with CH_2Cl_2, the organic phase was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. Purification by column chromatography (eluent: n-hexane/ethyl acetate 40:1 to 20:1) yielded

the product as a brownish liquid (0.23 g, 6%). R_f= 0.15 (n-hexane/ethyl acetate 3:1 v/v). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 3.46 (t, 4H, *J* 6.2 Hz), 3.67 (s, 4H), 3.81 (t, 4H, *J* 6.2 Hz). MS (CI, NH_3): *m/z* (%) 292/294/296 (54/100/49) $[M+NH_4]^+$, 214 (23) $[M-Br+NH_4]^+$. $C_6H_{12}Br_2O_2$ (275.97).

((Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(piperidine-1,4-diyl) bis(2,2-diphenylacetate) bis(hydrotrifluoroacetate) (54) A mixture of **47** (114 mg, 387 µmol), **53** (51 mg, 184 µmol), K_2CO_3 (153 mg, 1.11 mmol) and MeCN (2 mL) was stirred under argon atmosphere at 110 °C in a microwave reactor for 45 min. Solid material was filtered off and the reaction mixture was subjected to column chromatography (eluent: CH_2Cl_2/MeOH 40:1 to 20:1; R_f (free base) = 0.2 (CH_2Cl_2/MeOH 10:1 v/v)). Further purification was performed by preparative HPLC (column: Eurospher-100 C18 5 µm 250 × 4 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 19:81-82:18, t_R = 21 min) which gave the product as yellow oil (38.7 mg, 23%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.96 (m, 4H), 2.24 (m, 4H), 2.55 (m, 4H), 3.00 (s, 4H), 3.44 (m, 4H), 3.74 (s, 4H), 5.06 (s, 2H), 5.14 (brs, 2H), 7.29-7.36 (m, 20H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 26.9, 48.5, 57.2, 64.6, 64.3, 70.3, 127.6, 128.5, 128.8, 138.2, 171.0. RP-HPLC (220 nm): 99% (t_R = 17.9 min, *k* = 5.6). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{44}H_{53}N_2O_6]^+$ 705.3898, found: 705.3902. $C_{44}H_{52}N_2O_6 \cdot C_4H_2F_6O_4$ (704.91 + 228.05).

5-(2-(4-(4-(4-(2-Aminoethyl)piperazin-1-yl)butyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one tetrakis(hydrotrifluoroacetate) (55)

Compound **33** (280 mg, 0.60 mmol), *tert*-butyl (2-(piperazin-1-yl)ethyl)carbamate (**84**) (164 mg, 0.72 mmol) and potassium carbonate (247 mg, 1.79 mmol) were added to MeCN (20 mL) and the mixture was kept under reflux for 3 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 5 mL). The filtrate and washings were combined and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the residue was subjected to flash chromatography

(eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to afford the Boc-protected intermediate as white solid (270 mg). R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). The intermediate (270 mg, 0.436 mmol) was dissolved in CH_2Cl_2 (5mL), TFA (1 mL) was added slowly, and the mixture was stirred at room temperature for 8 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-30 min: MeCN/0.1% aq TFA 20:80-64:36, t_R = 8 min) afforded compound **55** as white fluffy solid (280 mg, 48%). Ratio of configurational isomers evident in the NMR spectra: ca 1.8:1. ^{1}H-NMR (600 MHz, [D_4]MeOH): δ (ppm) 1.29-1.42 (m, 4H), 1.42-1.60 (m, 3H), 1.69-1.74 (m, 2H), 1.83 -2.04 (m, 2H), 2.51 (s, 2H), 2.69 (t, *J* 5.7 Hz, 2H), 2.84-2.99 (m, 1H), 3.00-3.24 (m, 9H), 3.38-3.60 (m, 3H), 3.70-3.80 (m, 2H), 4.39 (d, *J* 17 Hz, 0.65H), 4.44 (d, *J* 17 Hz, 0.35H), 7.24-7.29 (m, 1H), 7.31-7.38 (m, 2H), 7.45-7.52 (m, 2H), 7.60-7.75 (m, 2H), 7.89 (d, *J* 7.8 Hz, 0.65H), 7.96 (d, *J* 7.8 Hz, 0.35H). ^{13}C-NMR (150 MHz, [D_4]MeOH): δ (ppm) 24.5, 24.9, 30.4, 34.3, 36.1, 37.3, 50.6, 53.0, 54.6, 54.9, 55.3, 57.7, 58.0, 123.1, 123.6, 126.8, 127.5, 127.9, 128.5, 128.9, 129.5, 130.1, 130.5, 130.9, 131.2, 131.7, 131.9, 132.3, 132.9, 133.4, 134.6, 134.9, 135.5, 135.7, 137.0, 141.0, 142.7, 164.9, 165.4, 168.6, 168.8. RP-HPLC (220 nm): 99% (t_R = 13.4 min, k = 3.7). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for $[C_{30}H_{43}N_6O_2]^+$ 519.3442, found: 519.3447. $C_{30}H_{42}N_6O_2 \cdot C_8H_4F_{12}O_8$ (518.71 + 456.09).

4-Amino-*N*-(5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)butanamide (56)

To a solution of **97** (51 mg, 0.25 mmol) in DMF (1 mL) were added HOBt (34 mg, 0.25 mmol), TBTU (80 mg, 0.25 mmol) and DIPEA (86 µL, 0.49 mmol) and the mixture was stirred at room temperature for 30 min. Compound **26** (70 mg, 0.25 mmol) dissolved in DMF (1 mL) was added and the mixture was stirred at 60 °C for 3 h. H_2O (5 mL) was added, followed by extraction with ethyl acetate (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to yield the Boc-protected intermediate *tert*-butyl (4-((5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)amino)

-4-oxobutyl)carbamate as yellow oil (80 mg). R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 1.46-1.57 (m, 4H), 1.73-1.80 (m, 2H), 1.82-1.91 (m, 2H), 2.19 (t, *J* 6.9 Hz, 2H), 2.49-2.55 (m, 5H), 2.63-2.81 (m, 2H), 3.12-3.18 (m, 2H), 3.23-3.29 (m, 2H), 3.51-3.73 (m, 2H), 4.45 (t, *J* 6.4 Hz, 2H), 4.90 (brs, 1H), 6.37 (brs, 1H), 7.07-7.09 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.4, 26.4, 26.6, 28.4, 28.5, 29.2, 33.6, 39.3, 39.6, 45.8, 51.1, 54.8, 70.7, 79.3, 128.3, 129.0, 146.6, 156.7, 162.4, 172.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{22}H_{38}N_5O_4S]^+$ 468.2639, found: 468.2650. This intermediate (80 mg, 0.17 mmol) was dissolved in CH_2Cl_2/TFA (4:1 v/v) (5 mL) and the mixture was stirred at room temperature overnight. CH_2Cl_2 (5 mL) was added followed by the addition of 25% aq NH_3 to adjust the pH of the aqueous phase to 11. The product was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give compound **56** as yellow oil (55 mg, 60%), which was used without further purification. R_f = 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 80:16:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.38-1.64 (m, 4H), 1.70-1.92 (m, 4H), 1.96 (brs, 2H), 2.22-2.28 (m, 2H), 2.35-2.48 (m, 5H), 2.52-2.56 (m, 2H), 3.00-3.37 (m, 4H), 3.39-3.42 (m, 2H), 4.41 (t, *J* 6.5 Hz, 2H), 6.88-7.13 (m, 1H), 8.56 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.5, 26.6, 28.5, 29.3, 31.0, 34.1, 39.3, 41.1, 45.9, 51.2, 55.0, 70.6, 128.4, 129.3, 146.8, 162.4, 172.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{17}H_{30}N_5O_2S]^+$ 368.2115, found: 368.2116. $C_{17}H_{29}N_5O_2S$ (367.51).

5-(Aminomethyl)-*N*^{1},*N*^{3}-bis(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)isophthalamide heptakis(hydrotrifluoroacetate) (58)

and

5-(Aminomethyl)-*N*^{1}-(4-((5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)amino)-4-oxobutyl)-*N*^{3}-(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)isophthalamide pentakis(hydrotrifluoroacetate) (60)

TBTU (244 mg, 0.76 mmol) and DIPEA (131 μL, 0.76 mmol) were added to a solution of **57** (113 mg, 0.38 mmol) and HOBt (103 mg, 0.76 mmol) in DMF (2 mL) and the mixture was

stirred at room temperature for 20 min. A solution of **56** (140 mg, 0.38 mmol), **55** (370 mg, 0.38 mmol) and DIPEA (131 µL, 0.76 mmol) in DMF (2 mL) was added dropwise and stirring was continued at 60 °C for 3 h. H_2O (10 mL) was added followed by extraction with ethyl acetate (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield the Boc-protected intermediate as yellow oil, which was dissolved in CH_2Cl_2/TFA/H_2O (10:10:1 v/v/v) (5 mL). The mixture was stirred at room temperature for 2 h. CH_2Cl_2 (10 mL) was added and the volatiles were evaporated. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 12:88-64:36, t_R (**58**) = 11 min, t_R (**60**) = 12 min) afforded compound **60** (101 mg, 16%) and compound **58** (60 mg, 8%) as white fluffy solids. **60**: ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.23-1.43 (m, 5H), 1.43-1.54 (m, 5H), 1.54-1.63 (m, 3H), 1.68-1.73 (m, 2H), 1.82-2.01 (m, 7H), 2.28 (t, *J* 7.5 Hz, 2H), 2.69-2.81 (m, 2H), 2.89-2.95 (m, 4H), 3.02-3.05 (m, 1H), 3.05 (s, 3H), 3.06-3.11 (m, 3H), 3.15-3.22 (m, 3H), 3.31-3.39 (m, 3H), 3.39-3.47 (m, 4H), 3.58-3.68 (m, 3H), 3.70-3.73 (m, 1.5H), 3.78 (d, *J* 18 Hz, 0.5H), 4.02-4.05 (m, 1H), 4.23 (s, 2H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.51 (t, *J* 6.5 Hz, 2H), 7.23-7.26 (m, 1H), 7.27-7.39 (m, 2H), 7.46-7.53 (m, 2H), 7.59-7.76 (m, 3H), 7.89-7.90 (m, 0.6 H), 7.95-7.96 (m, 0.4H), 8.04-8.10 (m, 2H), 8.29-8.30 (m, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 22.5, 23.0, 23.1, 23.8, 25.4, 28.1, 28.7, 29.0, 32.9, 33.2, 34.7, 36.1, 38.8, 39.3, 41.9, 42.4, 48.2, 49.6, 50.9, 51.8, 53.5, 53.9, 55.7, 56.3, 56.6, 70.9, 121.7, 122.2, 124.1, 125.5, 126.1, 126.3, 126.5, 126.8, 127.1, 127.5, 127.5, 128.0, 128.7, 129.2, 129.5, 129.8, 130.3, 130.6, 130.9, 131.6, 132.0, 133.2, 133.5, 134.1, 134.2, 134.3, 135.4, 135.6, 135.8, 139.5, 139.6, 141.3, 144.2, 160.2 (TFA), 160.4 (TFA), 160.6 (TFA), 160.8 (TFA), 162.4, 163.6, 164.0, 167.1, 167.2, 167.4, 167.6, 174.0. RP-HPLC (220 nm): 96% (t_R = 14.9 min, *k* = 4.2). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{56}H_{77}N_{12}O_6S]^+$ 1045.5810, found: 1045.5803. $C_{56}H_{76}N_{12}O_6S \cdot C_{10}H_5F_{15}O_{10}$ (1045.36 + 570.12). **58**: Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.29-1.42 (m, 8H), 1.41-1.60 (m, 6H), 1.63-1.77 (m, 4H), 1.88-1.96 (m, 4H), 2.83-2.97 (m, 2H), 2.98-3.10 (m, 6H), 3.11-3.14 (m, 4H), 3.16-3.28 (m, 4H), 3.30-3.36 (m, 4H), 3.26-3.60 (m, 10H), 3.69-3.72 (m, 6H), 3.77-3.89 (m, 2H), 4.23 (s, 2H), 4.40 (d, *J* 17 Hz, 1.2H), 4.44 (d, *J* 17 Hz, 0.8H), 7.21-7.35 (m, 4H), 7.36-7.38 (m, 1H),

7.44-7.54 (m, 4H), 7.58-7.71 (m, 4H), 7.55-7.73 (m, 1H), 7.86-7.91 (m, 1.2H), 7.95-7.96 (m, 0.8H), 8.10 (s, 2H), 8.34 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 23.1, 23.7, 29.0, 32.9, 34.7, 35.6, 42.4, 49.3, 50.1, 53.5, 53.9, 56.0, 56.3, 56.6, 113.7 (TFA), 115.6 (TFA), 117.6 (TFA), 119.5 (TFA), 121.7, 122.3, 125.5, 126.1, 126.5, 127.1, 127.5, 128.1, 128.7, 129.1, 129.5, 129.8, 130.3, 130.6, 130.8, 130.9, 131.6, 132.0, 133.2, 133.5, 134.1, 134.3, 135.2, 135.6, 139.6, 141.3, 161.0 (TFA), 161.4 (TFA), 163.6, 164.1, 167.2, 167.4, 167.7. RP-HPLC (220 nm): 98% (t_R = 14.4 min, k = 4.1). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{69}H_{91}N_{13}O_6$]$^{2+}$ 589.8602, found: 589.8601. $C_{69}H_{89}N_{13}O_6 \cdot C_{14}H_7F_{21}O_{14}$ (1196.56 + 798.16).

N^1,N^3-Bis(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)-5-(propionamidomethyl)isophthalamide hexakis(hydrotrifluoroacetate) (59)

Compound **59** was prepared from **58** (17 mg, 8.52 μmol) and **42** (2.3 mg, 13 μmol) according to the procedure for the synthesis of **44**. DIPEA: 16 μL, 93 μmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 μm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-64:36, t_R = 11 min), yielded compound **59** as white fluffy solid (13 mg, 79%). Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.14 (t, *J* 7.6 Hz, 3H), 1.30-1.48 (m, 10H), 1.48-1.61 (m, 4H), 1.68-1.79 (m, 4H), 1.85-2.01 (m, 4H), 2.28 (q, *J* 7.6 Hz, 2H), 2.81-2.99 (m, 4H), 2.99-3.08 (m, 6H), 3.08-3.17 (m, 6H), 3.17-3.26 (m, 4H), 3.34-3.48 (m, 8H), 3.48-3.65 (m, 4H), 3.38-3.83 (m, 6H), 4.36-4.51 (m, 4H), 7.20-7.31 (m, 2H), 7.32-7.35 (m, 2H), 7.36-7.39 (m, 1H), 7.44-7.51 (m, 2H), 7.51-7.53 (m, 2H), 7.61-7.69 (m, 4H), 7.72-7.78 (m, 1H), 7.89 (d, *J* 7.7 Hz, 1.2H), 7.93 (s, 2H), 7.96 (d, *J* 7.7 Hz, 0.8H), 8.25 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.4, 24.5, 25.1, 30.1, 30.4, 34.2, 36.1, 37.2, 43.5, 50.8, 52.0, 54.9, 55.3, 57.5, 57.8, 58.1, 116.9 (TFA), 118.9 (TFA), 123.1, 123.7, 126.3, 126.9, 127.5, 127.9, 128.5, 128.9, 129.5, 130.1, 130.5, 130.7, 130.9, 131.2, 131.7, 131.9, 132.3, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 136.0, 137.0, 141.0, 141.6, 142.7, 162.4 (TFA), 162.6 (TFA), 165.0, 165.5, 168.6, 168.8, 169.6, 177.1. RP-HPLC (220 nm): 95% (t_R = 15.3 min, k = 4.3). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{72}H_{94}N_{13}O_7$]$^+$ 1252.7394, found: 1252.7375. $C_{72}H_{93}N_{13}O_7 \cdot C_{12}H_6F_{18}O_{12}$ (1252.62 + 684.14).

N^1-(4-((5-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)amino)-4-oxobutyl)-N^3-(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5H-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)-5-(propionamidomethyl)isophthalamide tetrakis(hydrotrifluoroacetate) (61)

Compound **61** was prepared from **60** (16 mg, 8.7 μmol) and **42** (2.3 mg, 13 μmol) according to the procedure for the synthesis of **44**. DIPEA: 17 μL, 98 μmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 μm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-95:5, t_R = 9 min), yielded compound **61** as white fluffy solid (12 mg, 89%). Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.14 (t, *J* 7.6 Hz, 3H), 1.31-1.43 (m, 6H), 1.43-1.61 (m, 7H), 1.64-1.79 (m, 2H), 1.84-1.94 (m, 6H), 1.92-1.99 (m, 1H), 2.24-2.30 (m, 4H), 2.61-2.68 (m, 1H), 2.69-2.83 (m, 3H), 2.85-2.97 (m, 4H), 2.99-3.14 (m, 9H), 3.18 (t, *J* 6.6 Hz, 2H), 3.39-3.41 (m, 3H), 3.42-3.53 (m, 1H), 3.61 (t, *J* 6.2 Hz, 3H), 3.70-3.80 (m, 2H), 4.03 (d, *J* 15 Hz, 1H), 4.39 (d, *J* 17 Hz, 0.6H), 4.41 (d, *J* 17 Hz, 0.4H), 4.44 (d, *J* 4.5 Hz, 2H), 4.50 (t, *J* 6.5 Hz, 2H), 7.23-7.24 (m, 1H), 7.26-7.40 (m, 2H), 7.46-7.48 (m, 1H), 7.50-7.53 (m, 1H), 7.59-7.68 (m, 2H), 7.68-7.76 (m, 1H), 7.88 (s, 2H), 7.89-7.90 (m, 0.6H), 7.96-7.97 (m, 0.4H), 8.14-8.15 (m, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.4, 23.9, 24.4, 24.5, 25.2, 26.5, 26.8, 29.5, 30.0, 30.1, 30.4, 34.3, 34.6, 36.1, 37.5, 40.2, 40.6, 43.3, 43.7, 51.0, 52.3, 53.2, 54.9, 55.3, 57.4, 57.8, 58.0, 72.4, 115.1 (TFA), 116.4 (TFA), 117.0 (TFA), 118.9 (TFA), 123.1, 123.6, 125.4, 126.1, 126.9, 127.5, 127.9, 128.2, 128.5, 128.9, 129.4, 130.1, 130.3, 130.6, 130.9, 131.2, 131.7, 132.3, 133.0, 133.4, 134.6, 134.9, 135.5, 136.7, 136.2, 136.5, 137.0, 141.0, 141.5, 142.7, 145.6, 163.8, 164.9, 165.4, 168.6, 168.8, 169.2, 169.6, 171.1, 171.9, 175.4, 177.1. RP-HPLC (220 nm): 98% (t_R = 15.9 min, *k* = 4.5). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{59}H_{81}N_{12}O_7S$]$^+$ 1101.6072, found: 1101.6066. $C_{59}H_{80}N_{12}O_7S \cdot C_8H_4F_{12}O_8$ (1101.43 + 456.09).

1-(1'-(2-Aminoethyl)-[1,4'-bipiperidin]-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (62)

Compound **32** (570 mg, 1.89 mmol), *tert*-butyl (2-bromoethyl) carbamate (compound **83**) (508 mg, 2.27 mmol) and potassium carbonate (525 mg, 3.80 mmol) were added to MeCN (60 mL) and the mixture was stirred under reflux overnight. Insoluble material was removed

by filtration. The filtrate was concentrated under reduced pressure to yield a yellow oily residue, which was dissolved in CH_2Cl_2 (10 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded a yellow oil, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 to 90:9:1 v/v/v) to afford the Boc-protected intermediate as colorless oil (350 mg). R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.43 (s, 9H), 1.54-1.67 (m, 2H), 1.72-1.84 (m, 2H), 1.87-1.91 (m, 2H), 2.01-2.10 (m, 2H), 2.27-2.60 (m, 7H), 3.01-3.05 (m, 2H), 3.08-3.24 (m, 4H), 4.20-4.43 (m, 1H), 6.89-7.16 (m, 3H), 7.24-7.57 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 28.8, 28.9, 29.9, 38.7, 50.1, 52.0, 54.4, 58.7, 63.1, 80.2, 110.7, 110.9, 122.3, 122.6, 129.7, 130.3, 156.3, 158.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{38}N_5O_3]^+$ 444.2969, found: 444.2966. The intermediate (150 mg, 0.34 mmol) was dissolved in CH_2Cl_2/TFA (4:1 v/v) (5 mL) and the mixture was stirred at room temperature overnight. 25% aq NH_3 was added to adjust the pH to 11 followed by extraction with CH_2Cl_2/MeOH (9:1 v/v) (5 × 10 mL). Removal of the volatiles from the combined extracts *in vacuo* gave compound **62** as colorless oil (100 mg, 86%), which was used without further purification. R_f = 0.1 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.50-1.71 (m, 2H), 1.76-1.79 (m, 2H), 1.89-1.94 (m, 2H), 2.00-2.11 (m, 2H), 2.32-2.52 (m, 7H), 2.74-2.78 (m, 1H), 3.00-3.17 (m, 4H), 3.39-3.45 (m, 1H), 4.18-4.44 (m, 1H), 6.95-7.16 (m, 3H), 7.34-7.52 (m, 1H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 28.9, 29.8, 39.3, 50.2, 52.1, 54.5, 61.2, 63.2, 110.6, 110.9, 122.3, 122.6, 129.7, 130.3, 156.3. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{19}H_{30}N_5O]^+$ 344.2445, found: 344.2443. $C_{19}H_{29}N_5O$ (343.48).

5-(Aminomethyl)-*N*^{1}-(2-(4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)-[1,4'-bipiperidin]-1'-yl)ethyl)-*N*^{3}-(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)isophthalamide hexakis(hydrotrifluoroacetate) (63)

Compound **63** was prepared from **57** (80 mg, 0.27 mmol), **55** (263 mg, 0.27 mmol) and **62** (93 mg, 0.27 mmol) according to the procedure for the synthesis of **60** and **58**. TBTU: 173 mg,

0.54 mmol; HOBt: 73 mg, 0.54 mmol; DIPEA: 189 + 189 µL, 1.1 + 1.1 mmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 15:85-64:36, t_R (**112**) = 10 min, t_R (**114**) = 12 min) yielded compounds **58** (25 mg, 5%) and **63** (45 mg, 10%) as white fluffy solids. Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH) δ (ppm) 1.31-1.42 (m, 4H), 1.43-1.59 (m, 3H), 1.66-1.77 (m, 2H), 1.84-1.99 (m, 2H), 2.11 (d, *J* 12 Hz, 2H), 2.22-2.28 (m, 2H), 2.49 (d, *J* 13 Hz, 2H), 2.80-2.96 (m, 3H), 2.98-3.07 (m, 3H), 3.09-3.14 (m, 3H), 3.15-3.28 (m, 5H), 3.31-3.38 (m, 3H), 3.40-3.50 (m, 6H), 3.64-3.81 (m, 7H), 3.85 (t, *J* 5.8 Hz, 2H), 3.98 (d, *J* 12 Hz, 2H), 4.24 (s, 2H), 4.40 (d, *J* 18 Hz, 0.4H), 4.43 (d, *J* 18 Hz, 0.6H), 4.58-4.67 (m, 1H), 7.02-7.09 (m, 3H), 7.24-7.29 (m, 1H), 7.32-7.88 (m, 2H), 7.45-7.48 (m, 1H), 7.49-7.52 (m, 1H), 7.60-7.76 (m, 3H), 7.88-7.90 (m, 0.6H), 7.95-7.97 (m, 0.4H), 8.13 (d, *J* 15 Hz, 2H), 8.37 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH) δ (ppm) 24.2, 24.5, 25.1, 27.4, 30.4, 34.3, 36.0, 36.1, 37.2, 43.8, 49.6, 50.5, 50.8, 51.7, 52.3, 54.9, 55.3, 57.4, 57.7, 57.9, 58.0, 61.6, 110.1, 110.7, 115.1 (TFA), 117.0 (TFA), 118.9 (TFA), 120.9 (TFA), 122.4, 122.9, 123.1, 123.6, 126.9, 127.5, 127.8, 127.9, 128.5, 128.8, 129.4, 129.7, 130.0, 130.1, 130.5, 130.9, 131.2, 132.7, 131.9, 132.3, 132.4, 132.9, 133.4, 134.6, 134.9, 135.4, 135.5, 135.7, 136.1, 136.7, 137.0, 140.9, 142.7, 156.1, 162.3 (TFA), 162.6 (TFA), 162.8 (TFA), 163.0 (TFA), 164.9, 165.5, 168.6, 168.8, 168.9, 169.4. RP-HPLC (220 nm): 98% (t_R = 14.6 min, *k* = 4.1). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{58}H_{77}N_{12}O_5$]$^+$ 1021.6140, found: 1021.6134. $C_{58}H_{76}N_{12}O_5 \cdot C_{12}H_6F_{18}O_{12}$ (1021.33 + 684.14).

N^1-(2-(4-(2-Oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)-[1,4'-bipiperidin]-1'-yl)ethyl)-N^3-(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)-5-(propionamidomethyl)isophthalamide pentakis(hydrotrifluoroacetate) (64)

Compound **64** was prepared from **63** (20 mg, 11.7 µmol) and **42** (3.2 mg, 18.7 µmol) according to the procedure for the synthesis of **44**. DIPEA: 22 µL, 130 µmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-64:36, t_R = 9 min), yielded compound **64** as white fluffy solid (17 mg, 88%). IR (KBr): 3400, 3070, 2690, 1675, 1545, 1505, 1485, 1460, 1430, 1365, 1200,

1135, 835, 800, 720. Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D_6]DMSO) δ (ppm) 1.02 (t, *J* 7.6 Hz, 3H), 1.15-1.29 (m, 4H), 1.31-1.47 (m, 3H), 1.53-1.66 (m, 2H), 1.73-1.80 (m, 2H), 1.87-2.05 (m, 4H), 2.16 (q, *J* 7.6 Hz, 2H), 2.34-2.38 (m, 2H), 2.60-2.72 (m, 2H), 2.75-3.97 (m, 4H), 2.97-3.05 (m, 4H), 3.05-3.21 (m, 4H), 3.22-3.31 (m, 4H), 3.31-3.45 (m, 3H), 3.46-3.55 (m, 4H), 3.55-3.62 (m, 4H), 3.65-3.70 (m, 2H), 3.73-3.97 (m, 3H), 4.33 (d, *J* 5.9 Hz, 2H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.60 (t, *J* 12 Hz, 1H), 6.93-7.02 (m, 3H), 7.22-7.30 (m, 2H), 7.33-7.35 (m, 1H), 7.42-7.47 (m, 1H), 7.50-7.60 (m, 1H), 7.68-7.77 (m, 2H), 7.80-7.82 (m, 0.6H), 7.86-7.88 (m, 0.4H), 7.88 (s, 2H), 8.21 (s, 1H), 8.41-8.43 (m, 1H), 8.75 (brs, 1H), 8.91 (brs, 1H), 9.61 (brs, 0.6H), 10.66 (Brs, 0.4H), 10.73 (s, 0.4H), 10.78 (s, 0.6H), 10.94 (s, 1H). ^{13}C-NMR (150 MHz, [D_6]DMSO) δ (ppm) 9.9, 23.0, 23.5, 23.7, 23.8, 25.4, 25.8, 28.5, 28.6, 32.7, 34.4, 34.8, 35.5, 40.1, 41.8, 46.5, 48.4, 49.0, 50.4, 52.7, 53.2, 54.9, 55.9, 59.5, 108.5, 109.1, 113.6, 115.6, 117.6, 119.5, 120.5, 120.9, 122.3, 124.7, 124.9, 125.5, 127.3, 127.7, 128.3, 128.4, 128.7, 128.9, 129.0, 129.7, 130.0, 130.4, 131.0, 131.6, 133.0, 133.1, 133.8, 134.1, 134.4, 134.7, 135.8, 139.5, 140.4, 141.0, 153.6, 158.2 (TFA), 158.4 (TFA), 158.6 (TFA), 158.8 (TFA), 164.2, 165.7, 166.1, 166.4, 170.3, 173.1. RP-HPLC (220 nm): 99% (t_R = 15.0 min, *k* = 4.2). HRMS (ESI): m/z $[M+H]^+$ calcd. for $[C_{61}H_{81}N_{12}O_6]^+$ 1077.6397, found: 1077.6392. $C_{61}H_{80}N_{12}O_6 \cdot C_{10}H_5F_{15}O_{10}$ (1077.39 + 570.12).

1-(2-Aminoethyl)piperidin-4-yl 2,2-diphenylacetate (65)

Compound **110** (500 mg, 1.14 mmol) was dissolved in CH_2Cl_2 (4 mL), TFA (1 mL) was added slowly and the mixture was stirred at room temperature for 8 h. 25% aq NH_3 was added slowly to adjust the pH to 11, followed by extraction with CH_2Cl_2/MeOH (9:1 v/v) (5 × 10 mL). The combined extracts were dried over Na_2SO_4 and the volatiles were evaporated to afford compound **65** as colorless oil (320 mg, 83%), which was used without further purification. R_f = 0.3 (CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.59-1.77 (m, 2H), 1.84-1.93 (m, 2H), 2.26 (t, *J* 8.5 Hz, 2H), 2.38-2.47 (m, 2H), 2.55 (brs, 2H), 2.79 (t, *J* 6.0 Hz, 4H), 4.84-4.92 (m, 1H), 5.00 (s, 1H), 7.23-7.26 (m, 2H), 7.28-7.37 (m, 8H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 30.6, 38.5, 50.5, 57.3, 59.5, 70.7, 127.2, 128.57, 128.62, 138.7, 171.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{21}H_{27}N_2O_2]^+$

339.2067, found: 339.2072. $C_{21}H_{26}N_2O_2$ (338.45).

1-(2-(3-(Aminomethyl)-5-((2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)carbamoyl)benzamido)ethyl)piperidin-4-yl 2,2-diphenylacetate pentakis(hydrotrifluoroacetate) (66)

Compound **66** was prepared from **57** (80 mg, 0.27 mmol), **55** (262 mg, 0.27 mmol) and **65** (92 mg, 0.27 mmol) according to the procedure for the synthesis of **60** and **58**. TBTU: 173 mg, 0.54 mmol; HOBt: 73 mg, 0.54 mmol; DIPEA: 95 + 95 µL, 0.54 + 0.54 mmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-95:5, t_R (**58**) = 9 min, t_R (**66**) = 11 min) afforded compounds **58** (30 mg, 6%) and **66** (120 mg, 28%) as white fluffy solids. Ratio of configurational isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.26-1.40 (m, 4H), 1.40-1.58 (m, 3H), 1.68-1.73 (m, 2H), 1.81-1.99 (m, 3H), 2.05-2.14 (m, 2H), 2.25-2.26 (m, 1H), 2.78-2.96 (m, 2H), 2.99 (t, *J* 6.7 Hz, 2H), 3.03-3.05 (m, 1H), 3.06-3.10 (m, 2H), 3.11-3.22 (m, 3H), 3.23-3.26 (m, 2H), 3.39-3.46 (m, 6H), 3.55-3.57 (m, 2H), 3.66 (t, *J* 6.2 Hz, 2H), 3.69-3.88 (m, 5H), 4.23 (s, 2H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 5.04-5.09 (m, 1H), 5.18 (d, *J* 18 Hz, 1H), 7.25-7.28 (m, 4H), 7.31-7.38 (m, 8H), 7.45-7.49 (m, 1H), 7,51 (d, *J* 7.8 Hz, 1H), 7.56-7.81 (m, 3H), 7.88-7.90 (m, 0.6H), 7.95-7.96 (M, 0.4H), 8.11-8.13 (m, 2H), 8.36 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 24.5, 25.1, 28.1, 28.9, 30.4, 34.3, 35.8, 36.1, 37.3, 43.8, 49.6, 50.9, 51.9, 54.9, 55.3, 57.4, 57.8, 58.0, 58.1, 66.0, 115.1, 116.9, 117.1 (TFA), 118.9 (TFA), 123.1, 123.7, 126.9, 127.5, 127.8, 127.9, 128.5, 128.9, 129.5, 129.7, 130.1, 130.5, 130.9, 131.2, 131.7, 131.9, 132.2, 132.3, 132.4, 133.0, 133.4, 134.6, 134.9, 135.4, 135.7, 136.1, 136.7, 137.0, 140.0, 141.0, 142.7, 158.8, 159.1, 162.4 (TFA), 162.6 (TFA), 162.8 (TFA), 163.1 (TFA), 164.9, 165.4, 168.6, 168.8, 168.9, 169.4. RP-HPLC (220 nm): 99% (t_R = 17.9 min, k = 5.2). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{60}H_{74}N_9O_6$]$^+$ 1016.5757, found: 1016.5750. $C_{60}H_{73}N_9O_6 \cdot C_{10}H_5F_{15}O_{10}$ (1016.30 + 570.12).

1-(2-(3-((2-(4-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)carbamoyl)-5-(propionamidomethyl)benzamido)ethyl)piperidin-4-yl 2,2-diphenylacetate tetrakis(hydrotrifluoroacetate) (67)

Compound **67** was prepared from **66** (15 mg, 9.5 μmol) and **42** (2.9 mg, 16.9 μmol) according to the procedure for the synthesis of **44**. DIPEA: 16 μL, 92 μmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 μm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-95:5, t_R = 11 min), afforded compound **67** as hygroscopic white fluffy solid (12.1 mg, 83%). Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.14 (t, *J* 7.6 Hz, 3H), 1.30-1.41 (m, 4H), 1.43-1.57 (m, 3H), 1.68-1.73 (m, 2H), 1.83-1.96 (m, 3H), 2.03-2.13 (m, 2H), 2.27 (q, *J* 7.6 Hz, 2H), 2.80-2.89 (m, 2H), 2.90-2.94 (m, 3H), 2.98-3.02 (m, 2H), 3.05-3.11 (m, 3H), 3.12-3.19 (m, 2H), 3.23-3.26 (m, 2H), 3.34-3.37 (m, 4H), 3.40-3.48 (m, 2H), 3.55-3.57 (m, 1H), 3.63 (t, *J* 6.2 Hz, 2H), 3.67-3.85 (m, 5H), 4.36-4.42 (m, 1H), 4.44 (s, 2H), 5.04-5.19 (m, 2H), 7.24-7.28 (m, 3H), 7.29-7.39 (m, 10H), 7.46-7.53 (m, 2H), 7.61-7.64 (m, 1H), 7.65-7.76 (m, 1H), 7.89-7.90 (m, 0.6H), 7.92 (d, *J* 9.3 Hz, 2H), 7.96-7.97 (m, 0.4H), 8.21 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.4, 24.5, 25.2, 28.2, 29.0, 30.1, 30.4, 34.3, 35.9, 36.1, 37.4, 43.7, 49.6, 50.9, 52.1, 54.9, 55.3, 57.5, 57.8, 58.1, 65.9, 116.9 (TFA), 118.9 (TFA), 123.1, 123.6, 126.4, 126.9, 127.5, 127.9, 128.5, 128.9, 129.4, 129.7, 130.1, 130.5, 130.6, 130.8, 130.9, 131.9, 132.4, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 136.2, 137.0, 140.0, 141.0, 141.7, 142.7, 162.0 (TFA), 162.3 (TFA), 162.5 (TFA), 162.8 (TFA), 164.9, 165.4, 168.6, 168.8, 169.5, 170.1, 177.1. RP-HPLC (220 nm): 98% (t_R = 18.9 min, *k* = 5.6). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{63}H_{78}N_9O_7$]$^+$ 1072.6024, found: 1072.6013. $C_{63}H_{77}N_9O_7 \cdot C_8H_4F_{12}O_8$ (1072.37 + 456.09).

2-(4-(2-Aminoethyl)piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate (68)

Compound **116** (1.0 g, 2.08 mmol) was dissolved in CH_2Cl_2 (8 mL), TFA (2 mL) was added slowly, and the mixture was stirred at room temperature overnight. 25% aq NH_3 was added to adjust the pH to 11, followed by extraction with CH_2Cl_2/MeOH (9:1 v/v) (5 × 15 mL). The combined extracts were dried over Na_2SO_4. Removal of the solvent *in vacuo* gave compound **68** as colorless oil (700 mg, 88%), which was used without further purification. R_f = 0.2

(CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 2.20-2.42 (m, 8H), 2.41-2.61 (m, 4H), 2.67-2.79 (m, 2H), 4.05-4.23 (m, 2H), 4.90 (s, 1H), 7.01-7.21 (m, 4H), 7.23-7.44 (m, 4H). ^{13}C-NMR (75 MHz, [D_4]MeOH): δ (ppm) 38.9, 46.1, 53.9, 54.0, 57.4, 60.9, 64.4, 117.8, 119.9, 124.6, 130.32, 130.34, 152.9, 173.2. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for $[C_{22}H_{28}N_3O_3]^+$ 382.2125, found: 382.2123. $C_{22}H_{27}N_3O_3$ (381.48).

2-(4-(2-(3-(Aminomethyl)-5-((2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)carbamoyl)benzamido)ethyl)piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate hexakis(hydrotrifluoroacetate) (69)

Compound **69** was prepared from **57** (80 mg, 0.27 mmol), **55** (262 mg, 0.27 mmol) and **68** (102 mg, 0.27 mmol) according to the procedure for the synthesis of **60** and **58**. TBTU: 172 mg, 0.54 mmol; HOBt: 73 mg, 0.54 mmol; DIPEA: 95 + 95 µL, 0.55 + 0.55 mmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-95:5, t_R (**58**) = 9 min, t_R (**69**) = 11 min) afforded compounds **58** (20 mg, 4%) and **69** (70 mg, 15%) as white fluffy solids. Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D_4]MeOH): δ (ppm) 1.29-1.39 (m, 5H), 1.41-1.60 (m, 3H), 1.67-1.72 (m, 2H), 1.83-2.00 (m, 2H), 2.78 (t, *J* 4.8 Hz, 2H), 2.69-2.72 (m, 4H), 2.97 (t, *J* 6.2 Hz, 2H), 3.03-3.12 (m, 6H), 3.15-3.25 (m, 4H), 3.30-3.51 (m, 8H), 3.66 (t, *J* 6.3 Hz, 2H), 3.68-3.82 (m, 4H), 4.20-4.24 (m, 2H), 4.25 (brs, 2H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 5.10 (s, 1H), 7.07-7.17 (m, 4H), 7.23-7.30 (m, 1H), 7.31-7.39 (m, 6H), , 7.46-7.53 (m, 2H), 7.61-7.65 (m, 1H), 7.66-7.71 (m, 0.6H), 7.73-7.76 (m, 0.4H), 7.89-7.90 (m, 0.6H), 7.94-7.99 (m, 0.4H), 8.10-8.18 (m, 2H), 8.38-8.39 (m, 1H). ^{13}C-NMR (150 MHz, [D_4]MeOH): δ (ppm) 23.1, 23.8, 29.0, 32.9, 34.7, 35.0, 35.9, 42.4, 45.2, 49.5, 50.1, 50.6, 51.3, 53.5, 53.9, 55.1, 55.9, 56.0, 56.4, 56.6, 61.7, 113.5 (TFA), 115.5 (TFA), 116.4, 117.4 (TFA), 118.7, 119.3 (TFA), 121.7, 122.2, 123.3, 125.5, 126.1, 126.4, 126.5, 127.1, 127.5, 128.0, 128.7, 129.0, 129.1, 129.5, 129.8, 130.3, 130.6, 130.8, 130.9, 131.0, 131.6, 132.0, 133.2, 133.5, 134.1, 134.2, 134.3, 135.0, 135.4, 135.6, 139.6, 141.3, 151.5, 160.8 (TFA), 161.0 (TFA), 161.3 (TFA), 163.5, 164.0, 167.2, 167.4, 167.5, 167.8, 171.3. RP-HPLC (220 nm): 96% (t_R = 17.9 min, *k* = 5.2). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for

$[C_{61}H_{75}N_{10}O_7]^+$ 1059.5815, found: 1059.5796. $C_{61}H_{74}N_{10}O_7 \cdot C_{12}H_6F_{18}O_{12}$ (1059.33 + 684.14).

2-(4-(2-(3-((2-(4-(4-(1-(2-Oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl) ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)carbamoyl)-5-(propionamidomethyl)benz amido)ethyl)piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate pentakis(hydrotrifluoroacetate) (70)

Compound **70** was prepared from **69** (16 mg, 9.18 μmol) and **42** (2.3 mg, 13.4 μmol) according to the procedure for the synthesis of **44**. DIPEA: 16 μL, 92 μmol. Purification by preparative HPLC (column: Kinetex XB-C18 5 μm 250 × 21 mm; gradient: 0-25 min: MeCN/0.1% aq TFA 20:80-95:5, t_R = 10 min), yielded compound **70** as hygroscopic white fluffy solid (13.3 mg, 86%). Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.14 (t, *J* 7.6 Hz, 3H), 1.27-1.41 (m, 5H), 1.41-1.57 (m, 3H), 1.67-1.72 (m, 2H), 1.88-1.95 (m, 2H), 2.28 (q, *J* 7.6 Hz, 2H), 2.65-2.71 (m, 4H), 2.78-2.83 (m, 2H), 2.81-2.97 (m, 2H), 2.96-2.98 (m, 3H), 3.01-3.09 (m, 6H), 3.12-3.25 (m, 5H), 3.35-3.45 (m, 4H), 3.65 (t, *J* 6.6 Hz, 2H), 3.69-3.72 (m, 3H), 3.73-3.81 (m, 1H), 4.18-4.25 (m, 2H), 4.39 (d, *J* 17 Hz, 0.6H), 4.43 (d, *J* 17 Hz, 0.4H), 4.46 (s, 2H), 5.10 (s, 1H), 7.10-7.14 (m, 4H), 7.24-7.30 (m, 1H), 7.30-7.34 (m, 3H), 7.34-7.41 (m, 3H), 7.45-7.50 (m, 1H), 7.49-7.53 (m, 1H), 7.59-7.66 (m, 1H), 7.66-7.71 (m, 0.6H), 7.73-7.76 (m, 0.4H), 7.89 (m, 0.6H), 7.93-7.97 (m, 2.4H), 8.23-8.24 (m, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 10.4, 24.5, 25.1, 30.1, 30.4, 34.3, 36.1, 36.4, 37.3, 43.7, 46.6, 50.9, 51.5, 52.0, 52.7, 54.9, 55.3, 56.5, 57.4, 57.5, 57.8, 58.0, 63.1, 116.9 (TFA), 117.9, 118.8 (TFA), 120.1, 123.1, 123.6, 124.6, 126.4, 126.9, 127.5, 127.9, 128.5, 128.9, 129.4, 130.1, 130.4, 130.5, 130.6, 130.7, 130.9, 131.2, 131.7, 132.0, 132.4, 133.0, 133.4, 134.6, 134.9, 135.5, 135.7, 136.1, 137.0, 141.0, 141.7, 142.7, 152.9, 162.1 (TFA), 162.4 (TFA), 162.6 (TFA), 164.9, 165.4, 168.6, 168.8, 169.6, 169.9, 172.7, 177.2. RP-HPLC (220 nm): 96% (t_R = 18.9 min, *k* = 5.6). HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{64}H_{79}N_{10}O_8]^+$ 1115.6082, found: 1115.6076. $C_{64}H_{78}N_{10}O_8 \cdot C_{10}H_5F_{15}O_{10}$ (1115.39 + 570.12).

1-(3-(4-(4-(4-(2-Aminoethyl)piperazin-1-yl)butyl)piperidin-1-yl)propyl)-3,4-dihydroquinolin-2(1*H*)-one (71)

Compound **122** (300 mg, 0.54 mmol) was dissolved in CH_2Cl_2/TFA (4:1 v/v) (5 mL) and the mixture was stirred at room temperature for 8 h. 25% aq NH_3 was added to adjust the pH to 11, followed by extraction with CH_2Cl_2/MeOH (9:1 v/v) (5 × 10 mL). The combined extracts were dried over Na_2SO_4. Removal of the volatiles *in vacuo* yielded compound **71** as yellow oil (240 mg, 97%), which was used without further purification. R_f = 0.1 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.16-1.32 (m, 7H), 1.44-1.54 (m, 2H), 1.62-1.70 (m, 2H), 1.76-1.86 (m, 2H), 1.89-1.98 (m, 2H), 2.32-2.40 (m, 6H), 2.42-2.67 (m, 10H), 2.78-2.82 (m, 2H), 2.81-2.98 (m, 4H), 3.86-4.09 (m, 2H), 6.89-7.08 (m, 1H), 7.08-7.31(m, 3H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 25.5, 25.8, 26.3, 27.7, 32.8, 33.0, 36.8, 37.6, 38.7, 41.3, 53.9, 55.1, 55.0, 57.1, 59.8, 60.1, 116.5, 124.4, 128.3, 128.7, 129.2, 140.4, 170.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{27}H_{46}N_5O]^+$ 456.3697, found: 456.3700. $C_{27}H_{45}N_5O$ (455.69).

5-(Aminomethyl)-N^1-(2-(4-(4-(1-(2-oxo-2-(11-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)ethyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)-N^3-(2-(4-(4-(1-(3-(2-oxo-3,4-dihydroquinolin-1(2*H*)-yl)propyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)isophthalamide heptakis(hydrotrifluoroacetate) (72)

Compound **72** was prepared from **57** (80 mg, 0.27 mmol), **55** (263 mg, 0.27 mmol) and **71** (123 mg, 0.27 mmol) according to the procedure for the synthesis of **60** and **58**. TBTU: 172 mg, 0.54 mmol; HOBt: 73 mg, 0.54 mmol; DIPEA: 94 + 94 µL, 0.54 + 0.54 mmol. Purification by preparative HPLC (Kinetex XB-C18 5 µm 250 × 21 mm; gradient: 0-20 min: MeCN/0.1% aq TFA 10:90-35:65, t_R (**58**) = 18.5 min, t_R (**72**) = 19.1 min) afforded compounds **58** (15 mg, 3%) and **72** (22 mg, 4%) as white fluffy solids. Ratio of isomers evident in the NMR spectra: ca 1.5:1. ^{1}H-NMR (600 MHz, [D$_4$]MeOH): δ (ppm) 1.30-1.41(m, 10H), 1.48-1.62 (m, 4H), 1.69-1.79 (m, 4H), 1.89-1.92 (m, 1H), 1.93-1.98 (m, 2H), 2.06-2.14 (m, 2H), 2.59-2.69 (m, 2H), 2.89-2.95 (m, 5H), 3.00-3.09 (m, 6H), 3.14-3.18 (m, 7H), 3.20-3.27 (m, 5H), 3.37-3.49 (m, 8H), 3.54-3.59 (m, 4H), 3.68-3.80 (m, 7H), 4.06 (t, *J* 6.3 Hz, 2H), 4.24 (s, 2H), 4.39-4.46 (m, 1H), 7.04-7.06 (m, 1H), 7.17-7.23 (m, 2H), 7.24-7.39 (m, 4H),

7.46-7.49 (m, 1H), 7.50-7.53 (m, 1H), 7.61-7.64 (m, 1H), 7.67-7.76 (m, 1H), 7.89 (d, *J* 7.5 Hz, 0.6H), 7.96 (d, *J* 7.6 Hz, 0.4H), 8.12 (s, 2H), 8.38 (s, 1H). ^{13}C-NMR (150 MHz, [D$_4$]MeOH): δ (ppm) 23.7, 24.5, 25.1, 26.1, 30.4, 30.7, 32.6, 34.3, 34.5, 36.0, 36.1, 36.2, 37.1, 37.2, 40.2, 43.8, 49.6, 50.8, 51.7, 51.8, 54.1, 54.9, 55.0, 55.3, 55.7, 57.4, 57.8, 57.9, 58.1, 61.0, 116.1, 116.9 (TFA), 118.1 (TFA), 118.9 (TFA), 123.1, 123.7, 124.8, 126.9, 127.5, 127.9, 128.2, 128.5, 128.8, 128.9, 129.3, 129.5, 130.1, 130.5, 130.9, 131.2, 131.7, 131.9, 132.2, 132.3, 133.0, 133.4, 134.6, 134.9, 135.4, 135.5, 135.7, 136.6, 137.0, 139.6, 141.0, 142.7, 162.0 (TFA), 162.3 (TFA), 162.6 (TFA), 164.9, 165.5, 168.6, 168.8, 168.9, 173.3. RP-HPLC (220 nm): 98% (t_R = 15.4 min, *k* = 4.4). HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{66}H_{93}N_{12}O_5$]$^+$ 1133.7392, found: 1133.7386. $C_{66}H_{92}N_{12}O_5 \cdot C_{14}H_7F_{21}O_{14}$ (1133.54 + 798.16).

Ethyl 2-(benzylamino)-2-oxoacetate (75)[1]

Diethyl oxalate (**73**) (2.0 g, 13.68 mmol) was mixed in chloroform (100 mL) in a 250-mL three-necked round bottom flask. A solution of benzylamine (**74**) (1.3 g, 13.68 mmol) in chloroform (50 mL) was added slowly to the reaction mixture. The reaction mixture was refluxed overnight. The solid formed during the reaction was removed by filtration and discarded. The combined filtrate and washings were concentrated under reduced pressure to give compound **75** as yellow oil (1.8 g, 65%). After cooling in the refrigerator (ca. -20 °C) overnight the oil crystallized to form a yellow solid, m.p. 45-48 °C (Lit[1] m.p. 50-51 °C). R_f = 0.2 (light petroleum/ethyl acetate 6:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.38 (t, *J* 7.1 Hz, 3H), 4.34 (q, *J* 7.1 Hz, 2H), 4.52 (d, *J* 6.0 Hz, 2H), 7.27-7.39 (m, 5H), 7.41 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.0, 43.9, 63.3, 127.9, 128.0, 128.9, 136.8, 156.5, 160.7. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{11}H_{14}NO_3$]$^+$ 208.0968, found: 208.0971. $C_{11}H_{13}NO_3$ (207.23).

***N*^{1}-Benzyl-*N*^{2}-methyloxalamide (76)**[1]

To a solution of compound **75** (1.0 g, 4.83 mmol) in abs. ethanol (20 mL) was added a 2 M solution of methylamine (3.62 mL, 7.24 mmol) in THF. A white solid was formed instantly. After 8 h, collected the solid by filtration, evaporation of the filtrate provided a second portion of product. Combined two portions of product to yield compound **76** as white powder (900

mg, 97%), m.p. 160-163 °C (Lit[1]. m.p. 184-185 °C), which was used without further purification. R_f = 0.3 (light petroleum/ethyl acetate 3:1 v/v).^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.91 (d, *J* 6.0 Hz, 3H), 4.49 (d, *J* 6.0 Hz, 2H), 7.25-7.38 (m, 5H), 7.55 (brs, 1H), 7.83 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.2, 43.7, 127.8, 127.9, 128.8, 136.8, 159.7, 160.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{10}H_{13}N_2O_2]^+$ 193.0972, found: 193.0976. $C_{10}H_{12}N_2O_2$ (192.22).

N^1-Benzyl-N^2-methylethane-1,2-diamine (77)[1]

Lithium aluminum hydride (143 mg, 3.77 mmol) was placed in a 50 mL three-necked round bottom flask with abs. THF (15 mL) under an atmosphere of argon. The suspension was immersed in an ice bath and compound **76** (290 mg, 1.51 mmol) dissolved in abs. THF (10 mL) was added to the solution dropwise. The reaction mixture was refluxed overnight. The flask was immersed in an ice bath for quenching, water (0.15 mL), 15% aq NaOH (0.45 mL) and water (0.15 mL) were added dropwise. The suspension was stirred at 0 °C for 30 min. Filtered the white solid, washed the white solid with chloroform (3 × 10 mL). The filtrate was concentrated under reduced pressure to give the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to provide compound **77** as colorless oil (150 mg, 60%). R_f = 0.3 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.91 (s, 2H), 2.39 (s, 3H), 2.64-2.71 (m, 2H), 2.72-2.74 (m, 2H), 3.77 (s, 2H), 7.18-7.24 (m, 1H), 7.27-7.29 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 36.3, 48.4, 51.4, 53.9, 126.9, 128.1, 128.4, 140.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{10}H_{17}N_2]^+$ 165.1386, found: 165.1387. $C_{10}H_{16}N_2$ (164.25).

(1- Benzyl-4-methyl-6-nitro-1,4-diazepan-6-yl) methanol (79)

Compound **77** (4.6 g, 28.04 mmol) and 2-nitroethanol (compound **78**) (1985 µL, 27.70 mmol) were dissolved in toluene/ethanol (1:1 v/v) (60 mL). Paraformaldehyde (2.5 g, 83.33 mmol) was added in small portions under stirring, and the suspension was heated to reflux for 6 h. The solvent was evaporated, and the crude product was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (3 x 20 mL). The organic phase was dried over Na_2SO_4. The product was purified by flash chromatography (eluent: light petroleum/ethyl acetate 4:1 to 2:1 v/v) to

provide compound **79** as yellow oil (6.9 g, 88%). R_f = 0.3 (light petroleum/ethyl acetate 2:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 2.53-2.76 (m, 4H), 2.96-3.16 (m, 2H), 3.42-3.50 (m, 2H), 3.54-3.76 (m, 3H), 3.76-3.88 (m, 2H), 7.22-7.37 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 48.3, 57.9, 59.0, 61.2, 61.6, 63.8, 66.2, 93.9, 127.6, 128.5, 129.1, 138.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{14}H_{22}N_3O_3]^+$ 280.1656, found: 280.1661. $C_{14}H_{21}N_3O_3$ (279.34)

1-Benzyl-4-methyl-6-nitro-1,4-diazepane (80)[13]

Potassium *tert*-butoxide (2.2 g, 19.61 mmol) was added portionwise to a solution of compound **79** (3.7 g, 13.25 mmol) in MeOH (50 mL). The mixture was heated at 40 ^{o}C for 30 min and cooled slowly to room temperature. The solvent was evaporated and the residue dissolved in a solution of $NH_2OH{\cdot}HCl$ (1.4 g, 20.15 mmol) in water (100 mL) followed by extraction with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated at ca 25 ^{o}C to afford compound **80** as yellow oil (2.2 g, 67%). R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 95:5:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.45 (s, 3H), 2.54-2.77 (m, 4H), 3.09-3.26 (m, 2H), 3.32-3.42 (m, 2H), 3.67-3.78 (m, 2H), 4.53-4.69 (m, 1H), 7.21-7.39 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 47.4, 56.7, 56.9, 58.9, 59.9, 62.9, 84.6, 127.4, 128.5, 128.8, 138.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{13}H_{20}N_3O_2]^+$ 250.1550, found: 250.1552. $C_{13}H_{19}N_3O_2$ (249.31).

***tert*-Butyl (1-benzyl-4-methyl-1,4-diazepan-6-yl)carbamate (81)**[14]

Compound **80** (4.3 g, 17.25 mmol) was dissolved in 95% ethanol (65 mL), Raney 2800 (slurry in H_2O, ca 6 mL) was carefully added, and the suspension was stirred in an autoclave (1 L) under an atmosphere of hydrogen at 10 atm at room temperature overnight. The catalyst was filtered off and the filtrate was concentrated to afford the compound 1-benzyl-4-methyl-1,4-diazepan-6-amine as a brown oily residue (3.7 g). This material (3.7 g, 16.87 mmol) was dissolved in chloroform (50 mL) and di-*tert*-butyl dicarbonate (4.5 g, 20.64 mmol) dissolved in chloroform (50 mL) was slowly added to this solution. The mixture was stirred at room temperature overnight. H_2O (50 mL) was added followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and the volatiles were

evaporated to afford the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to yield compound **81** as yellow oil (2.9 g, 53%). R_f = 0.8 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H), 2.35 (s, 3H), 2.39-2.69 (m, 5H), 2.71-2.91 (m, 3H), 3.55 (d, *J* 13 Hz, 1H), 3.67 (d, *J* 13 Hz, 1H), 3.72-3.79 (m, 1H), 5.50 (br. s, 1H), 7.18-7.39 (m, 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 28.5, 48.2, 48.8, 56.5, 58.9, 59.5, 62.2, 63.5, 78.9, 127.2, 128.4, 128.9, 139.3, 155.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{18}H_{30}N_3O_2]^+$ 320.2333, found: 320.2342. $C_{18}H_{29}N_3O_2$ (319.45).

***tert*-Butyl (2-bromoethyl)carbamate (83)**[15]

2-bromoethan-1-amine hydrobromide (compound **82**) (3.0 g, 14.63 mmol) and di-*tert*-butyl dicarbonate (3.2 g, 14.67 mmol) were dissolved in CH_2Cl_2 (80 mL). Triethylamine (2.05 mL, 14.71 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. CH_2Cl_2 (20 mL) was added, the mixture was washed with brine, and the organic phase was dried over Na_2SO_4 followed by removal of the solvent under reduced pressure. The product was purified by flash chromatography (eluent: light petroleum/ethyl acetate 8:2 v/v) to give compound **83** as yellow oil (2.6 g, 80%). R_f = 0.7 (light petroleum/ethyl acetate 2:1 v/v). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44 (s, 9H), 3.44 (t, *J* 5.5 Hz, 2H), 3.47-3.57 (m, 2H), 4.98 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): 28.4, 32.8, 42.4, 79.8, 155.5. $C_7H_{14}BrNO_2$ (224.10).

***tert*-Butyl (2-(piperazin-1-yl)ethyl)carbamate (84)**[16]

Compound **83** (1.0 g, 4.46 mmol), piperazine (compound **31**) (1.5 g, 17.44 mmol) and K_2CO_3 (1.2 g, 8.70 mmol) were added to MeCN (50 mL) and the mixture was kept under reflux for 3 h. The mixture was filtered and the filtrate was concentrated to afford a yellow oily residue, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to yield compound **84** as yellow oil (0.93 g, 91%).

R_f = 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm)1.45 (s, 9H), 2.42-2.46 (m, 6H), 2.57 (brs, 1H), 2.83-3.01 (m, 4H), 3.19-3.27 (m, 2H), 4.97 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.5, 36.9, 45.7, 53.6, 57.7, 82.6, 160.0. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{11}H_{24}N_3O_2]^+$ 230.1863, found: 230.1869. $C_{11}H_{23}N_3O_2$ (229.32).

2-Amino-2-(pyridin-3-yl)acetonitrile (86)[5]

To a cooled (5 °C) solution of potassium cyanide (10.4 g, 159.7 mmol) in water (100 mL) was added 3-pyridinecarbaldehyde (compound **85**) (11.4 g, 106.5 mmol) dropwise. Afterwards, acetic acid (9.1 mL, 159.7 mmol) was added over a period of 30 min. The mixture was stirred at room temperature for 2 h followed by extraction with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the intermediate 2-hydroxy-2-(pyridin-3-yl)acetonitrile as yellow solid (14 g), which was used without further purification. R_f = 0.4 (CH_2Cl_2/MeOH 10:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 5.65 (s, 1H), 7.38 (dd, *J* 7.9, 4.9 Hz, 1H), 7.93 (d, *J* 9.5 Hz, 1H), 8.45 (dd, *J* 4.9, 1.3 Hz, 1H), 8.58 (d, *J* 1.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 60.7, 118.9, 124.6, 133.2, 135.7, 146.8, 149.4. The intermediate (14 g, 104.4 mmol) was added to a solution of NH_4Cl (33.9 g, 633.7 mmol) in H_2O (100 mL) followed by the addition of 25% aq NH_4OH (10 mL). The mixture was stirred at room temperature for 20 h. The product was extracted with ethyl acetate (10 × 30 mL), the combined organic phases were dried over Na_2SO_4, and removal of the volatiles under reduced pressure gave compound **86** as brown oil (9.3 g, 67%). R_f = 0.3 (CH_2Cl_2/MeOH 10:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.09 (brs, 2H), 4.91 (s, 1H), 7.24-7.34 (m, 1H), 7.78-7.87 (m, 1H), 8.54 (dd, *J* 4.8, 1.5 Hz, 1H), 8.65-8.77 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 45.2, 120.2, 123.8, 132.2, 134.5, 148.3, 150.3. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_7H_8N_3]^+$ 134.0713, found: 134.0713. $C_7H_7N_3$ (133.15).

3-Chloro-4-(pyridin-3-yl)-1,2,5-thiadiazole (87)[5]

To a cooled (5-10 °C) solution of S_2Cl_2 (10.8 mL, 137.2 mmol) in DMF (50 mL) was added a solution of compound **86** (9.1 g, 68.34 mmol) in DMF (65 mL) over a period of 1 h. The mixture was stirred at 5-10 ^{o}C for additional 45 min and ice water (30 mL) was added. The

formed precipitate was removed by filtration. To the filtrate was added 20% NaOH solution to adjust a pH of 8, thereby keeping the temperature below 20 °C. The product was extracted with ethyl acetate (3 × 20 mL), the combined organic phases were dried over Na_2SO_4, and the volatiles were removed under reduced pressure. The residue was subjected to flash chromatography (eluent: light petroleum/ethyl acetate 3:2 v/v) to afford compound **87** as a white solid (9.4 g, 69%), m.p. 40-42 °C (Lit[5]. m.p. 48-49 °C). R_f = 0.7 (light petroleum/acetone 1:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.41-7.46 (m, 1H), 8.24-8.28 (m, 1H), 8.72 (dd, *J* 4.9, 1.6 Hz, 1H), 9.20 (dd, *J* 2.2, 0.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 123.4, 126.9, 135.7, 143.6, 149.4, 150.9, 155.2. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_7H_5ClN_3S]^+$ 197.9887, found: 197.9893. $C_7H_4ClN_3S$ (197.64).

3-((4-(Pyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propan-1-ol (89)[7]

A suspension of 60% NaH in mineral oil (363 mg, 9.47 mmol) was added to abs. THF (10 mL) under an atmosphere of argon. The mixture was cooled to 0 °C and propane-1,3-diol (compound **88**) (460 mg, 6.04 mmol) was added under stirring. The mixture was then kept under reflux for 1 h. A solution of compound **87** (600 mg, 3.03 mmol) in abs. THF (10 mL) was added and reflux was continued for 8 h. The solvent was removed under reduced pressure and ice-cold water (20 mL) was added dropwise to the residue followed by extraction with ethyl acetate (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to flash chromatography (eluent: light petroleum/acetone 2:1 v/v) to afford compound **89** as yellow oil (370 mg, 52%). R_f = 0.3 (light petroleum/acetone 2:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.08-2.20 (m, 2H), 2.19 (brs, 1H), 3.87 (t, *J* 6.0 Hz, 2H), 4.69 (t, *J* 6.1 Hz, 2H), 7.36-7.40 (m, 1H), 8.30-8.54 (m, 1H), 8.62 (dd, *J* 4.8, 1.6 Hz, 1H), 9.36 (dd, *J* 2.1, 0.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 31.9, 59.0, 68.2, 123.6, 127.7, 134.9, 144.8, 148.4, 149.9, 162.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{10}H_{12}N_3O_2S]^+$ 238.0645, found: 238.0651. $C_{10}H_{11}N_3O_2S$ (237.28).

3-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)propan-1-ol (90)[7]

To a solution of compound **89** (370 mg, 1.56 mmol) in acetone (5 mL) was added methyliodide (0.97 mL, 15.6 mmol) and the mixture was stirred at room temperature for 24 h. The formed precipitate was collected by filtration and washed with acetone (5 mL). Drying *in vacuo* gave the N-methylated, but non-reduced intermediate as yellow solid (480 mg). R_f = 0.1 (CH_2Cl_2/MeOH 10:1 v/v). ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 1.99-2.06 (m, 2H), 3.59-3.65 (m, 2H), 4.45 (s, 3H), 4.62 (t, *J* 6.3 Hz, 2H), 8.28 (dd, *J* 8.2, 6.2 Hz, 1H), 9.07 (dd, *J* 12, 7.3 Hz, 2H), 9.54 (s, 1H). The intermediate (470 mg, 1.24 mmol) was dissolved in MeOH (10 mL). The solution was cooled to -5 °C and $NaBH_4$ (143 mg, 3.76 mmol) was added carefully. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 10 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v) to afford compound **90** as brown oil (130 mg, 33%). R_f = 0.3 (CH_2Cl_2/MeOH/25% aq NH_3 85:15:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 2.03-2.11 (m, 2H), 2.38-2.51 (m, 5H), 2.56 (brs, 1H), 2.59 (t, *J* 5.6 Hz, 2H), 3.40-3.54 (m, 2H), 3.78 (t, *J* 6.1 Hz, 2H), 4.59 (t, *J* 6.1 Hz, 2H), 6.87-7.13 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 26.5, 32.0, 45.9, 51.2, 54.9, 59.3, 67.9, 128.4, 129.2, 146.7, 162.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{11}H_{18}N_3O_2S]^+$ 256.1114, found: 256.1115. $C_{11}H_{17}N_3O_2S$ (255.34).

5-((4-(Pyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentan-1-ol (92)

A suspension of 60% NaH in mineral oil (908 mg, 23.69 mmol) was added to abs. THF (40 mL) under an atmosphere of argon. The suspension was cooled to 0 °C, 1,5-pentanediol (compound **91**) (2.0 g, 19.20 mmol) was added under stirring, and the mixture was refluxed for 1 h. A solution of compound **87** (1.5 g, 7.58 mmol) in abs. THF (10 mL) was added and reflux was continued for 8 h. The solvent was removed under reduced pressure and ice-cold water (40 mL) was added dropwise to the residue followed by extraction with ethyl acetate (3

× 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to flash chromatography (eluent: light petroleum/acetone 2:1 v/v) to afford compound **92** as colorless oil (960 mg, 48%). R_f = 0.3 (light petroleum/acetone 2:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.50-1.76 (m, 4H), 1.86 (brs, 1H), 1.89-1.98 (m, 2H), 3.69 (t, *J* 6.2 Hz, 2H), 4.54 (t, *J* 6.5 Hz, 2H), 7.40 (dd, *J* 8.0, 4.9 Hz, 1H), 8.42 (d, *J* 8.0 Hz, 1H), 8.64 (d, *J* 4.8 Hz, 1H), 9.40 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 21.6, 28.2, 32.6, 62.2, 71.4, 123.4, 127.4, 134.7, 144.5, 147.9, 150.4, 162.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{12}H_{16}N_3O_2S]^+$ 266.0958, found: 266.0966. $C_{12}H_{15}N_3O_2S$ (265.33).

5-((4-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentan-1-ol (93)

To a solution of compound **92** (0.96 g, 3.62 mmol) in acetone (15 mL) was added methyliodide (2.3 mL, 36.2 mmol) and the mixture was stirred at room temperature for 24 h. The formed precipitate was collected by filtration, washed with acetone and dried under vacuum to yield the N-methylated, but non-reduced intermediate as yellow solid (1.4 g). R_f = 0.1 (CH_2Cl_2/MeOH 6:1 v/v). ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 1.51-1.73 (m, 4H), 1.87-2.07 (m, 2H), 3.60 (t, *J* 5.9 Hz, 2H), 4.52 (s, 3H), 4.65 (t, *J* 6.5 Hz, 2H), 8.22 (dd, *J* 8.1, 6.2 Hz, 1H), 8.96 (d, *J* 6.1 Hz, 1H), 9.24 (d, *J* 8.3 Hz, 1H), 9.57 (s, 1H). The intermediate (1.4 g, 3.44 mmol) was dissolved in MeOH (20 mL) and the solution was cooled to -5 °C. $NaBH_4$ (519 mg, 13.66 mmol) was added carefully. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:3:1 v/v/v) to afford **93** as brown oil (900 mg, 88%). R_f = 0.3 (CH_2Cl_2/MeOH/25% aq NH_3 85:15:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.47-1.59 (m, 2H), 1.59-1.69 (m, 2H), 1.78-1.98 (m, 2H), 2.39- 2.49 (m, 5H), 2.57 (t, *J* 5.6 Hz, 2H), 3.44 (dd, *J* 4.4, 2.4 Hz, 2H), 3.66 (t, *J* 6.3 Hz, 2H), 4.44 (t, *J* 6.6 Hz, 2H), 7.00-7.09 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 22.3,

26.6, 28.6, 32.3, 45.9, 51.2, 54.9, 62.6, 70.8, 128.4, 129.2, 146.8, 162.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{13}H_{22}N_3O_2S]^+$ 284.1427, found: 284.1430. $C_{13}H_{21}N_3O_2S$ (283.39).

***tert*-Butyl (5-((4-(pyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)carbamate (95)**

To a cooled (0 °C) solution of 5-amino-1-pentanol (1.0 g, 9.67 mmol) and triethylamine (1.2 mL, 8.89 mmol) in CH_2Cl_2 (50 mL) was slowly added di-*tert*-butyl dicarbonate (1.9 g, 8.71 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C for 30 min and stirring was continued at room temperature for additional 12 h. Saturated aq NH_4Cl (20 mL) was added followed by extraction with CH_2Cl_2 (3 x 20 mL). The combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the intermediate *tert*-butyl (5-hydroxypentyl)carbamate (compound **94**)[17] as colorless oil (1.9 g) without purification. R_f = 0.5 (light petroleum/acetone 2:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.42 (s, 9H), 1.46-1.61 (m, 6H), 1.63 (brs, 1H), 3.12 (t, *J* 6.9 Hz, 2H), 3.64 (t, *J* 6.4 Hz, 2H), 4.53 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 22.9, 28.4, 29.8, 32.2, 40.4, 62.5, 79.2, 156.0. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{10}H_{22}NO_3]^+$ 204.1594, found: 204.1595. To a stirred and cooled (0 °C) solution of compound **94** (307 mg, 1.51 mmol) in abs. THF (5 mL) was added the suspension of 60% NaH in mineral oil (73 mg, 1.90 mmol) in portions under an atmosphere of argon, followed by the addition of **87** (200 mg, 1.01 mmol) dissolved in abs. THF (2 mL). The mixture was stirred at 0 °C for 5 min and slowly warmed up until reflux. Reflux was continued for 2 h. The solvent was removed under reduced pressure and ice-cold water (10 mL) was added dropwise to the residue followed by extraction with ethyl acetate (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to flash chromatography (eluent: light petroleum/acetone 5:1 v/v) to afford compound **95** as colorless oil (100 mg, 27%). R_f = 0.4 (light petroleum/acetone 2:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (s, 9H), 1.47-1.67 (m, 4H), 1.82-1.99 (m, 2H), 3.12-3.18 (m, 2H), 4.52 (t, *J* 6.5 Hz, 2H), 4.70 (brs, 1H), 7.33-7.51 (m, 1H), 8.33-8.51 (m, 1H), 8.65 (dd, *J* 4.8, 1.5 Hz, 1H), 9.39 (d, *J* 1.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.3, 28.4, 28.6, 29.8, 40.4, 71.1, 79.1, 123.5, 127.6, 134.7, 144.9, 148.5, 150.1, 156.0, 162.7. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{17}H_{25}N_4O_3S]^+$ 365.1642, found: 365.1644.

$C_{17}H_{24}N_4O_3S$ (364.46).

***tert*-Butyl (5-((4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazol-3-yl)oxy)pentyl)carbamate (96)**

To a solution of compound **95** (3.3 g, 9.05 mmol) in acetone (10 mL) was added methyliodide (5.7 mL, 91.2 mmol) and the mixture was stirred at room temperature for 24 h. The formed precipitated was collected, washed with acetone and dried under vacuum to afford the N-methylated, but non-reduced intermediate as yellow solid (3.3 g, 96%). R_f = 0.1 (CH_2Cl_2/MeOH 6:1 v/v). This intermediate (3.0 g, 7.91 mmol) was dissolved in MeOH (50 mL) and the solution was cooled to -5 °C followed by the careful addition of $NaBH_4$ (2.1 g, 55.26 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 97:3:1 v/v/v) to afford compound **96** as brown oil (2.4 g, 79%). R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 9H), 1.38-1.62 (m, 4H), 1.76-1.94 (m, 2H), 2.49 (s, 3H), 2.41-2.52 (m, 2H), 2.60 (t, *J* 5.6 Hz, 2H), 3.14 (dd, *J* 13, 6.3 Hz, 2H), 3.46-3.48 (m, 2H), 4.44 (t, *J* 6.6 Hz, 2H), 4.57 (brs, 1H), 7.00-7.08 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 23.3, 26.4, 28.4, 28.5, 29.8, 40.4, 45.8, 51.2, 54.8, 70.7, 79.1, 128.3, 129.0, 146.6, 156.0, 162.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{18}H_{31}N_4O_3S]^+$ 383.2111, found: 383.2103. $C_{18}H_{30}N_4O_3S$ (382.52).

4-((*tert*-Butoxycarbonyl)amino)butanoic acid (97)[18]

4-aminobutanoic acid (200 mg, 1.93 mmol) was dissolved in H_2O/THF (1:1 v/v) (10 mL) and di-*tert*-butyl dicarbonate (507 mg, 2.32 mmol) was slowly added followed by the addition of triethylamine (810 μL, 5.82 mmol). The mixture was stirred at room temperature overnight. THF was removed under reduced pressure and 0.1 M aq $KHSO_4$ solution was slowly added to

adjust the pH to 3. The product was extracted with ethyl acetate (3 × 10 mL), the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to yield the product as colorless oil (270 mg, 69%), which was used without further purification. R_f = 0.8 (CH_2Cl_2/MeOH/acetic acid 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.43 (s, 9H), 1.75-1.86 (m, 2H), 2.38 (t, *J* 7.2 Hz, 2H), 3.16 (t, *J* 6.7 Hz, 2H), 4.75 (brs, 1H), 10.06 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 25.1, 28.4, 31.3, 39.8, 60.5, 171.4, 178.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_9H_{16}NO_4]^+$ 202.1085, found: 202.1090.

Ethyl 4-((2-nitrophenyl)amino)piperidine-1-carboxylate (100)[19]

Ethyl 4-aminopiperidine-1-carboxylate (compound **99**) (244 mg, 1.42 mmol) and potassium carbonate (587 mg, 4.25 mmol) were added to a stirred solution of 1-fluoro-2-nitrobenzene (compound **98**) (200 mg, 1.42 mmol) in DMF (1.5 mL) followed by the addition of sodium iodide (106 mg, 0.71 mmol). The mixture was stirred at 180 ^{o}C under microwave irradiation for 10 min, cooled to room temperature and diluted with water (50 mL). The product was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave compound **100** as yellow solid (300 mg, 72%), which was used without further purification. R_f = 0.2 (light petroleum/ethyl acetate 5:1 v/v), m.p. 80-82 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.28 (t, *J* 7.1 Hz, 3H), 1.51-1.63 (m, 2H), 1.70 (brs, 1H), 2.05-2.11 (m, 2H), 3.04-3.20 (m, 2H), 3.66-3.74 (m, 1H), 4.05-4.19 (m, 4H), 6.63-6.68 (m, 1H), 6.87 (d, *J* 8.4 Hz, 1H), 7.37-7.50 (m, 1H), 8.19 (dd, *J* 8.6, 1.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 14.7, 31.7, 42.2, 49.1, 61.6, 113.9, 115.5, 127.3, 132.0, 136.3, 144.3, 155.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{14}H_{20}N_3O_4]^+$ 294.1448, found: 294.1453. $C_{14}H_{19}N_3O_4$ (293.32).

Ethyl 4-((2-aminophenyl)amino)piperidine-1-carboxylate (101)[20]

A mixture of compound **100** (200 mg, 0.68 mmol), 10% Pd/C (20 mg) and MeOH (10 mL) was stirred in an autoclave (1 L) under an atmosphere of hydrogen at 10 atm at room temperature overnight. The catalyst was removed by filtation through a pad of celite, which was washed with MeOH (2 × 5 mL). The combined filtrates were concentrated under reduced pressure to give compound **101** as purple solid (160 mg, 89%), which was used without

further purification. R_f= 0.4 (light petroleum/acetone = 4:1), m.p. 138-140 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.27 (t, *J* 7.1 Hz, 3H), 1.35-1.48 (m, 2H), 1.98-2.12 (m, 2H), 2.90-3.09 (m, 3H), 3.20 (brs, 1H), 3.34-3.51 (m, 2H), 4.07 (brs, 2H), 4.15 (q, *J* 12 Hz, 2H), 6.64-6.89 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 14.7, 32.3, 42.6, 50.3, 61.4, 113.9, 117.1, 119.6, 120.6, 135.2, 135.3, 155.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{14}H_{22}N_3O_2]^+$ 264.1707, found: 264.1718. $C_{14}H_{21}N_3O_2$ (263.34).

Ethyl 4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxylate (102)

A solution of triphosgene (85 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over 10 min to a stirred and cooled (0 °C) mixture of compound **101** (50 mg, 0.19 mmol), sodium bicarbonate (24 mg, 0.28 mmol) in CH_2Cl_2 (10 mL). The mixture was slowly warmed up to room temperature and stirred for additional 2 h. Water (5 mL) was added slowly and the organic phase was separated followed by additional extraction with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was subjected to column chromatography (eluent: light petroleum/acetone 2:1 v/v) to give compound **102** as white solid (40 mg, 73%). R_f = 0.3 (light petroleum/ethyl acetate 1:1 v/v), m.p. 173-176 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.30 (t, *J* 7.1 Hz, 3H), 1.84-1.95 (m, 2H), 2.30-2.41 (m, 2H), 2.89-2.98 (m, 2H), 4.19 (q, *J* 7.1 Hz, 2H), 4.37-4.41 (m, 2H), 4.46-4.57 (m, 1H), 7.05-7.16 (m, 4H), 10.25 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 14.7, 30.9, 43.6, 50.8, 61.6, 109.4, 110.0, 121.2, 121.5, 128.1, 128.9, 155.5, 206.9. HRMS (ESI): *m/z* [*M*+H]+ calcd. for $[C_{15}H_{20}N_3O_3]^+$ 290.1499, found: 290.1515. $C_{15}H_{19}N_3O_3$ (289.34).

1-(Piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (103)[21]

Compound **102** (200 mg, 0.69 mmol) was suspended in 10% aq NaOH (16 mL), the mixture was kept under reflux for 5 h, and cooled to room temperature and acidified by the addition of 10% HCl solution until the evolution of gas had ceased (pH around 2). Afterwards, the pH was carefully adjusted to 9 using 15% NaOH solution, followed by extraction with CH_2Cl_2 (4 x 10 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give compound **103** as white solid (120 mg, 81%), m.p. 112-115 °C,

which was used without further purification. R_f = 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, [D_6]DMSO): δ (ppm) 1.56-1.60 (m, 2H), 2.08-2.30 (m, 2H), 2.53-2.61 (m, 2H), 3.04-3.08 (m, 2H), 3.29 (brs, 1H), 4.17-4.28 (m, 1H), 6.92-7.03 (m, 3H), 7.28 (dd, *J* 7.1, 2.4 Hz, 1H), 10.83 (brs, 1H). ^{13}C-NMR (75 MHz, [D_6]DMSO): δ (ppm) 29.8, 45.6, 50.1, 108.7, 108.8, 120.1, 120.3, 128.2, 129.0, 153.5. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{12}H_{16}N_3O$]$^+$ 218.1288, found: 218.1289. $C_{12}H_{15}N_3O$ (217.27).

tert-Butyl 4-oxopiperidine-1-carboxylate (104)[22]

4-Piperidine hydrochloride (5.0 g, 32.55 mmol) and sodium bicarbonate (5.5 g, 65.49 mmol) were added to THF/H_2O (1:1 v/v) (150 mL) followed by the slow addition of di-*tert*-butyl dicarbonate (5.7 g, 26.12 mmol) in THF (20 mL). The mixture was stirred at room temperature overnight. THF was evaporated and the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by column chromatography (eluent: light petroleum/ethyl acetate 7:1 v/v) to give **104** as white solid (6.4 g, 98%). R_f = 0.8 (CH_2Cl_2/MeOH 30:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.49 (s, 9H), 2.43 (t, *J* 6.0 Hz, 4H), 3.73 (t, *J* 6.0 Hz, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 28.4, 41.2, 43.1, 80.5, 154.6, 208.1. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for [$C_{10}H_{18}NO_3$]$^+$ 200.1281, found: 200.1279. $C_{10}H_{17}NO_3$ (199.25).

tert-Butyl 4-hydroxypiperidine-1-carboxylate (108)[23]

Di-*tert*-butyl dicarbonate (5.6 g, 25.68 mmol) in THF (20 mL) was slowly added to a solution of piperidin-4-ol (2.0 g, 19.77 mmol) and triethylamine (3.6 mL, 25.70 mmol) in THF/H_2O (1:7 v/v) (200 mL) and the mixture was stirred at room temperature overnight. THF was removed by evaporation followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography (eluent: CH_2Cl_2/MeOH 30:1 to 15:1 v/v) to yield **108** as white solid (3.7 g, 93%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 9H), 1.53-1.61 (m, 2H), 1.80-1.91 (m, 2H), 2.96-3.08 (m, 2H), 3.78-3.91 (m, 3H). $C_{10}H_{19}NO_3$ (201.27).

***tert*-Butyl 4-(2,2-diphenylacetoxy)piperidine-1-carboxylate (109)**[24]

Compound **108** (2.9 g, 14.41 mmol) and 2,2-diphenylacetic acid (compound **107**) (2.7 g, 12.74 mmol) were dissolved in CH_2Cl_2 (100 mL) and the solution was cooled to 0 °C. DMAP (173 mg, 1.42 mmol) was added and the mixture was allowed to clear up before the slow addition of *N*,*N'*-dicyclohexylcarbodiimide (3.2 g, 15.51 mmol) under stirring at 0 °C. The mixture was slowly warmed up to room temperature and kept under stirring overnight. H_2O (50 mL) was added, the phases were separated and the aqueous phase was treated with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was subjected to column chromatography (eluent: light petroleum/acetone 3:1 v/v) to afford compound **109** as yellow oil (4.9 g, 97%). R_f = 0.8 (light petroleum/acetone 3:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H), 1.49-1.59 (m, 2H), 1.72-1.82 (m, 2H), 3.15-3.24 (m, 2H), 3.15-3.24 (m, 2H), 4.93-5.00 (m, 2H), 7.18-7.29 (m, 10H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 28.4, 30.3, 57.3, 65.9, 70.4, 79.7, 127.3, 128.5, 128.6, 138.6, 154.7, 171.8. HRMS (ESI): *m/z* $[M+Na]^+$ calcd. for $[C_{24}H_{29}NNaO_4]^+$ 418.1989, found: 418.1988. $C_{24}H_{29}NO_4$ (395.50).

1-(2-((*tert*-Butoxycarbonyl)amino)ethyl)piperidin-4-yl 2,2-diphenylacetate (110)

Compound **47** (150 mg, 0.51 mmol), *tert*-butyl (2-bromoethyl) carbamate (**83**) (136 mg, 0.61 mmol) and potassium carbonate (140 mg, 1.01 mmol) were added to MeCN (50 mL) and the mixture was refluxed for 3 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 5 mL). The combined filtrate and washings were concentrated under reduced pressure to yield a brown residue, which was dissolved in CH_2Cl_2 (10 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 5 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to flash chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to yield compound **110** as colorless oil (150 mg, 67%). R_f = 0.6 (CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.40 (s, 9H), 1.58-1.70 (m, 2H), 1.81-1.95 (m, 2H), 2.21-2.30 (m, 2H), 2.39 (t, *J* 12 Hz, 2H), 2.49-2.59 (m, 2H), 3.16-3.18 (m, 2H), 4.82-4.89 (m, 1H), 4.96 (s,

1H), 5.03 (brs, 1H), 7.18-7.28 (m, 10H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 28.5, 30.2, 37.1, 50.2, 57.1, 57.3, 70.3, 79.3, 127.3, 128.59, 128.60, 138.7, 155.9, 171.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{26}H_{35}N_2O_4]^+$ 439.2591, found: 439.2619. $C_{26}H_{34}N_2O_4$ (438.57).

2-Bromoethyl 9*H*-xanthene-9-carboxylate (114)

9*H*-Xanthene-9-carboxylic acid (compound **111**) (1.0 g, 4.42 mmol) and 2-bromoethan-1-ol (1.1 g, 8.87 mmol) were dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to 0 °C. *N*,*N*′-Dicyclohexylcarbodiimide (1.1 g, 5.34 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise followed by the addition of DMAP (270 mg, 2.21 mmol). The mixture was allowed to warm up to room temperature and stirring was continued overnight. H_2O (50 mL) was added, the phases were separated and the aqueous phase was treated with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (eluent: light petroleum/acetone 7:1 v/v) afforded compound **114** as colorless oil (1.0 g, 68%). R_f = 0.7 (light petroleum/acetone 3:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 3.40 (t, *J* 6.1 Hz, 2H), 4.35 (t, *J* 6.1 Hz, 2H), 5.06 (s, 1H), 7.06-7.19 (m, 4H), 7.27-7.36 (m, 4H). ^{13}C-NMR (75 MHz, CDCl3): δ (ppm) 28.3, 45.2, 64.5, 117.1, 117.9, 123.4, 129.1, 129.3, 151.4, 171.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{16}H_{14}BrO_3]^+$ 333.0121, found: 333.0124. $C_{16}H_{13}BrO_3$ (333.18).

4-Bromobutyl 9*H*-xanthene-9-carboxylate (115)

9*H*-Xanthene-9-carboxylic acid (compound **111**) (2.0 g, 8.84 mmol) and 4-bromobutan-1-ol (1.6 g, 10.61 mmol) were dissolved in CH_2Cl_2 (30 mL) and the mixture was cooled to 0 °C. A solution of *N*, *N*′-dicyclohexylcarbodiimide (2.2 g, 10.61 mmol) in CH_2Cl_2 (5 mL) was added dropwise followed by the addition of DMAP (270 mg, 2.21 mmol). The mixture was allowed to warm up to room temperature and stirring was continued overnight. H_2O (20 mL) was added, the phases were separated and the aqueous phase was treated with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (eluent: light petroleum/acetone 7:1 v/v) yielded compound **115** as colorless oil (1.8 g, 56%). R_f= 0.7 (light

petroleum/acetone 4:1 v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.59-1.74 (m, 4H), 3.23 (t, *J* 9.0 Hz, 2H), 4.06 (t, *J* 6.0 Hz, 2H), 4.99 (s, 1H), 7.04-7.18 (m, 4H), 7.26-7.34 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 27.1, 29.0, 33.0, 45.7, 64.5, 117.1, 118.5, 123.4, 128.9, 129.3, 151.4, 171.9. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{18}H_{18}BrO_3]^+$ 361.0434, found: 361.0435. $C_{18}H_{17}BrO_3$ (361.24).

2-(4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)piperazin-1-yl)ethyl 9*H*-xanthene-9-carboxylate (116)

Compound **36** (1.27 g, 3.76 mmol), *tert*-butyl (2-bromoethyl) carbamate (**83**) (921 mg, 4.13 mmol) and potassium carbonate (1.3 g, 9.41 mmol) were added to MeCN (30 mL) and the mixture was kept under reflux for 2 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the volatiles were removed under reduced pressure yielding a yellow oily residue, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to afford compound **116** as yellow oil (1.03 g, 57%). R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.45 (d, *J* 5.3 Hz, 9H), 2.13-2.38 (m, 8H), 2.42 (t, *J* 5.9 Hz, 2H), 2.45-2.55 (m, 2H), 3.19-3.27 (m, 2H), 4.08-4.19 (m, 2H), 4.99 (s, 1H), 5.04 (brs, 1H), 7.04-7.11 (m, 2H), 7.04-7.13 (m, 2H), 7.23-7.31 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 28.5, 37.0, 45.5, 52.8, 53.5, 56.3, 57.0, 63.3, 79.2, 116.9, 118.4, 123.3, 129.0, 129.1, 151.3, 155.9, 171.6. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{27}H_{36}N_3O_5]^+$ 482.2649, found: 482.2645. $C_{27}H_{35}N_3O_5$ (481.59).

1-(3-Chloropropyl)-3,4-dihydroquinolin-2(1*H*)-one (119)[10]

3,4-Dihydroquinolin-2(1*H*)-one (compound **117**) (1.0 g, 6.80 mmol), 1-chloro-3-iodopropane (**118**) (1.7 mg, 8.32 mmol) and caesium carbonate (4.4 g, 13.51 mmol) were added to MeCN (50 mL) and the mixture was stirred and heated to 50 ^{o}C for 12 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 20 mL). The filtrate and washings were

combined and the volatiles were removed under reduced pressure yielding a yellow solid, which was dissolved in CH_2Cl_2 (20 mL). This solution was washed with brine, the phases were separated and the aqueous phase was treated with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to yield a yellow oil, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to afford compound **119** as yellow oil (1.05 g, 69%). R_f = 0.7 (CH_2Cl_2/MeOH/25% aq NH_3 90:3:1). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 2.07-2.21 (m, 2H), 2.59-2.70 (m, 2H), 2.81-2.98 (m, 2H), 3.56-3.71 (m, 2H), 4.00-4.20 (m, 2H), 6.97-7.10 (m, 2H), 7.15-7.31 (m, 2H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 25.5, 30.2, 31.8, 40.1, 42.8, 114.6, 122.9, 126.5, 127.6, 128.1, 139.4, 170.4. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for $[C_{12}H_{15}ClNO]^+$ 224.0837, found: 224.0846. $C_{12}H_{14}ClNO$ (223.70).

1-(3-(4-(4-Hydroxybutyl)piperidin-1-yl)propyl)-3,4-dihydroquinolin-2(1*H*)-one (121)

4-(Piperidin-4-yl)butanoic acid hydrochloride (1.0 g, 4.81 mmol) was suspended in anhydrous THF (20 mL) under an atmosphere of argon. The suspension was immersed in an ice bath and lithium aluminium hydride (456 mg, 12.01 mmol) was added in portions under stirring. The mixture was slowly warmed up to room temperature, then kept under reflux overnight, and cooled in an ice bath. For quenching, water (5 mL), 15% NaOH solution (10 mL) and water (10 mL) were added dropwise to reaction mixture. Insoluble material was separated by filtration and washed with chloroform (3 × 20 mL). The combined filtrate and washings were dried over Na_2SO_4 and concentrated under reduced pressure to give the intermediate 4-(piperidin-4-yl)butan-1-ol[25] (compound **120**) as colorless oil-like residue (510 mg, 68%), which was used without further purification. R_f = 0.1 (CH_2Cl_2/MeOH/25% aq NH_3 66:33:1 v/v/v). ^{1}H-NMR (300 MHz, [D$_4$]MeOH): δ (ppm) 1.04-1.18 (m, 2H), 1.20-1.31 (m, 2H), 1.31-1.44 (m, 3H), 1.47-1.57 (m, 2H), 1.70 (d, *J* 12 Hz, 2H), 2.55-2.57 (m, 2H), 2.99-3.01 (m, 2H), 3.54 (t, *J* 6.5 Hz, 2H). ^{13}C-NMR (75 MHz, [D$_4$]MeOH): δ (ppm) 23.9, 33.8, 33.9, 37.2, 38.2, 47.1, 62.9. HRMS (ESI): *m/z* [*M*+H]$^+$ calcd. for $[C_9H_{20}NO]^+$ 158.1539, found: 158.1541. The intermediate **120** (867 mg, 5.52 mmol) and compound **119** (1.1 g, 4.92 mmol) were dissolved in MeCN (30 mL), followed by the addition of potassium carbonate (1.4 g, 10.14 mmol) and sodium iodide (376 mg, 2.51 mmol). The mixture was kept at 50 ^{o}C for 24 h.

Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 10 mL). The filtrate and washings were combined and the solvent was removed under reduced pressure to yield a yellow residue, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v) to afford compound **121** as colorless oil (900 mg, 53%). R_f = 0.4 (CH_2Cl_2/MeOH/25% aq NH_3 90:10:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.26-1.42 (m, 7H), 1.45-1.59 (m, 2H), 1.68 (brs, 1H), 1.68-1.72 (m, 2H), 1.84-2.12 (m, 4H), 2.45-2.56 (m, 2H), 2.59-2.65 (m, 2H), 2.77-2.94 (m, 2H), 2.99-3.03 (m, 2H), 3.62 (t, *J* 6.4 Hz, 2H), 3.90-4.00 (m, 2H), 6.96-7.01 (m, 1H), 7.07 (d, *J* 7.7 Hz, 1H), 7.13-7.16 (m, 1H), 7.20-7.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.4, 22.9, 24.4, 25.4, 31.8, 32.9, 36.0, 40.5, 50.8, 53.9, 55.9, 62.8, 114.9, 122.9, 126.4, 127.6, 128.0, 139.4, 170.4. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{21}H_{33}N_2O_2]^+$ 345.2537, found: 345.2565. $C_{21}H_{32}N_2O_2$ (344.50).

***tert*-Butyl (2-(4-(4-(1-(3-(2-oxo-3,4-dihydroquinolin-1(2*H*)-yl)propyl)piperidin-4-yl)butyl)piperazin-1-yl)ethyl)carbamate (122)**

Compound **49** (1.21 g, 2.97 mmol), *tert*-butyl (2-(piperazin-1-yl) ethyl)carbamate (**84**) (1.5 g, 6.55 mmol) and potassium carbonate (1.24 g, 8.99 mmol) were added to MeCN (60 mL) and the stirred mixture was kept under reflux for 2 h. Insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure yielding a yellow oily residue, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with water. The aqueous phase was treated with CH_2Cl_2 (3 × 30 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 90:3:1 v/v/v) to afford compound **122** as yellow oil (1.02 g, 62%). R_f = 0.5 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 1.13-1.18 (m, 7H), 1.38 (s, 9H), 1.39-1.44 (m, 2H), 1.53-1.62 (m, 2H), 1.71-1.94 (m, 4H), 2.19-2.29 (m,

2H), 2.30-2.51 (m, 10H), 2.54-2.59 (m, 3H), 2.74-2.94 (m, 4H), 3.08-3.21 (m, 2H), 3.90 (t, *J* 6.0 Hz, 2H), 6.89-6.95 (m, 1H), 7.02-7.09 (m, 2H), 7.05-7.11 (m, 1H), 7.12-7.20 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) 24.7, 25.6, 27.1, 28.5, 31.9, 32.2, 35.6, 36.4, 37.1, 40.5, 52.9, 53.2, 54.1, 56.1, 57.1, 58.8, 65.9, 79.1, 114.9, 122.7, 126.5, 127.5, 127.9, 139.6, 155.9, 170.2. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{32}H_{54}N_5O_3]^+$ 556.4221, found: 556.4227. $C_{32}H_{53}N_5O_3$ (555.81)

5-(2-(4-(4-Hydroxybutyl)piperidin-1-yl)acetyl)-5,10-dihydro-11*H*-dibenzo[*b,e*][1,4]diazepin-11-one (124)

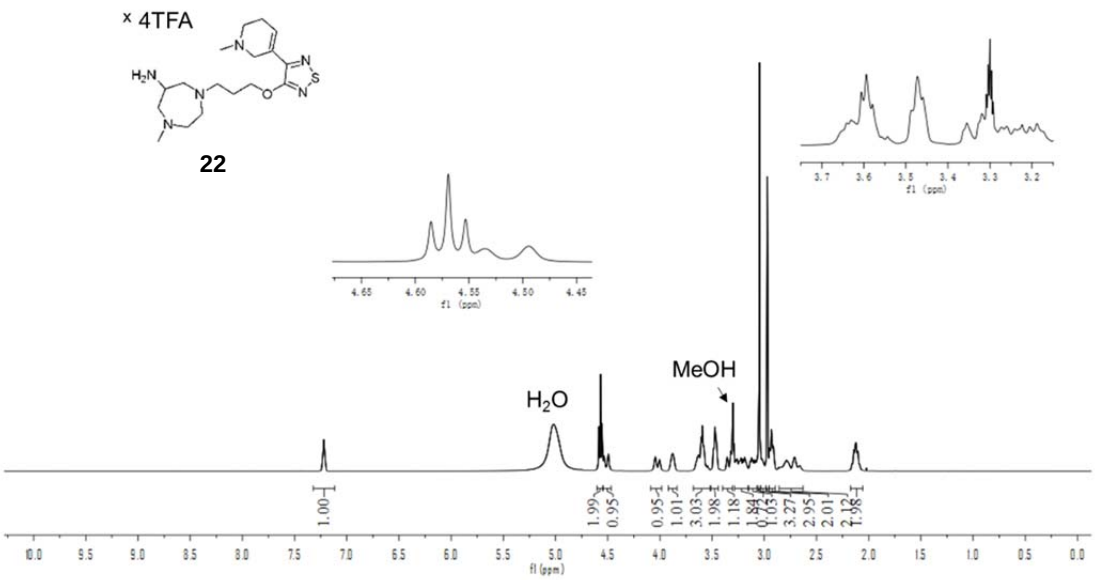
4-(Piperidin-4-yl)butan-1-ol (**120**) (1.81 g, 11.53 mmol), compound **123** (3.0 g, 10.46 mmol) and potassium carbonate (5.8 g, 42.03 mmol) were added to MeCN (80 mL) and the mixture was kept under reflux for 8 h. Insoluble material was separated by filtration and washed with CH_2Cl_2 (2 × 20 mL). The filtrate and washings were combined and the volatiles were removed under reduced pressure yielding a yellow oil, which was dissolved in CH_2Cl_2 (20 mL) followed by washing with brine. The aqueous phase was treated with CH_2Cl_2 (3 × 20 mL) and the organic extracts were collected. All organic phases were combined and dried over Na_2SO_4. Removal of the volatiles under reduced pressure gave the crude product, which was subjected to column chromatography (eluent: CH_2Cl_2/MeOH/25% aq NH_3 96:3:1 v/v/v) to afford compound **124** as white solid (2.9 g, 62%), m.p. 143-145 ^{o}C. R_f = 0.8 (CH_2Cl_2/MeOH/25% aq NH_3 90:9:1 v/v/v). Ratio of configurational isomers evident in the NMR spectra: ca 1.2:1. ^{1}H-NMR (300 MHz, [D_4]MeOH): δ (ppm) 0.86-1.13 (m, 2H), 1.13-1.21 (m, 3H), 1.27-1.38 (m, 2H), 1.40-1.64 (m, 4H), 1.78-2.04 (m, 2H), 2.48-2.65 (m, 1H), 2.74-2.85 (m, 1H), 3.02 (d, *J* 15 Hz, 0.55H), 3.11-3.16 (m, 1H), 3.22 (d, *J* 15 Hz, 0.45H), 3.51 (t, *J* 6.5 Hz, 2H), 7.18-7.30 (m, 2H), 7.30-7.39 (m, 1H), 7.40-7.56 (m, 3H), 7.61-7.66 (m, 1H), 7.80-7.94 (m, 1H). ^{13}C-NMR (75 MHz, [D_4]MeOH): δ (ppm) 24.0, 32.7, 32.9, 33.9, 36.4, 37.4, 54.8, 54.9, 62.9, 123.0, 123.1, 126.6, 127.0, 127.8, 128.9, 129.0, 129.5, 129.9, 130.6, 131.1, 132.1, 132.3, 134.3, 134.7, 135.9, 136.9, 143.7, 169.2, 169.4, 171.2, 171.5. HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $[C_{24}H_{30}N_3O_3]^+$ 408.2282, found: 408.2299. $C_{24}H_{29}N_3O_3$ (407.22).

4. Experimental protocol for the synthesis of the radioligands [^{3}H]44 and [^{3}H]64

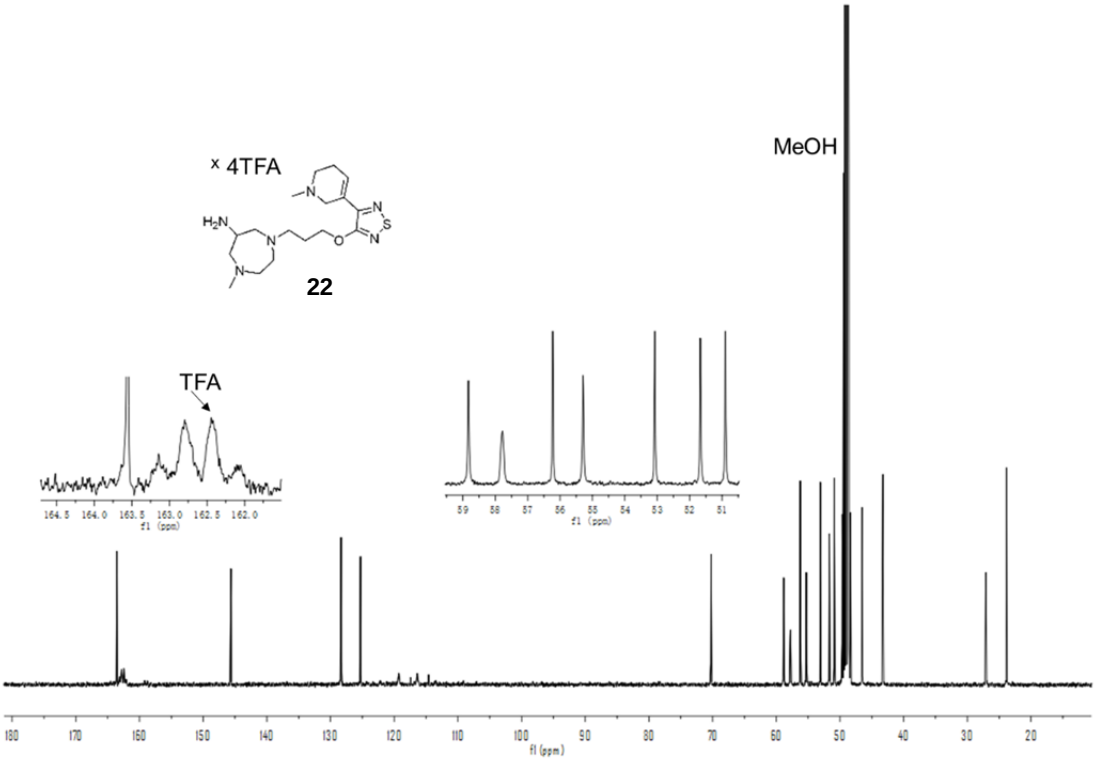
The tritiated heterodimeric ligands [^{3}H]**44** and [^{3}H]**64** were prepared by [^{3}H]propionylation of the precursor amines **43** and **63**, respectively. A solution of succinimidyl [2,3-^{3}H]proprionate (specific activity: 80 Ci/mmol, purchased from American Radiolabeled Chemicals, St. Louis, MO, via Hartman Analytics, Braunschweig, Germany) (2.5 mCi, 5.5 µg, 31.25 nmol (each)) in hexane/EtOAc (9:1) was transferred from the delivered ampoule to a 1.5-mL reaction vessel with screw cap, and the solvent was removed in a vacuum concentrator (ca 30 min at about 30 °C). A solution of the precursor molecule (**43**: 0.53 mg, 403 nmol; **63**: 0.52 mg, 305 nmol) in anhydrous DMF/DIPEA (50:1 v/v) (60 µL) was added, and the vessel was vigorously shaken at rt for 1.5 h. 2% aq TFA (40 µL) and MeCN/H_2O (1:9 v/v) (300 µL) were added and the radioligands were purified using an analytical HPLC system (Waters, Eschborn, Germany) consisting of two 510 pumps, a pump control module, a 486 UV/vis detector, and a Flow-one Beta series A-500 radiodetector (Packard, Meriden, CT). A Luna C18 (3 µm, 150 mm × 4.6 mm, Phenomenex, Aschaffenburg, Germany) was used as stationary phase at a flow rate of 0.8 mL/min. Mixtures of 0.05% aq TFA (A) and acetonitrile containing 0.04% TFA (B) were used as mobile phase. The following linear gradient was applied: 0-20 min: A/B 90:10-79:21, 20-25 min: 79:21 (isocratic), 25-27 min: 79:21-5:95, 27-35 min: 5:95. For the purification of each radioligand three HPLC runs were performed (UV detection: 220 nm; no radiometric detection). The radioligands were collected in a 2-mL reaction vessels with screw cap (t_R ([^{3}H]**44**) = 25.0 min, t_R ([^{3}H]**64**) = 25.2 min). The volume of the combined eluates was reduced in a vacuum concentrator to approx. 400 µL and approx. 300 µL, respectively, and ethanol (400 and 300 µL, respectively) was added. The solutions were transferred into 3-mL borosilicate glass vials with conical bottom (Wheaton NextGen 3-mL V-vials). The reaction vessels were rinsed twice with EtOH/water (1:1 v/v) (200 and 300 µL, respectively) and the washings were transferred to the 3-mL glass vials to obtain tentative stocks with volumes of 1200 µL. For the quantification of the radioligands, a four-point calibration was performed with the corresponding 'cold' forms **44** (0.1, 0.2, 0.5, and 0.8 µM) and **64** (0.1, 0.2, 0.5, and 1 µM) using the following HPLC conditions: HPLC system, stationary phase, eluents and flow rate as above; linear gradient for [^{3}H]**44**: 0-20 min: A/B 90:10-69:31, 20-22 min: 69:31-5:95, 22-29 min: 5:95; linear gradient for [^{3}H]**64**: 0-20 min: A/B 90:10-72:28, 20-22 min:

72:28-5:95, 22-29 min: 5:95; injection volume: 100 µL; UV detection: 220 nm. A 2-µL aliquot of each tentative radioligand stock solution was added to 128 µL of acetonitrile/0.05% aq TFA (1:9 v/v), 100 µL of this solution were analyzed by HPLC, and five times 2 µL were counted in 3 mL of scintillator (Rotiszint eco plus; Carl Roth, Karlsruhe, Germany) with a LS 6500 liquid scintillation counter (Beckmann-Coulter, Munich, Germany). These analyses were performed twice. The molarities of the tentative stock solutions of [^{3}H]**44** and [^{3}H]**64** were calculated from the mean of the peak areas and the linear calibration curves obtained from the peak areas of the standards. To determine the radiochemical purities and to prove the chemical identities, solutions (100 µL) of [^{3}H]**44** (0.18 µM) and [^{3}H]**64** (0.23 µM) spiked with **44** (3 µM) and **64** (3 µM), respectively, were analyzed by RP-HPLC using the system, column, eluents, flow rate, injection volume and UV detection as for the quantification and additionally radiometric detection (flow rate of the liquid scintillator (Rotiscint eco plus/acetonitrile (9:1 v/v)): 4.0 mL/min) The following linear gradient was used: 0-20 min: A/B 90:10-69:31, 20-30 min: 69:31-5:95, 30-38 min: 5:95). The radiochemical purities amounted to 98% and 99%, respectively (see Figure 4, main article). The analyses were repeated after storage at −20 °C for 10 months and revealed radiochemical purities of 88% and 98%, respectively. Calculated specific activities: [^{3}H]**44**, 2.420 TBq/mmol (65.40 Ci/mmol), [^{3}H]**64**, 1.815 TBq/mmol (49.06 Ci/mmol). The final activity concentrations were adjusted to 18.5 MBq/mL by the addition of EtOH/water (1:1 v/v), resulting in molarities of 7.64 µM ([^{3}H]**44**) and 10.2 µM ([^{3}H]**64**). Radiochemical yields: [^{3}H]**44**, 33.64 MBq, 36%; [^{3}H]**64**, 32.56 MBq, 35%.

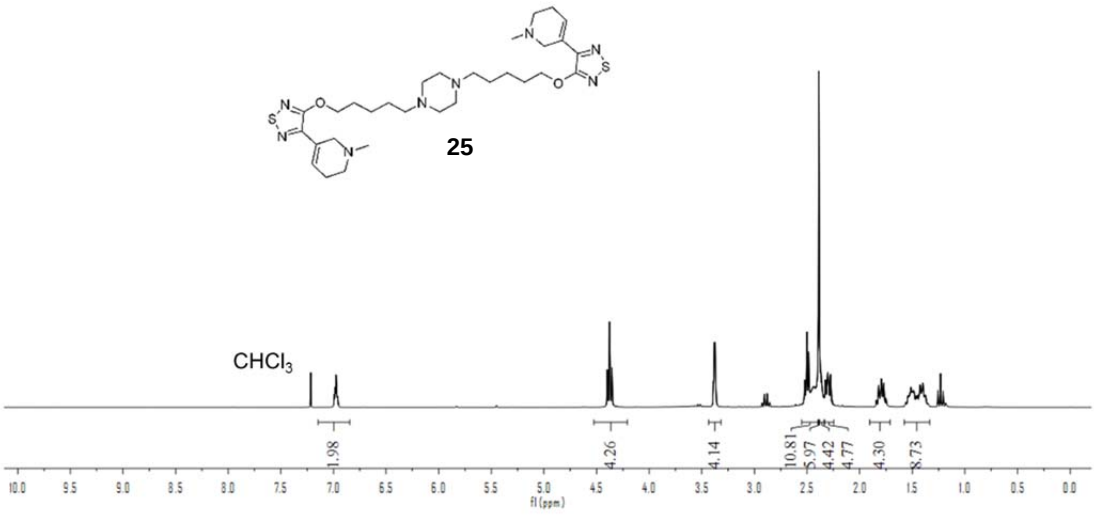
5. ^{1}H-NMR and ^{13}C-NMR spectra of compounds 22, 25, 27-29, 31, 34, 35, 38, 39, 43, 44, 46, 48, 50-52, 55, 58-61, 63, 64, 66, 67, 69, 70 and 72 (SI Figures 3-60)



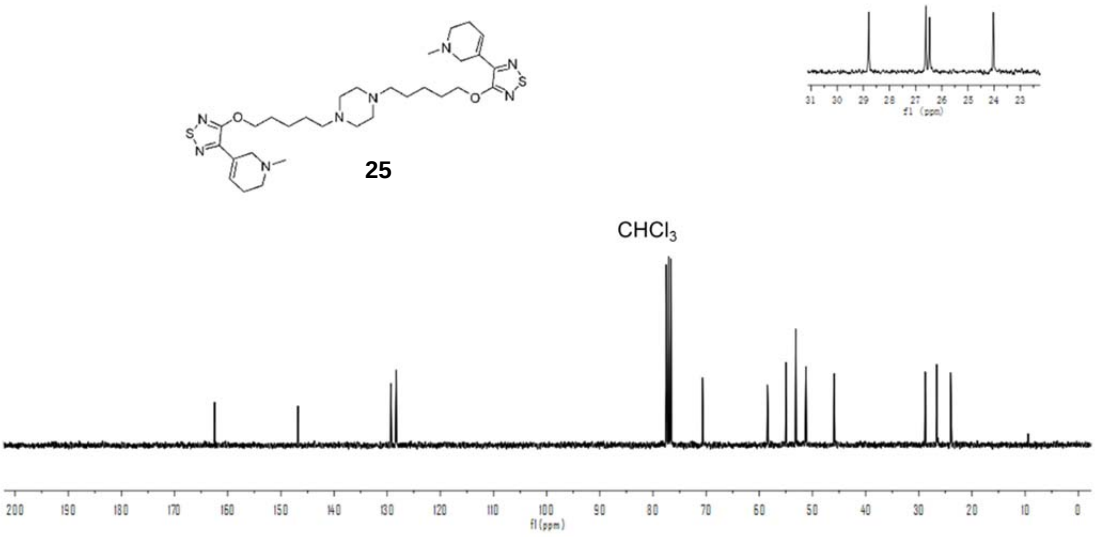
SI Figure 3. ^{1}H-NMR spectrum (400 MHz, [D_4]MeOH) of compound **22**.



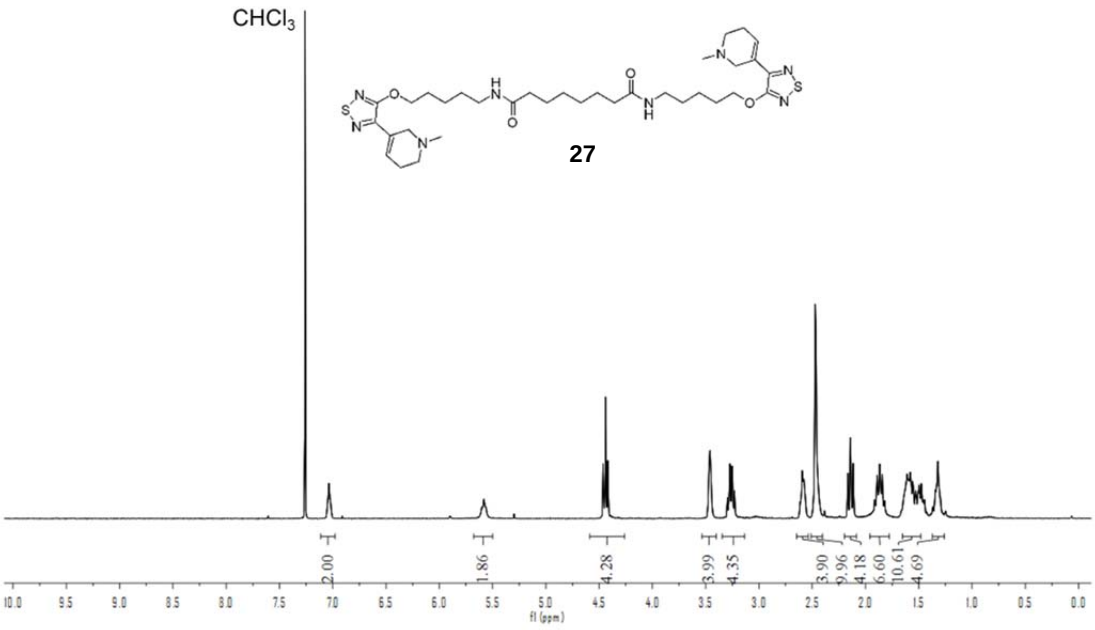
SI Figure 4. ^{13}C-NMR spectrum (100 MHz, [D_4]MeOH) of compound **22**.



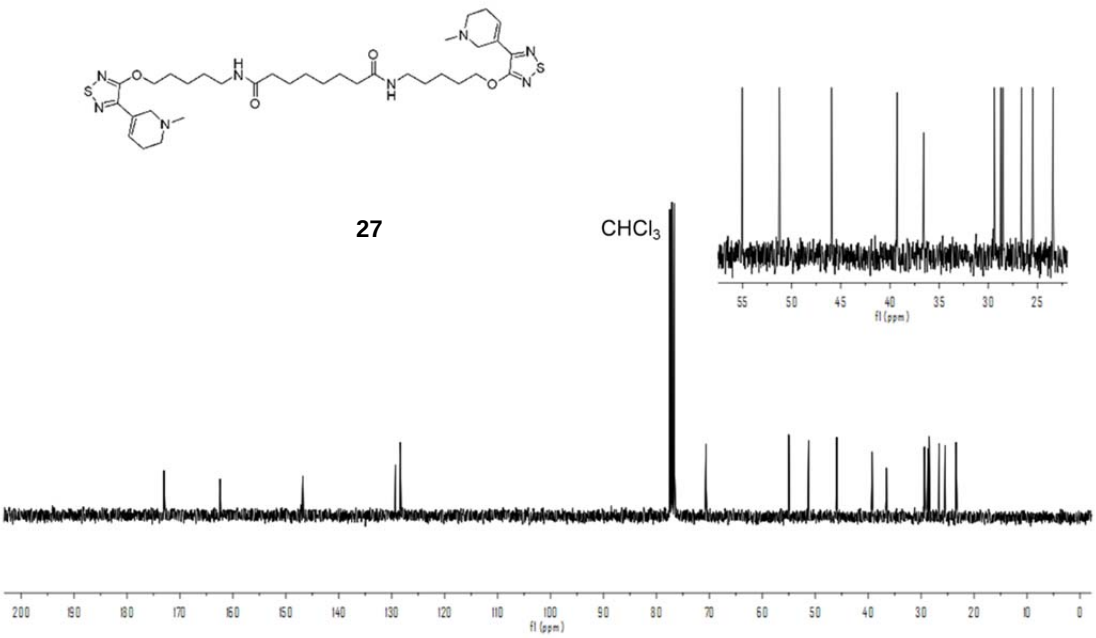
SI Figure 5. ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **25**.



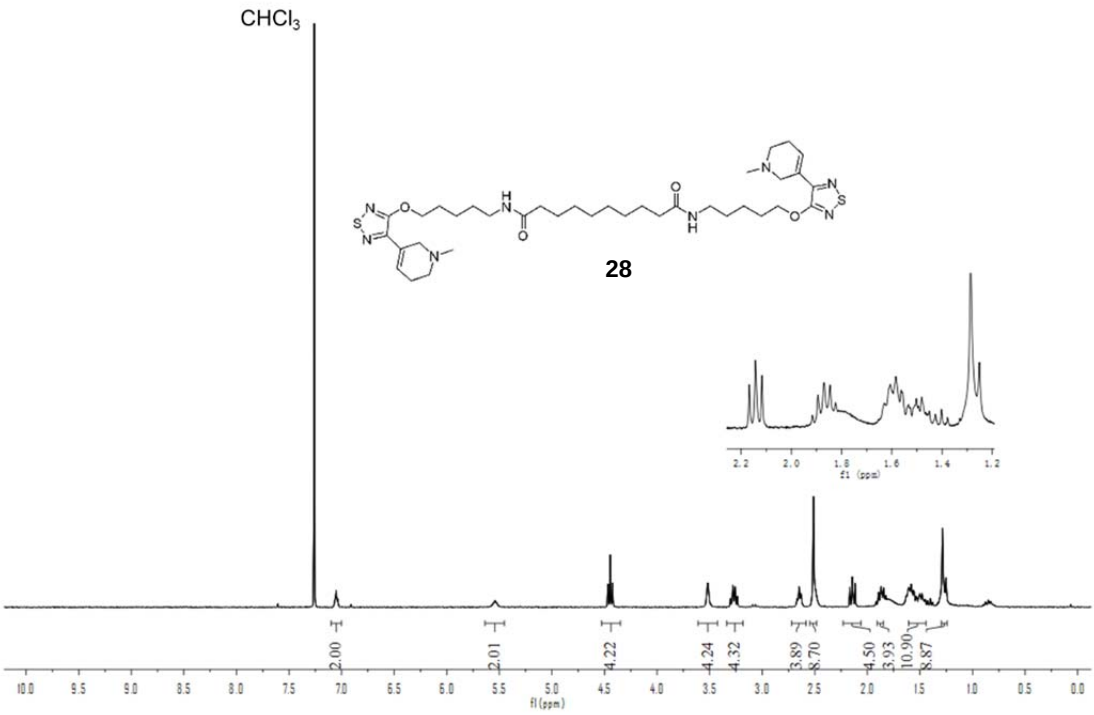
SI Figure 6. ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of compound **25**.



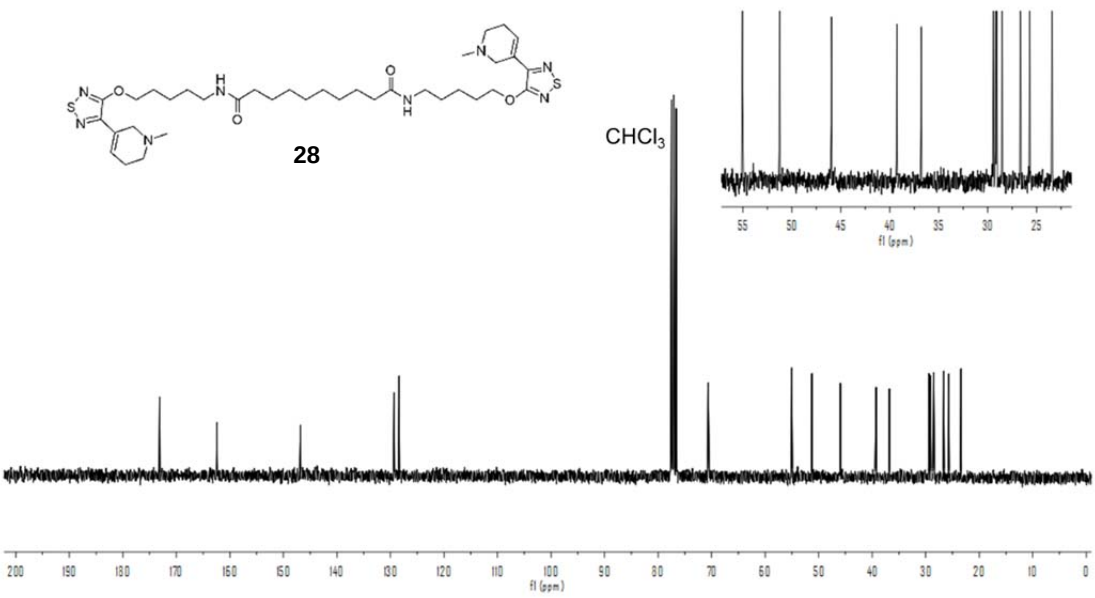
SI Figure 7. ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **27**.



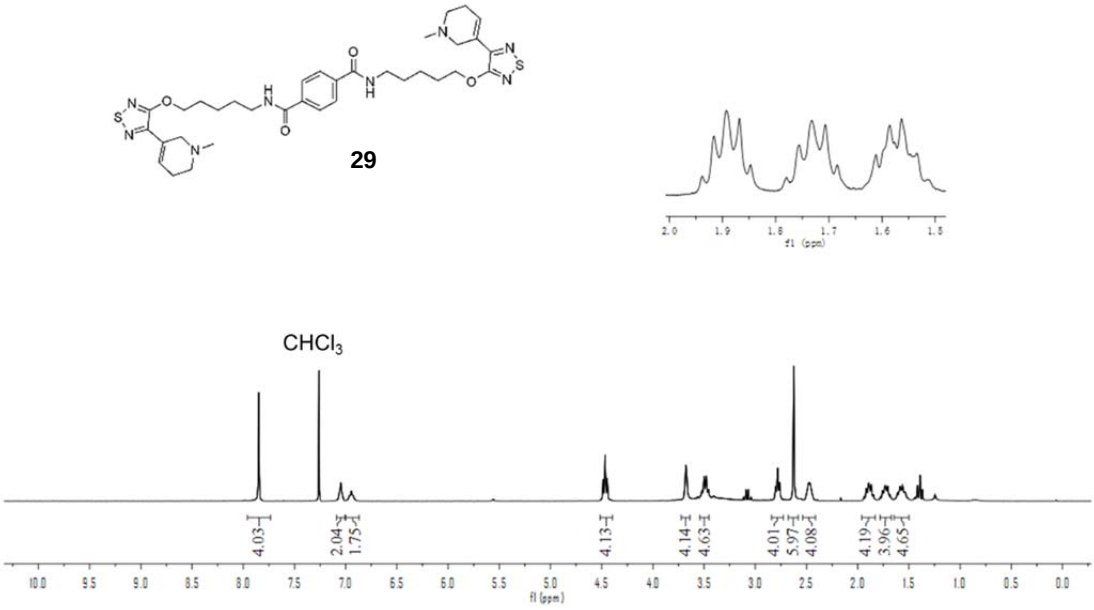
SI Figure 8. ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of compound **27**.



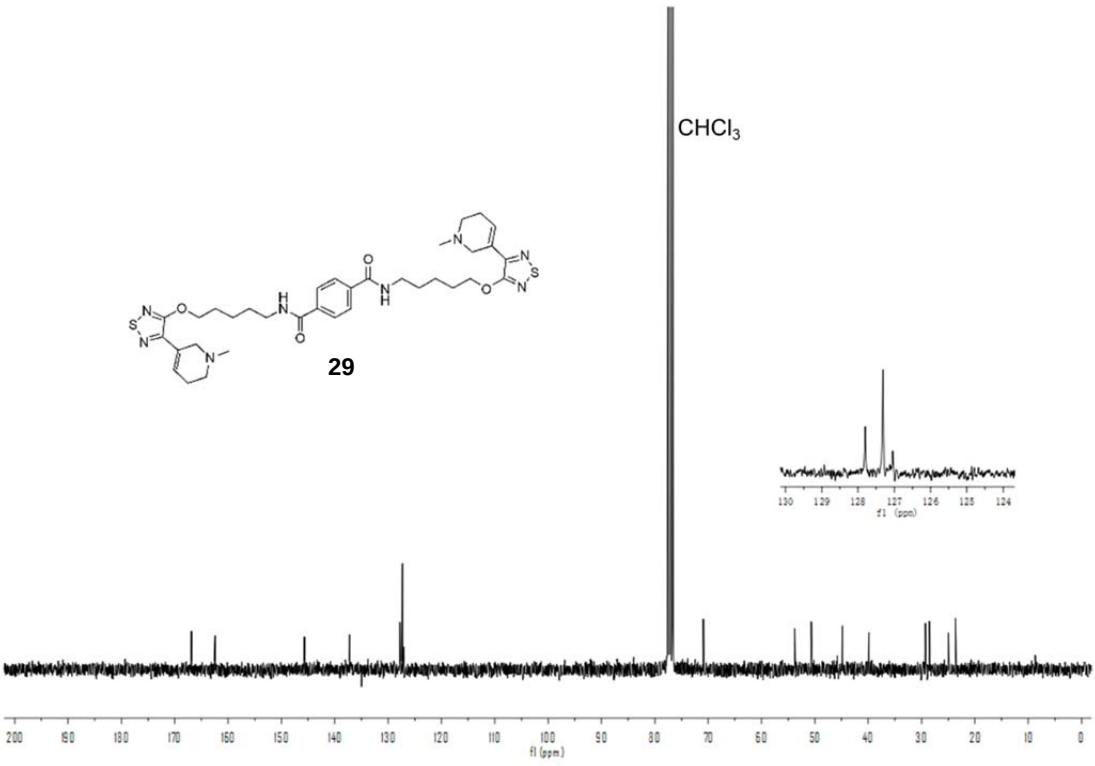
SI Figure 9. ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **28**.



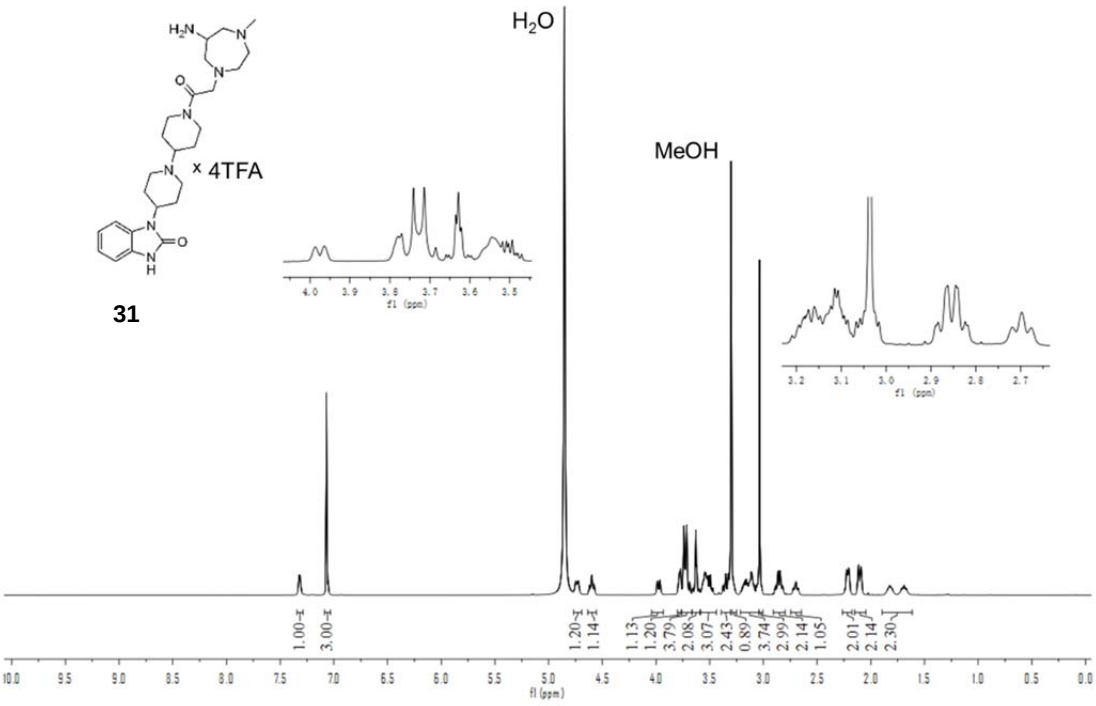
SI Figure 10. ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of compound **28**.



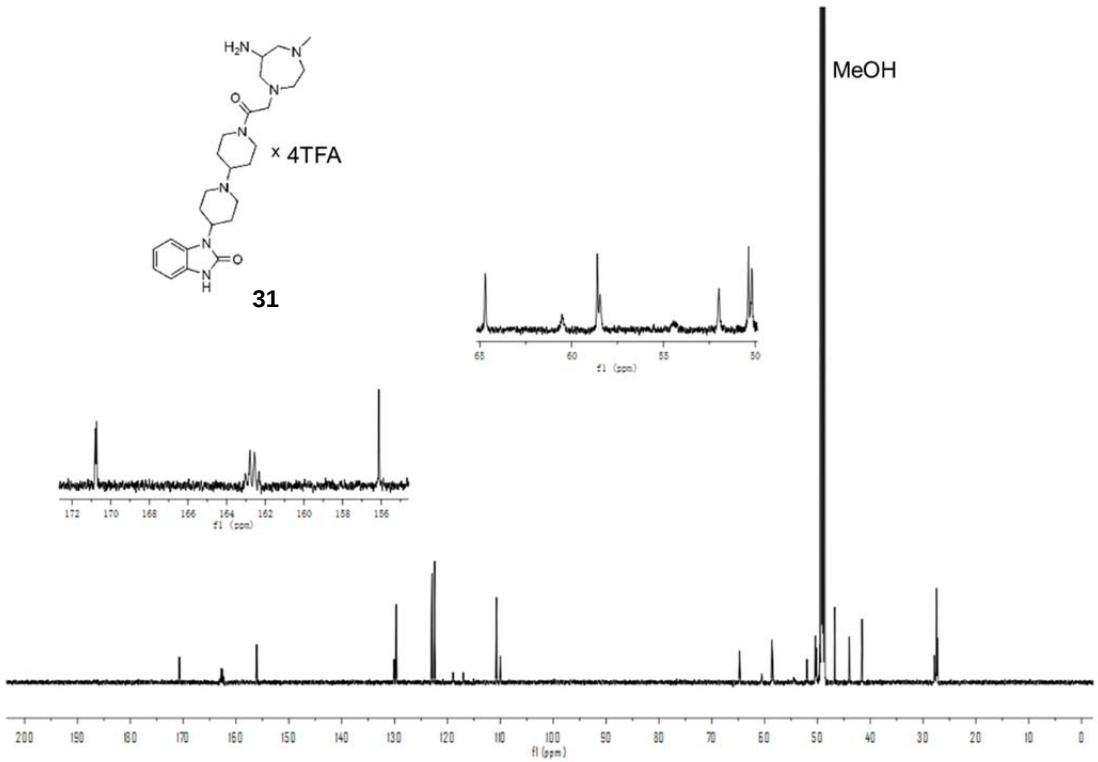
SI Figure 11. ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) of compound **29**.



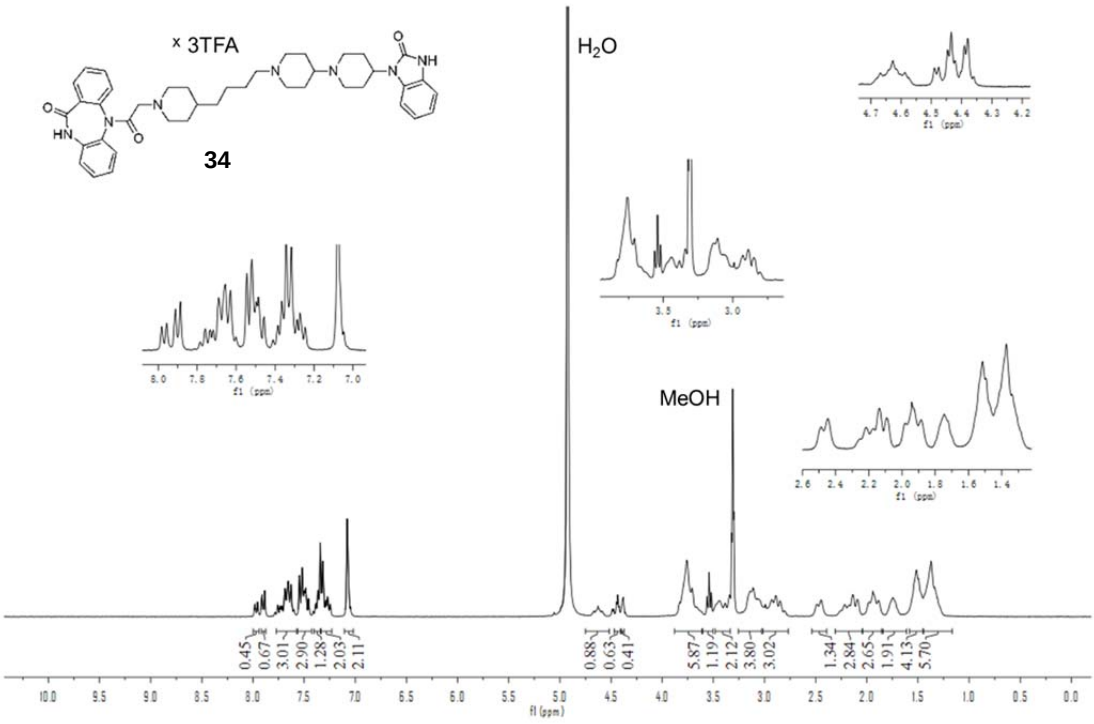
SI Figure 12. ^{13}C-NMR spectrum (75 MHz, $CDCl_3$) of compound **29**.



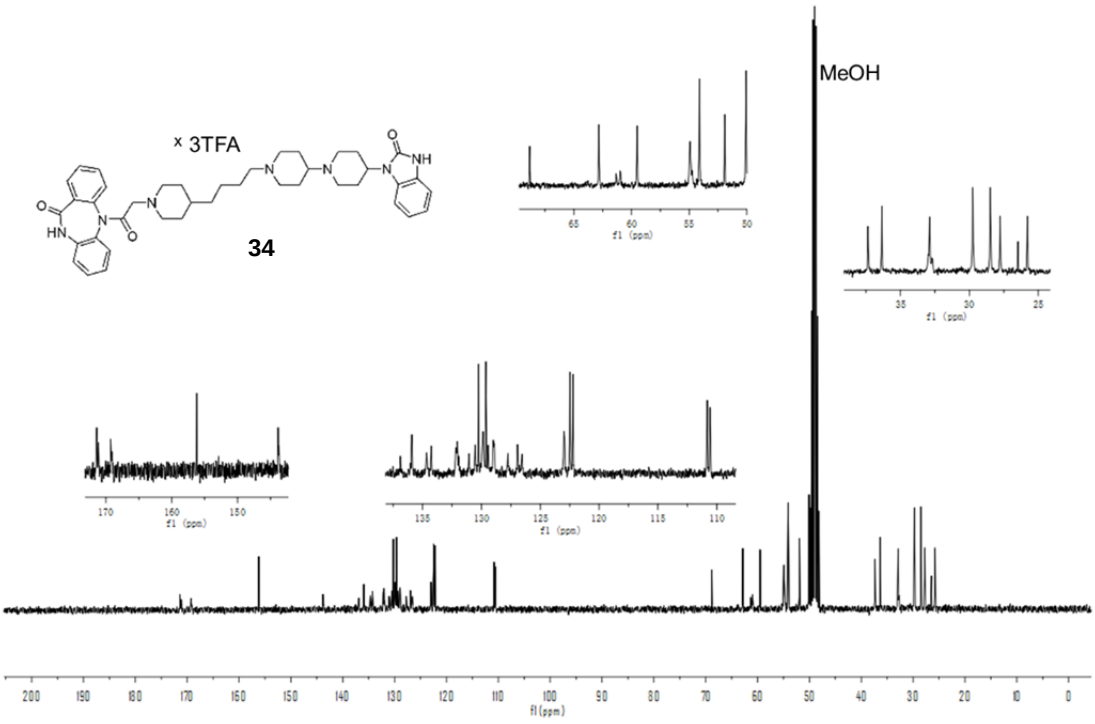
SI Figure 13. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **31**.



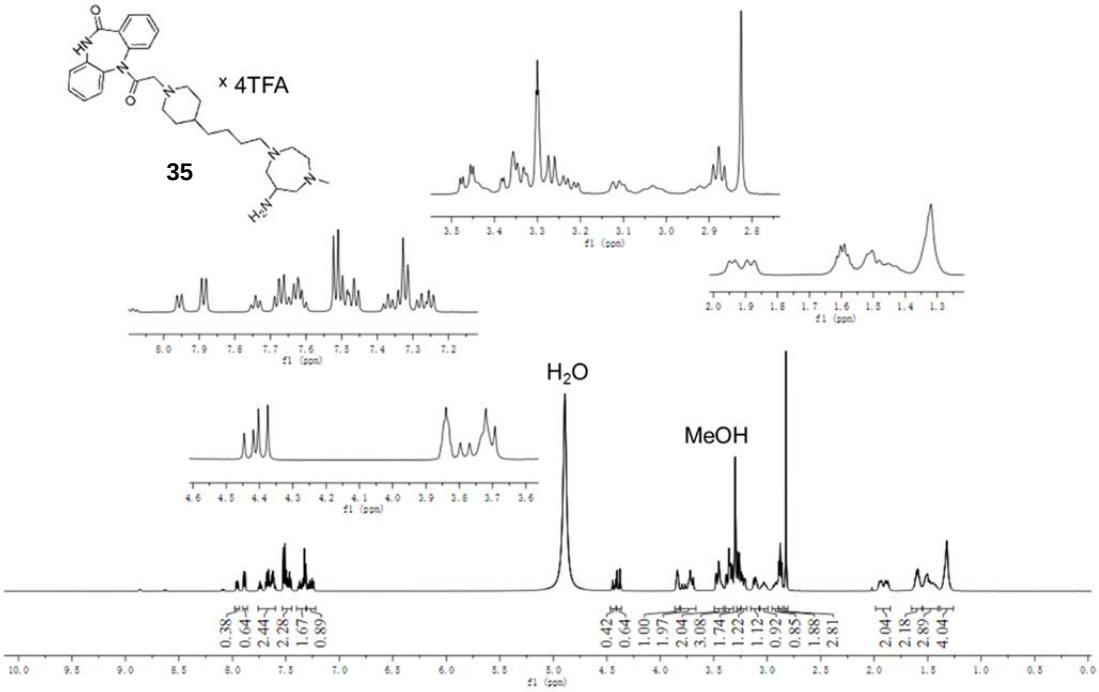
SI Figure 14. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **31**.



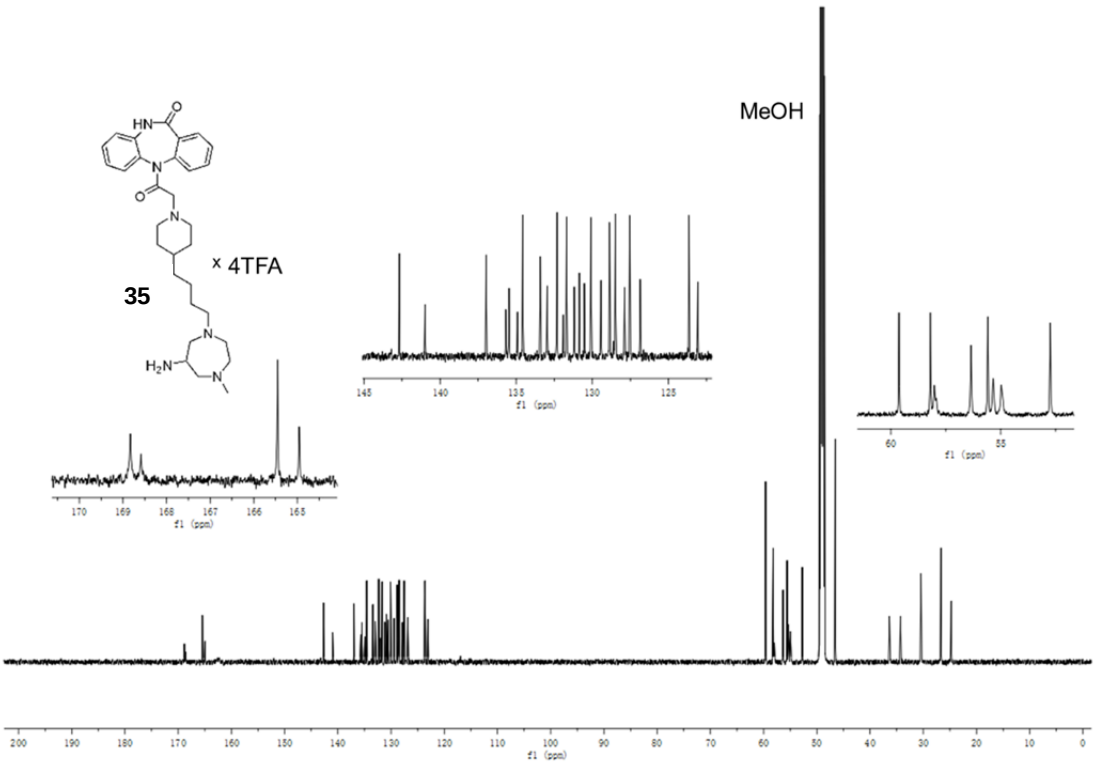
SI Figure 15. ^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **34**.



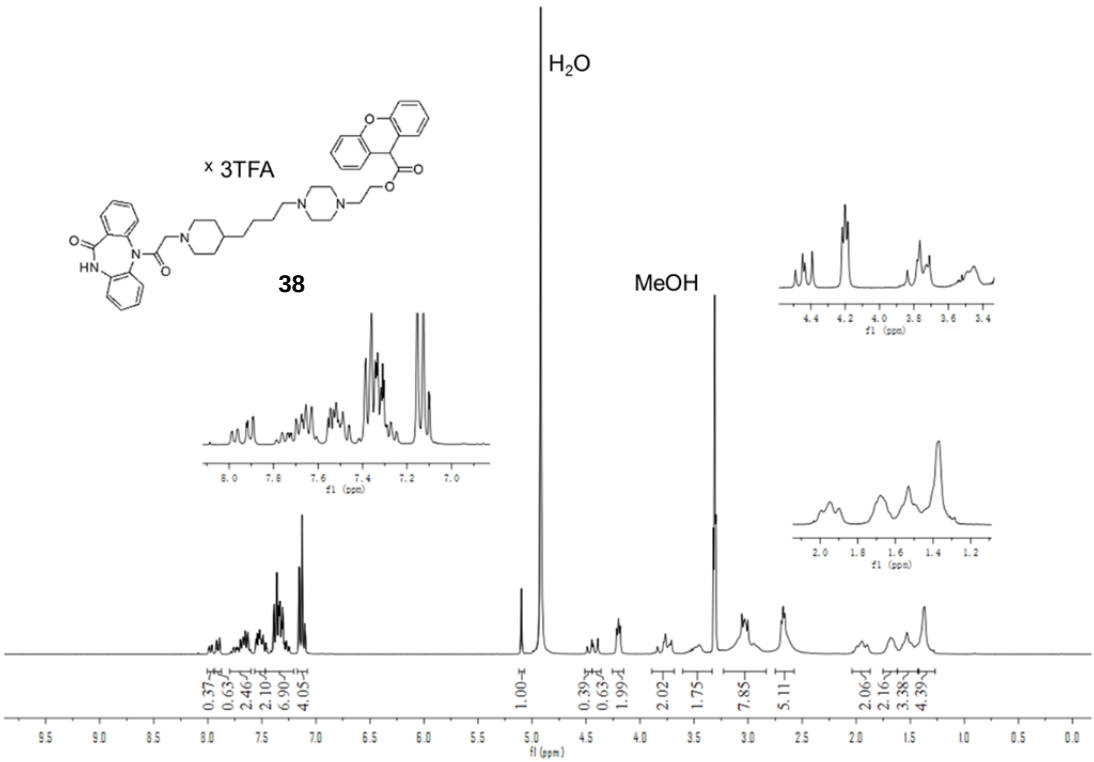
SI Figure 16. ^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **34**.



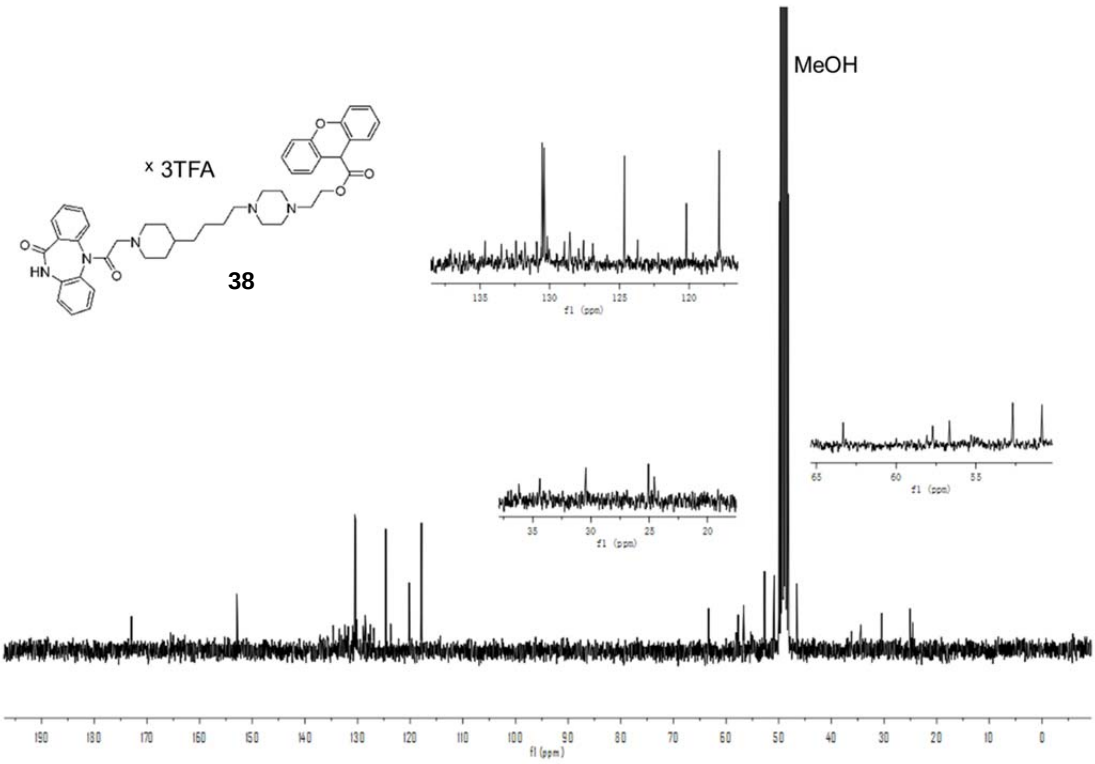
SI Figure 17. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **35**.



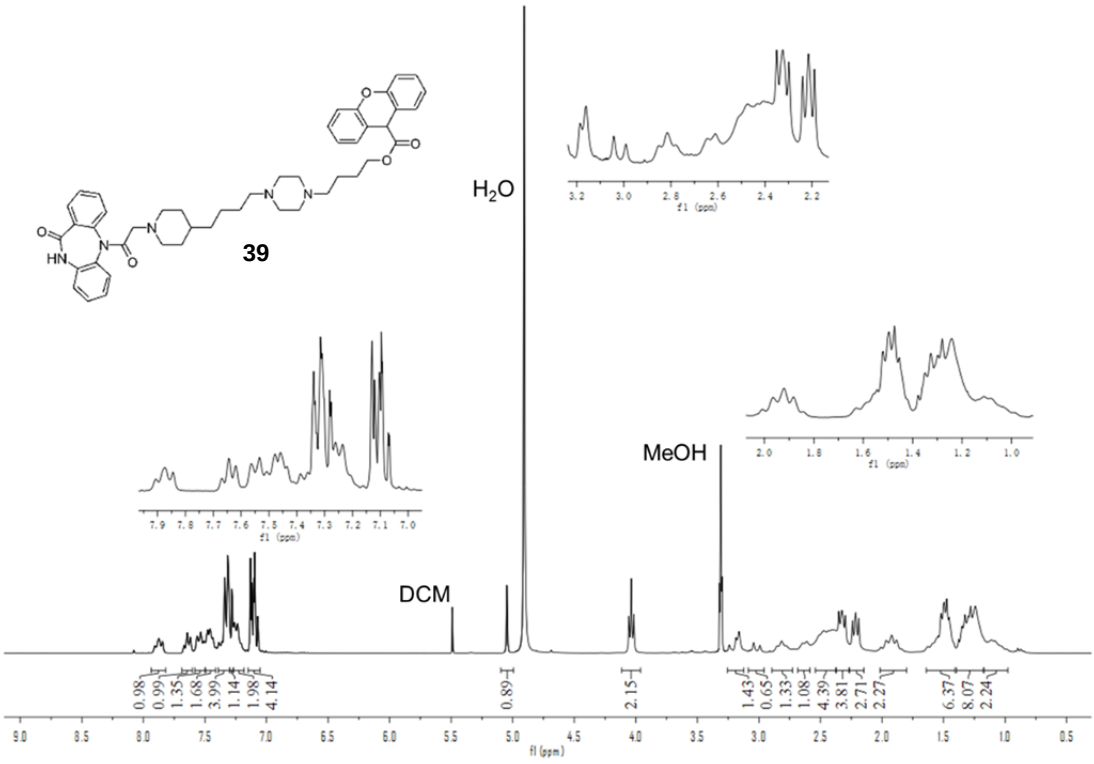
SI Figure 18. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **35**.



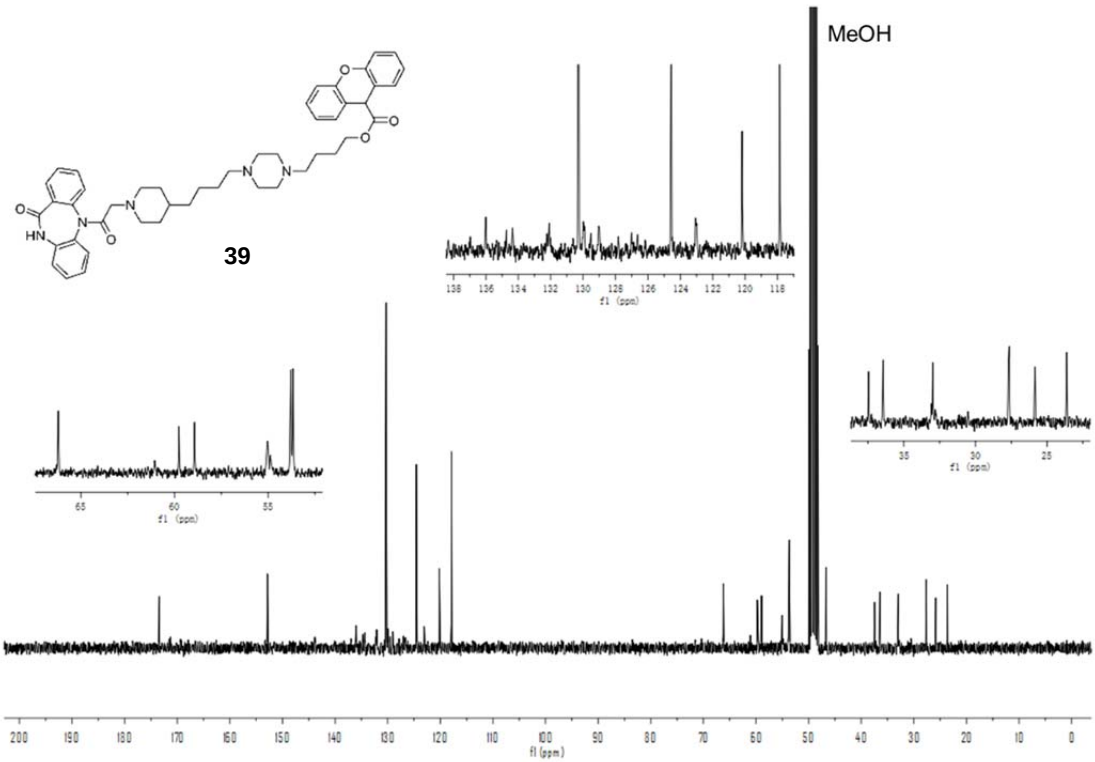
SI Figure 19. [1]H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **38**.



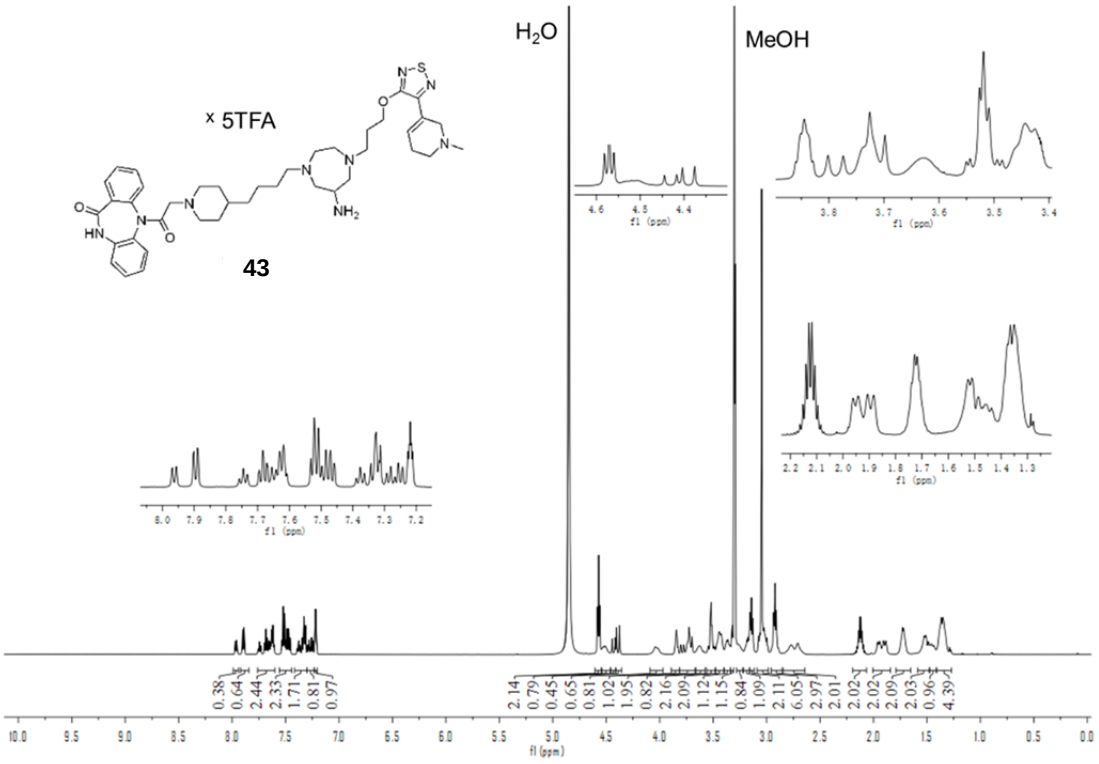
SI Figure 20. [13]C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **38**.



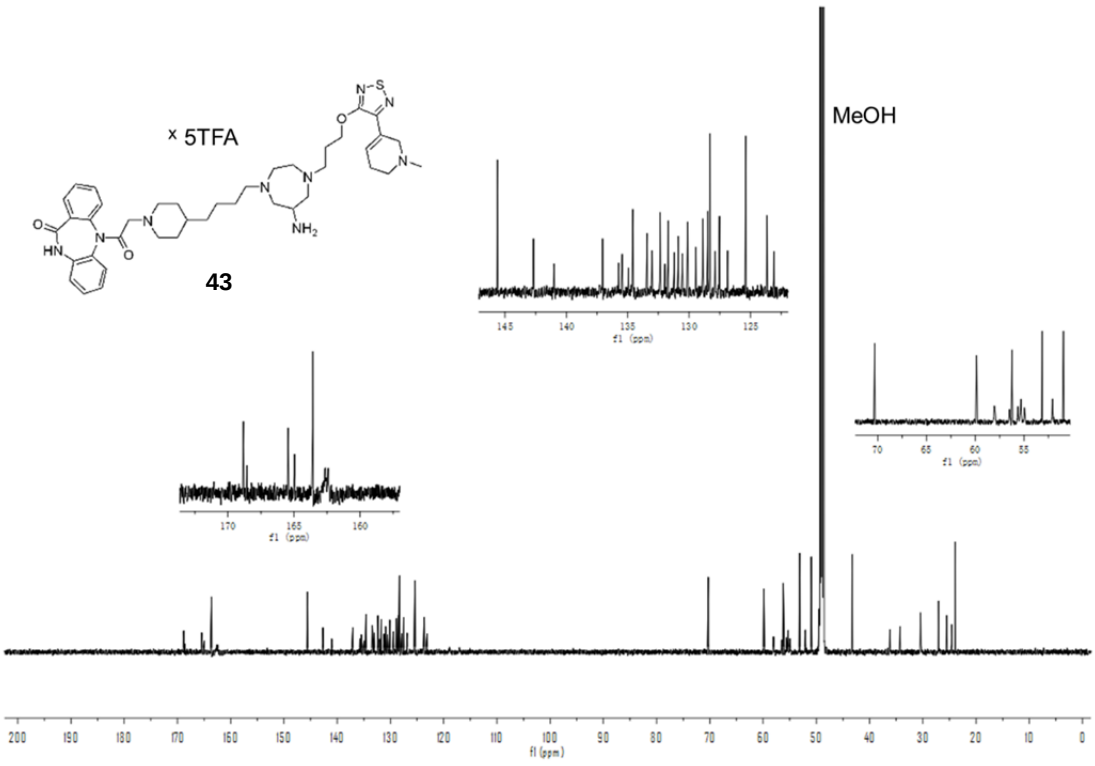
SI Figure 21. ^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **39**.



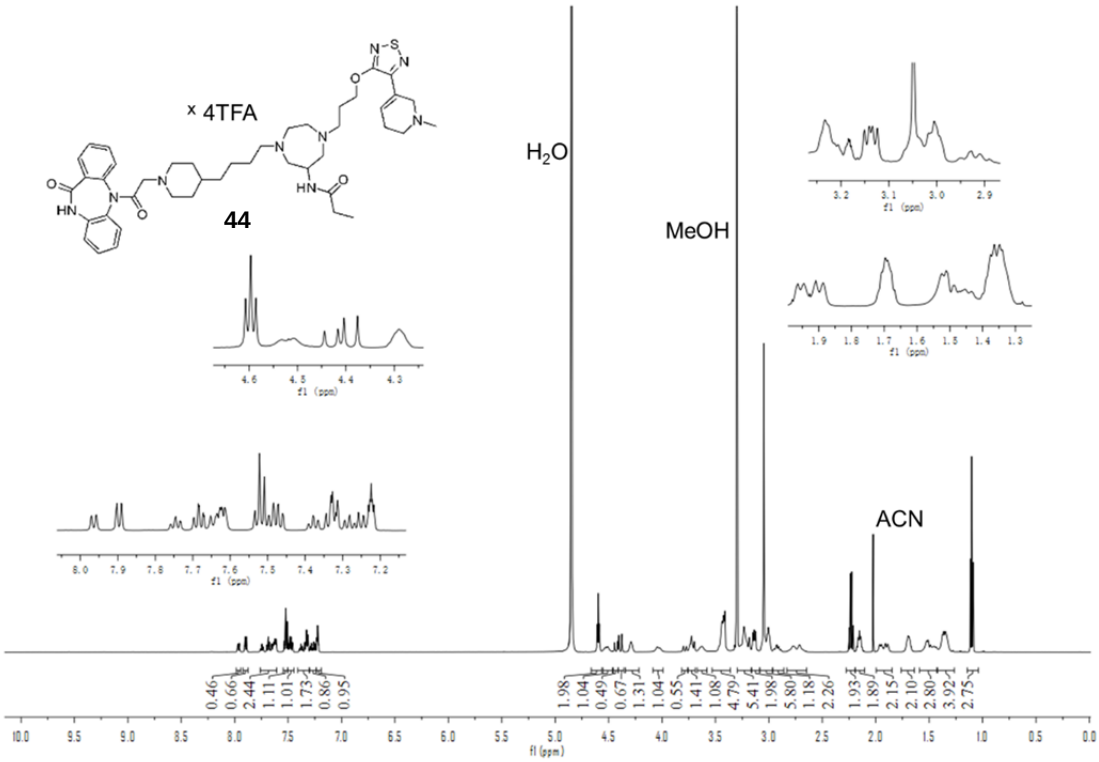
SI Figure 22. ^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **39**.



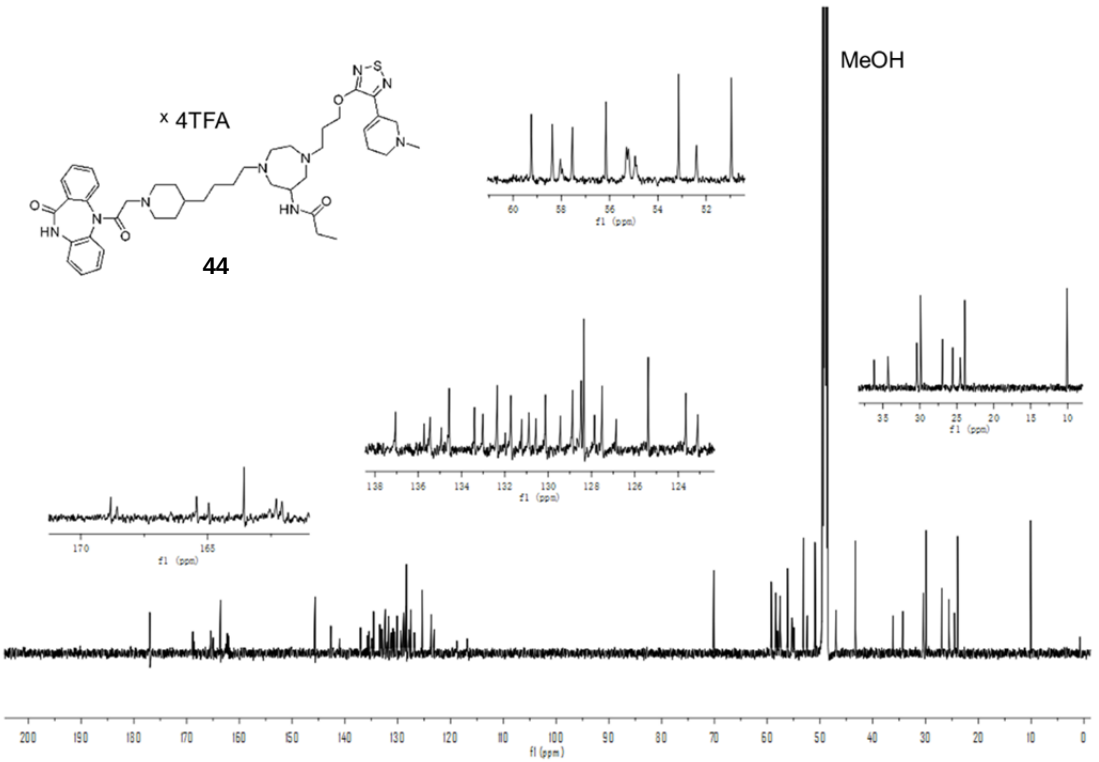
SI Figure 23. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **43**.



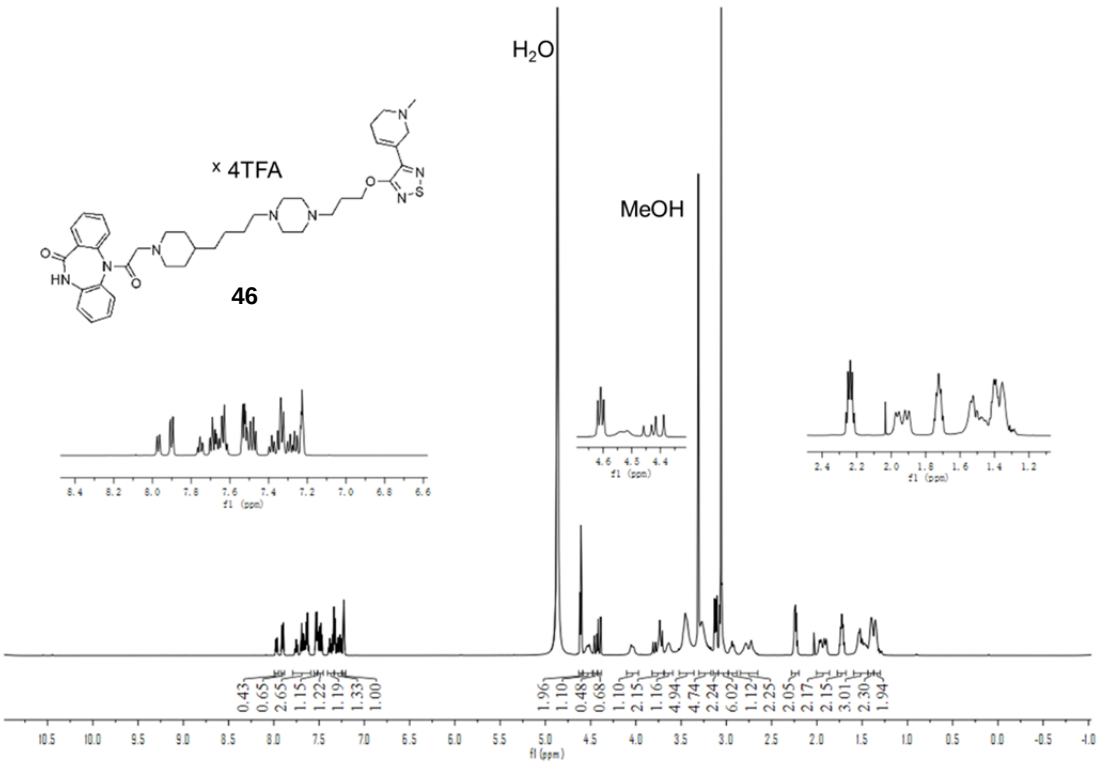
SI Figure 24. ^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **43**.



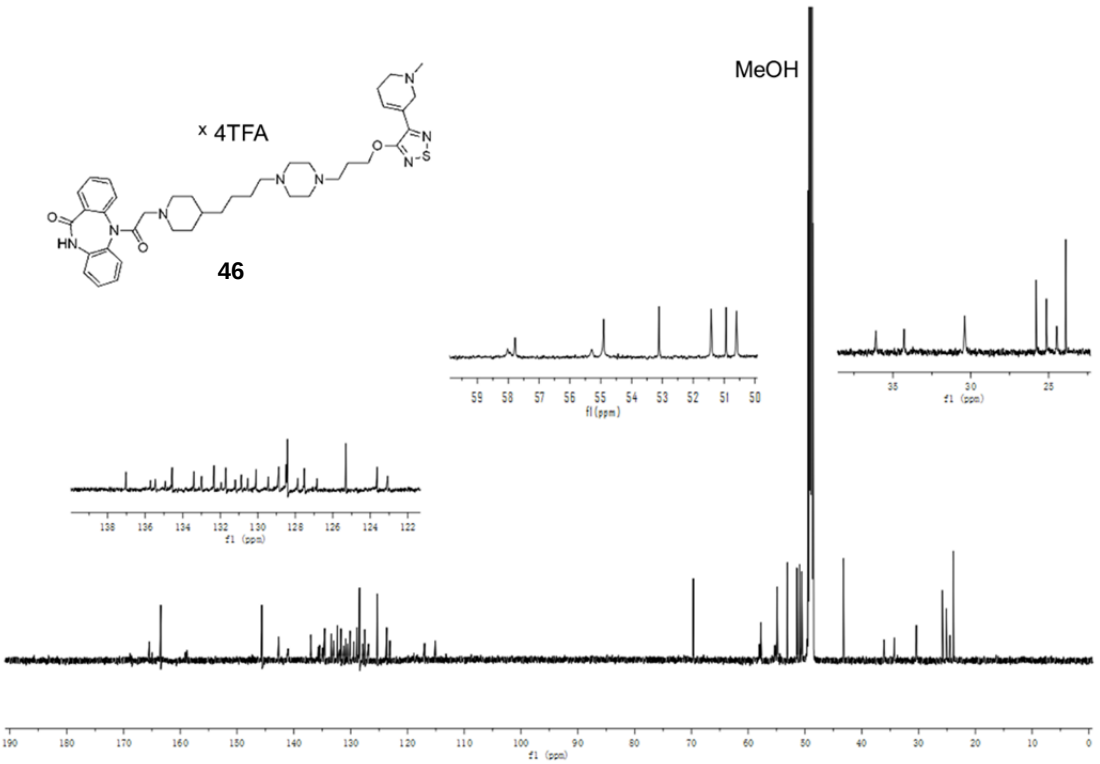
SI Figure 25. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **44**.



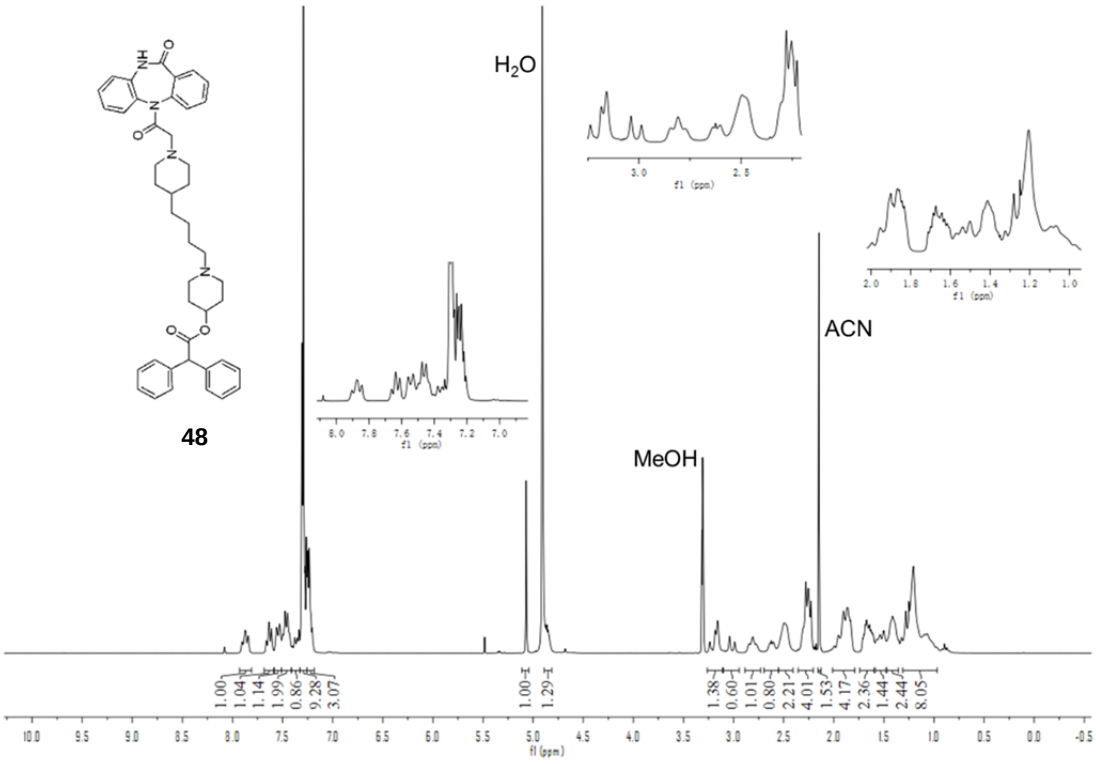
SI Figure 26. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **44**.



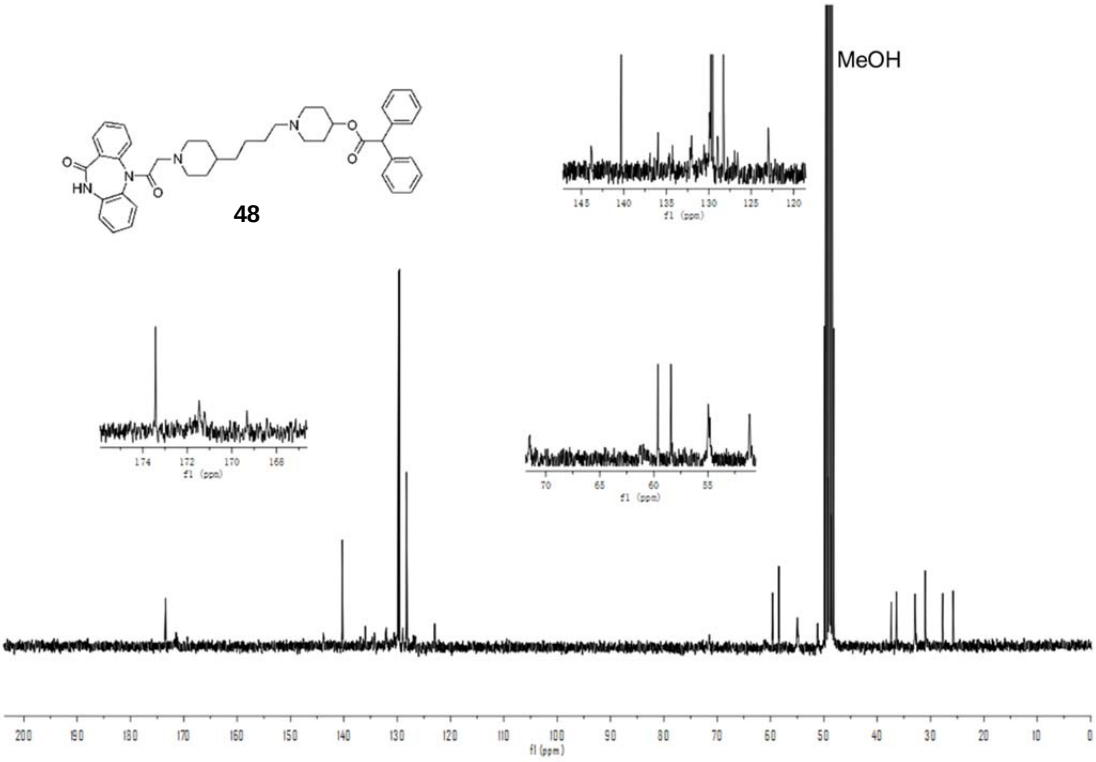
SI Figure 27. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **46**.



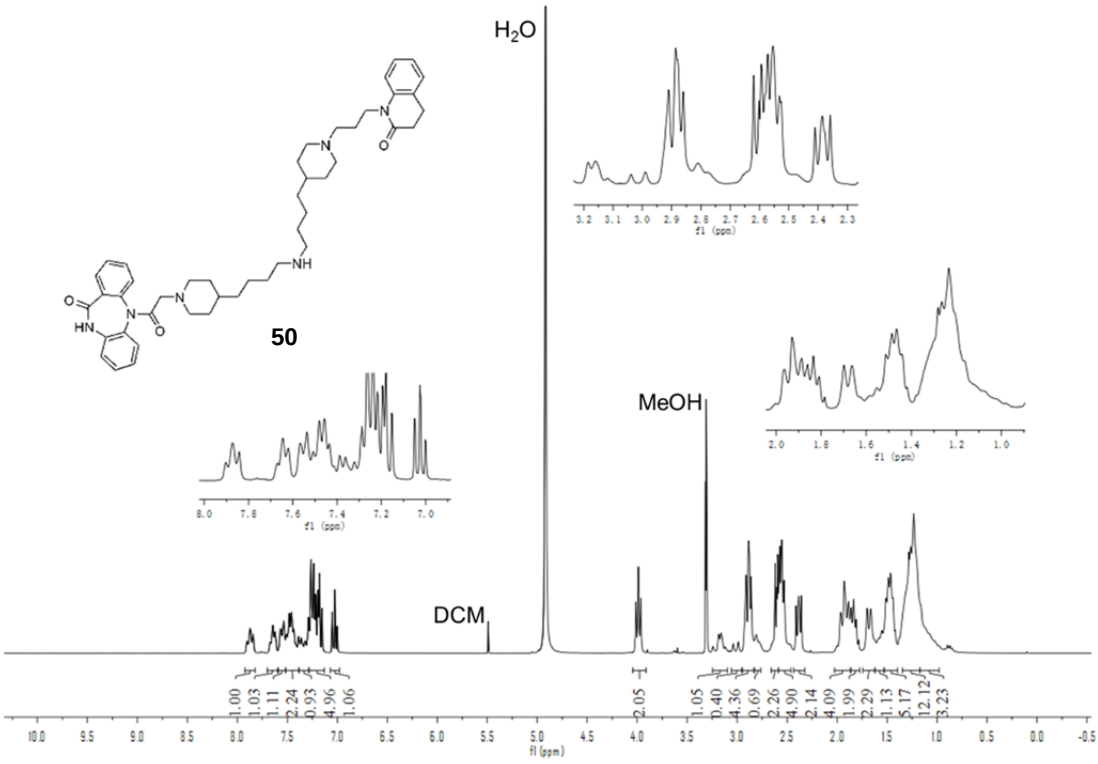
SI Figure 28. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **46**.



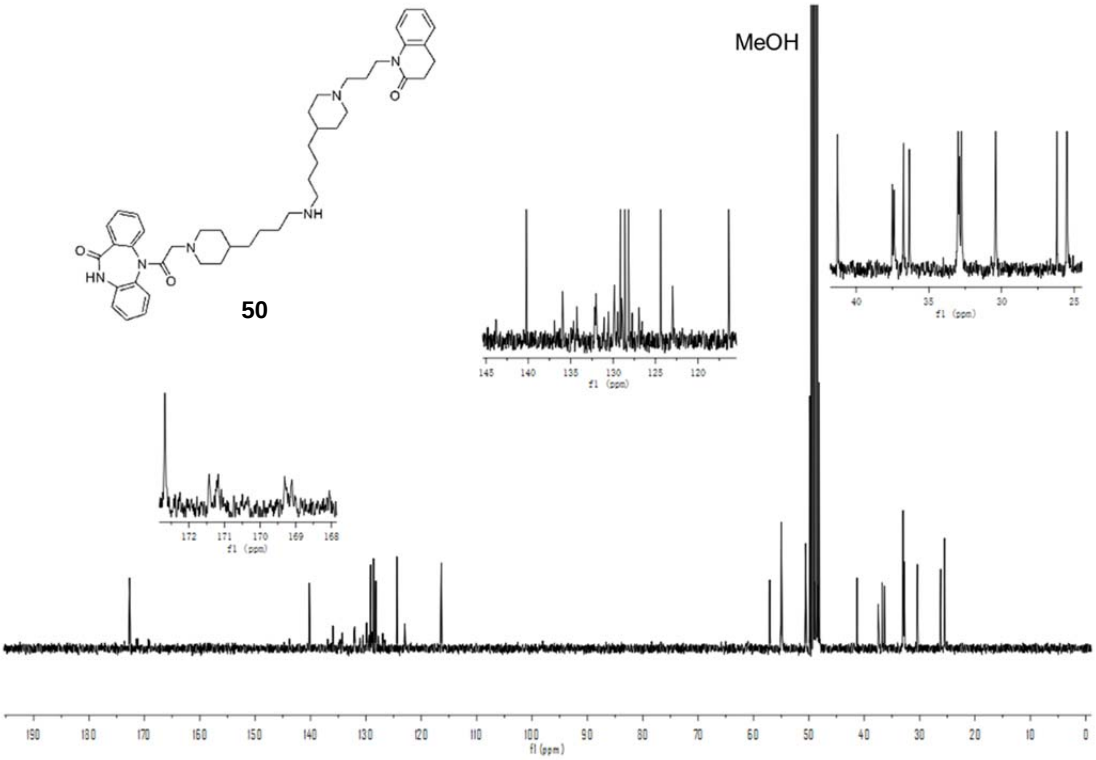
SI Figure 29. ^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **48**.



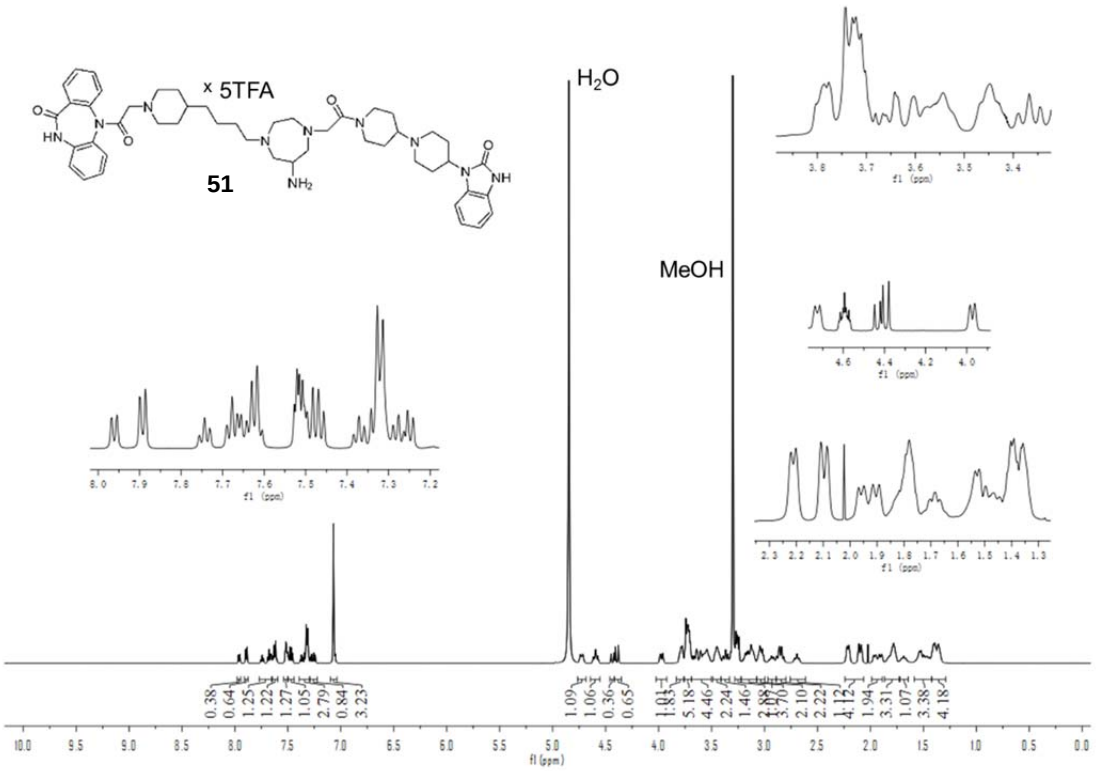
SI Figure 30. ^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **48**.



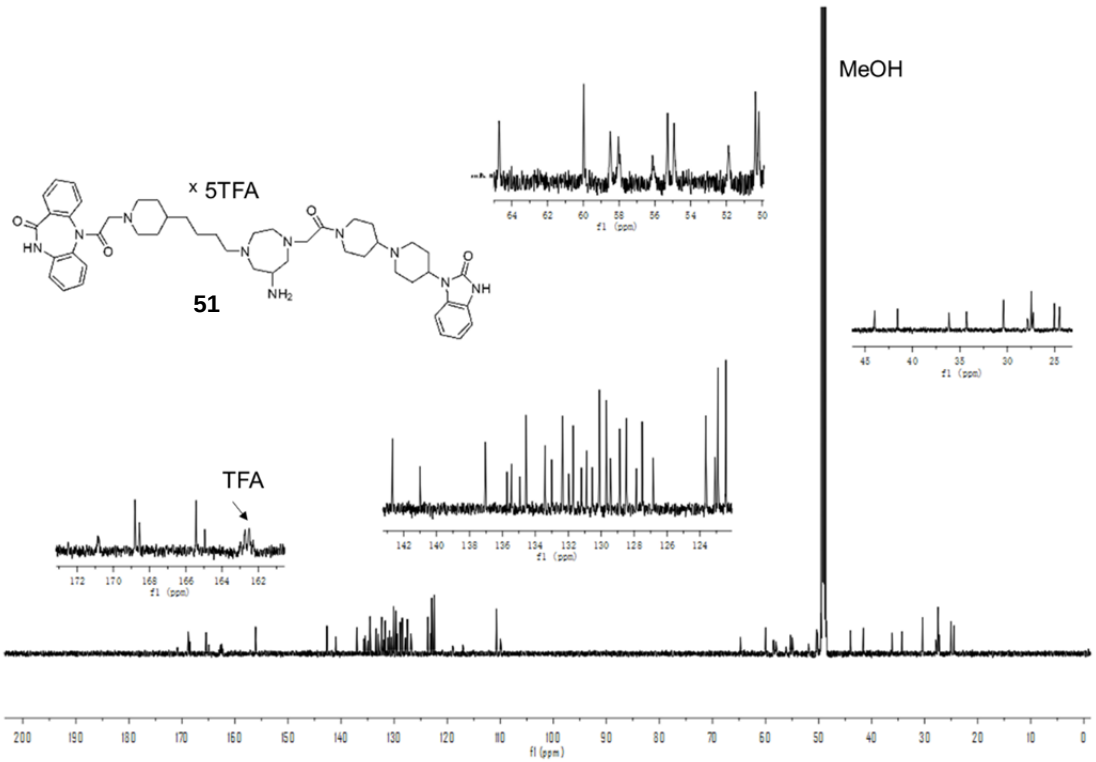
SI Figure 31. ^{1}H-NMR spectrum (300 MHz, [D_4]MeOH) of compound **50**.



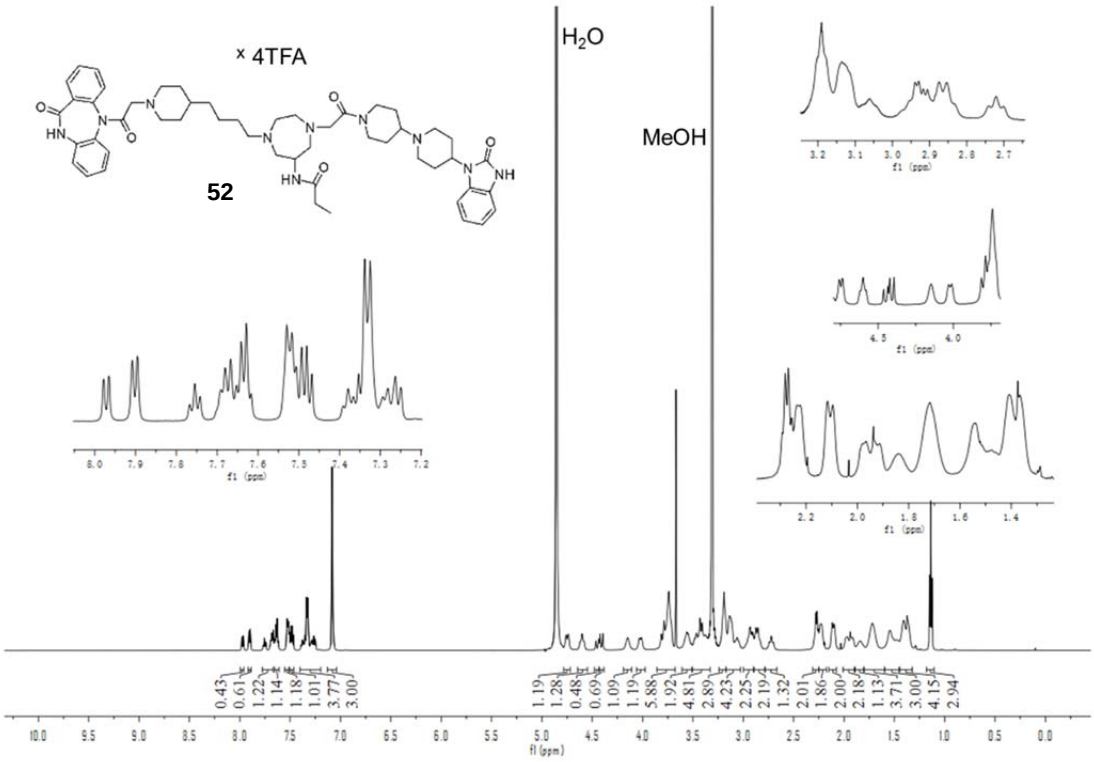
SI Figure 32. ^{13}C-NMR spectrum (75 MHz, [D_4]MeOH) of compound **50**.



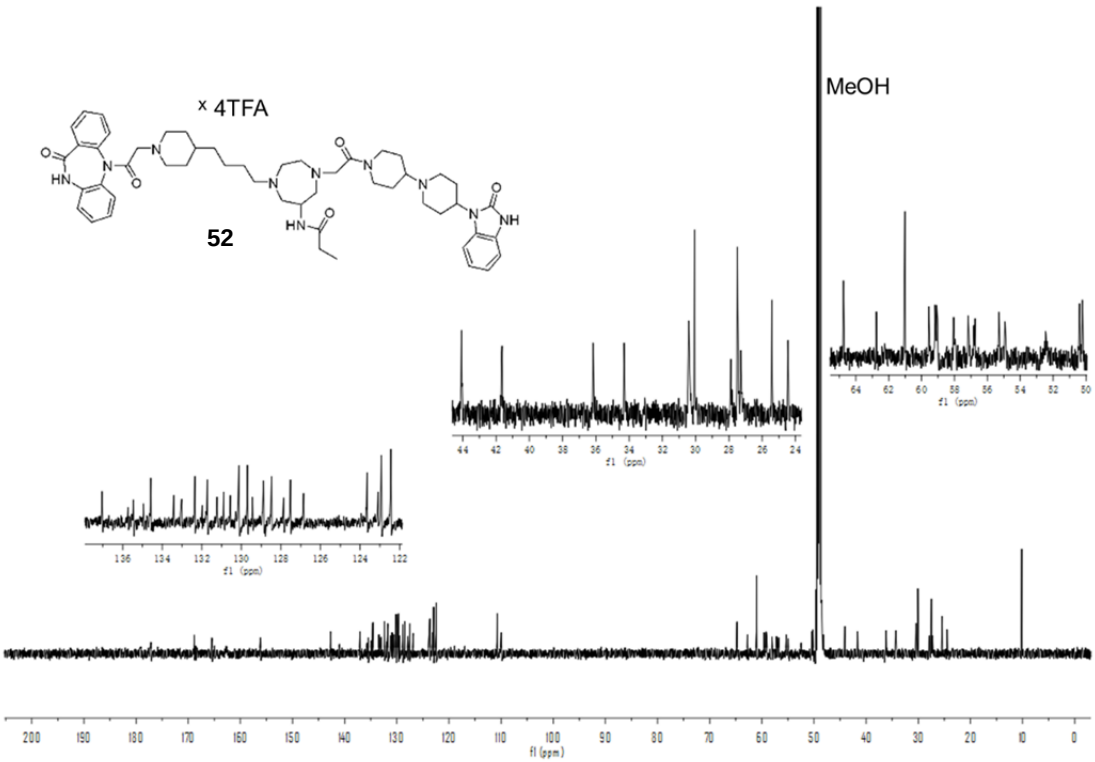
SI Figure 33. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **51**.



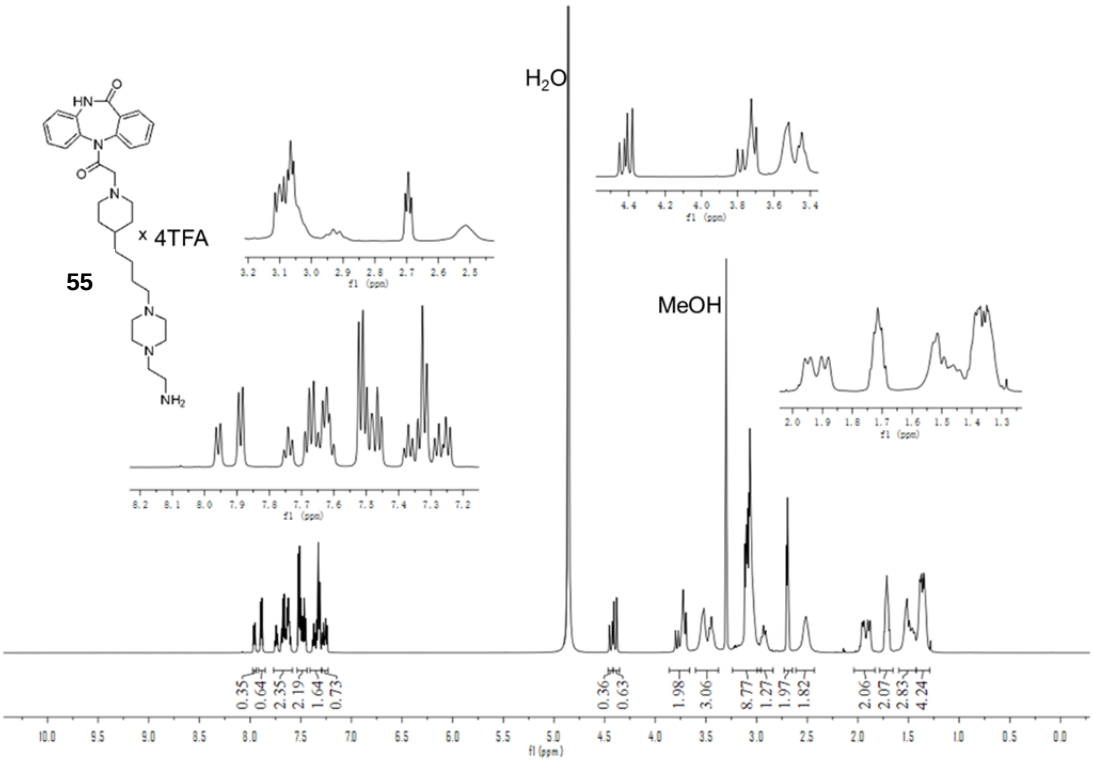
SI Figure 34. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **51**.



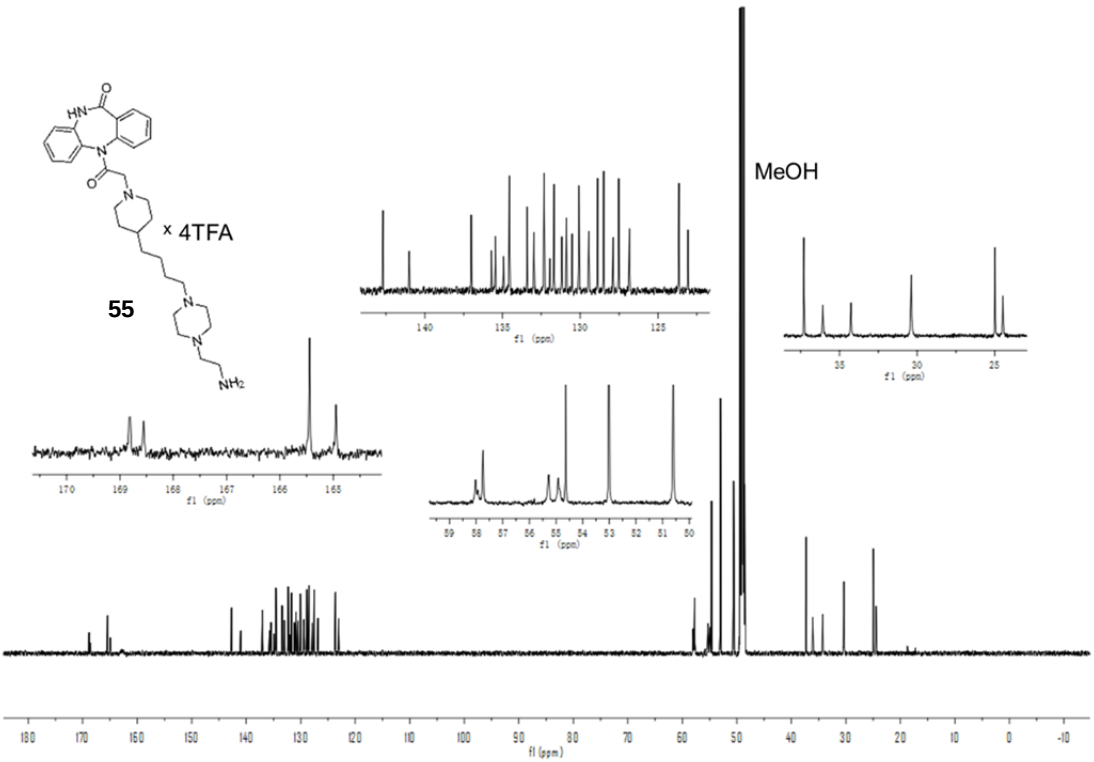
SI Figure 35. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **52**.



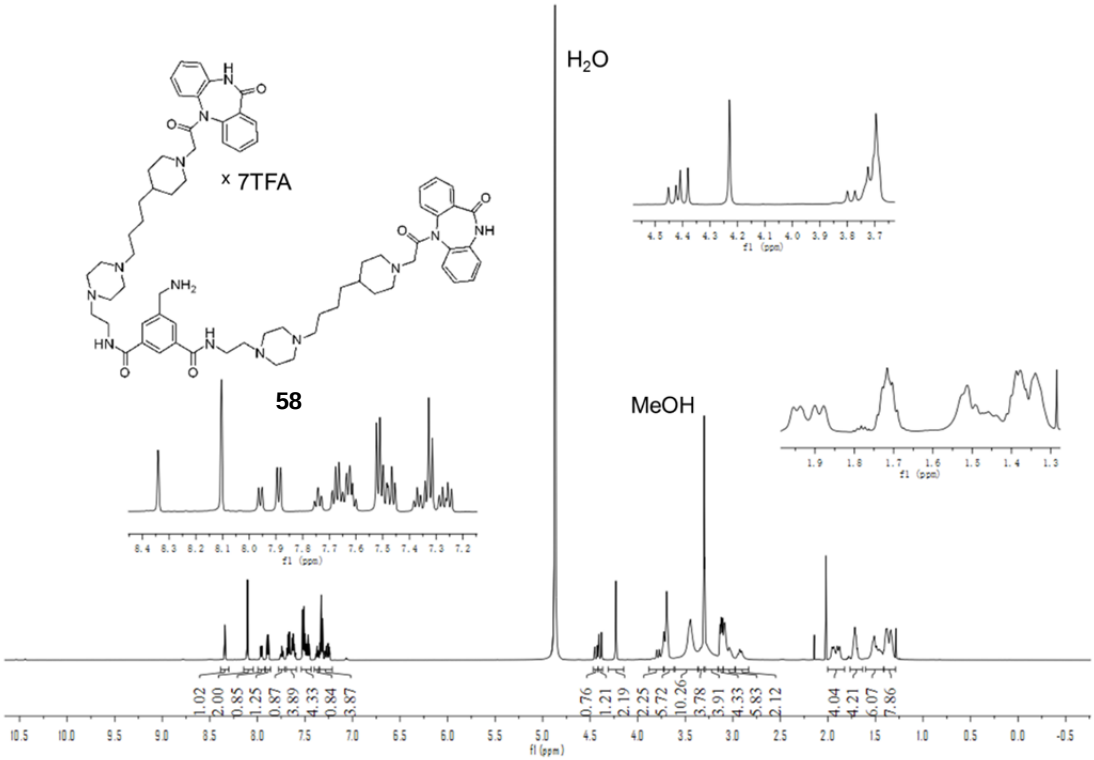
SI Figure 36. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **52**.



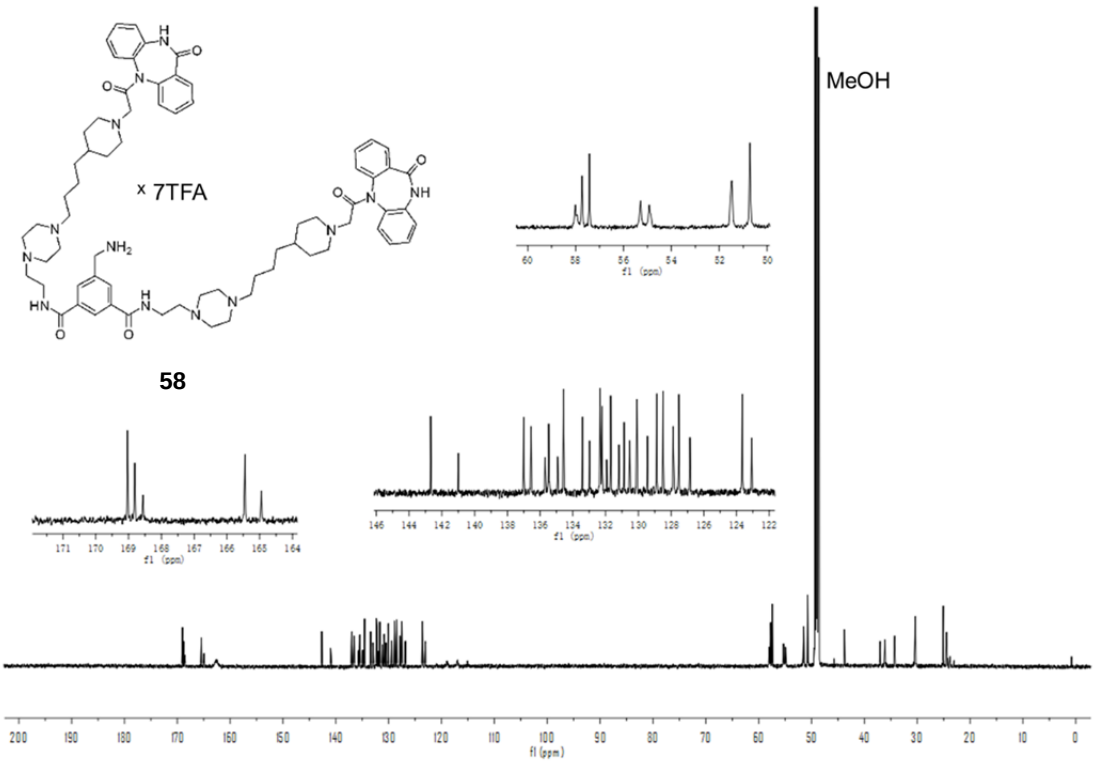
SI Figure 37. ^{1}H-NMR spectrum (600 MHz, [D$_4$]MeOH) of compound **55**.



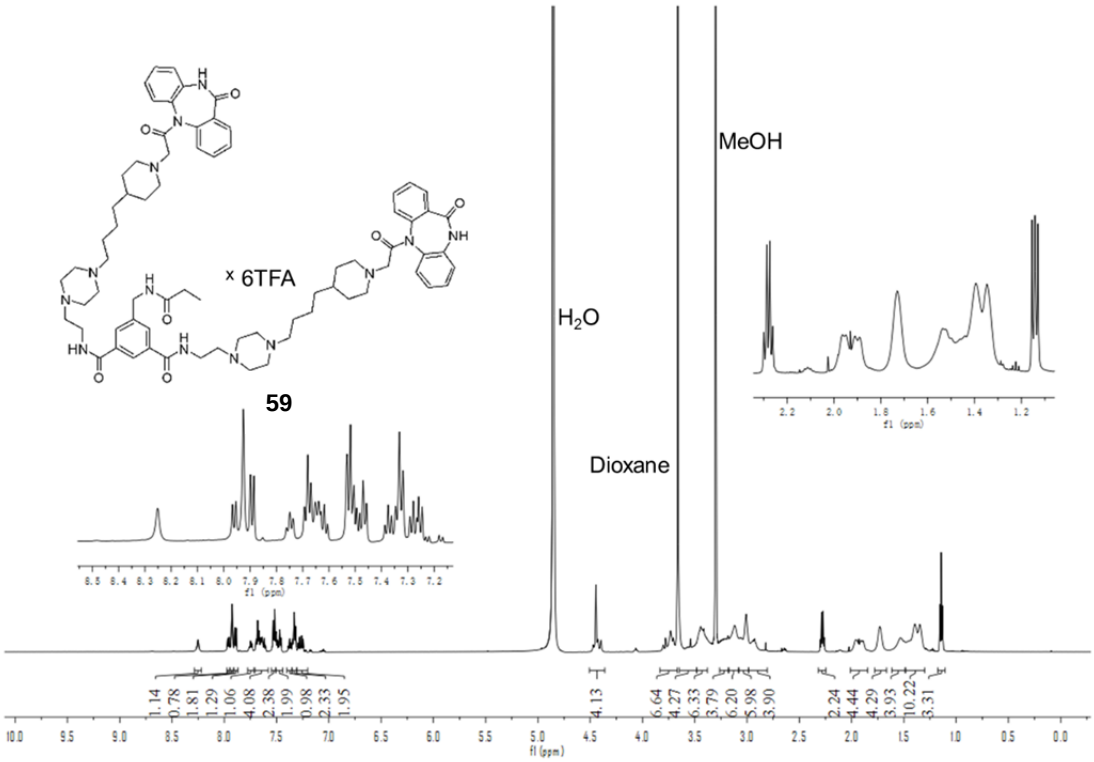
SI Figure 38. ^{13}C-NMR spectrum (150 MHz, [D$_4$]MeOH) of compound **55**.



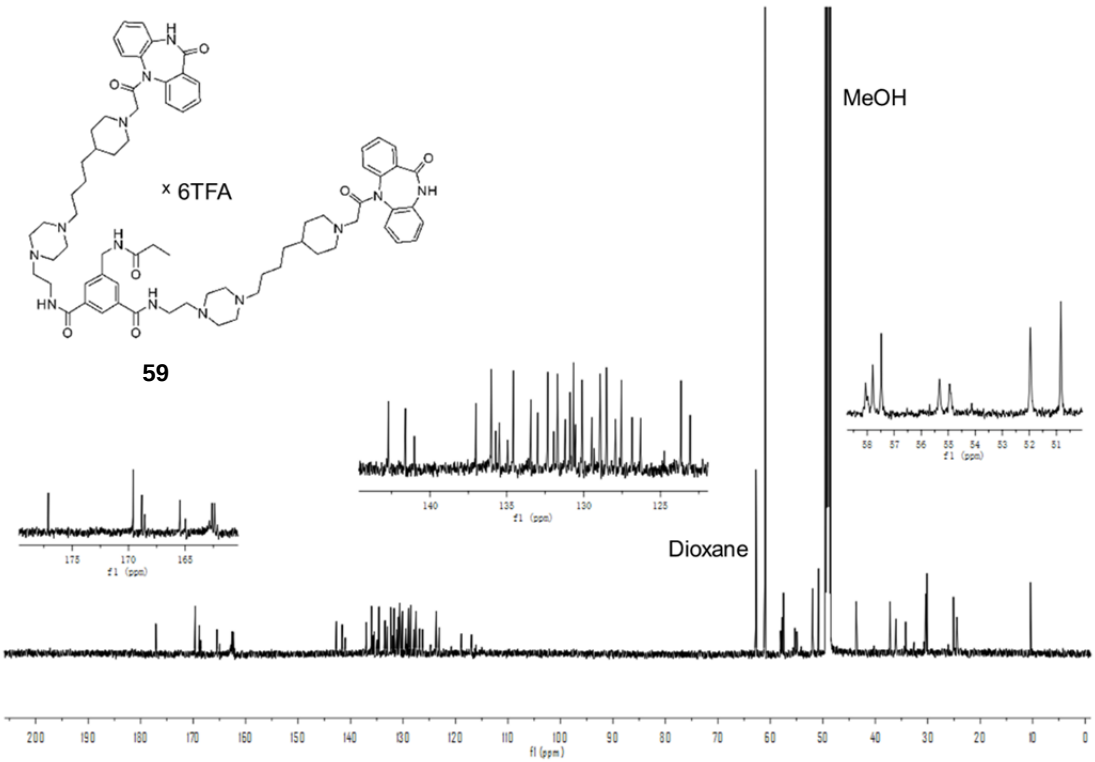
SI Figure 39. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **58**.



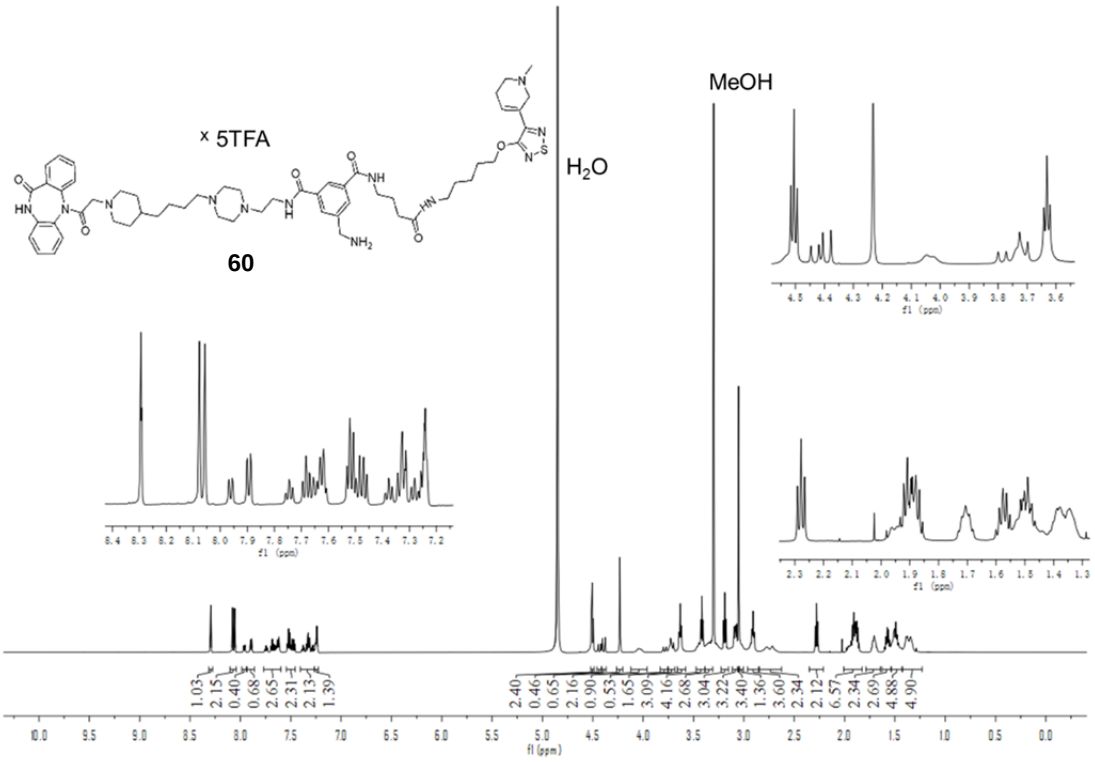
SI Figure 40. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **58**.



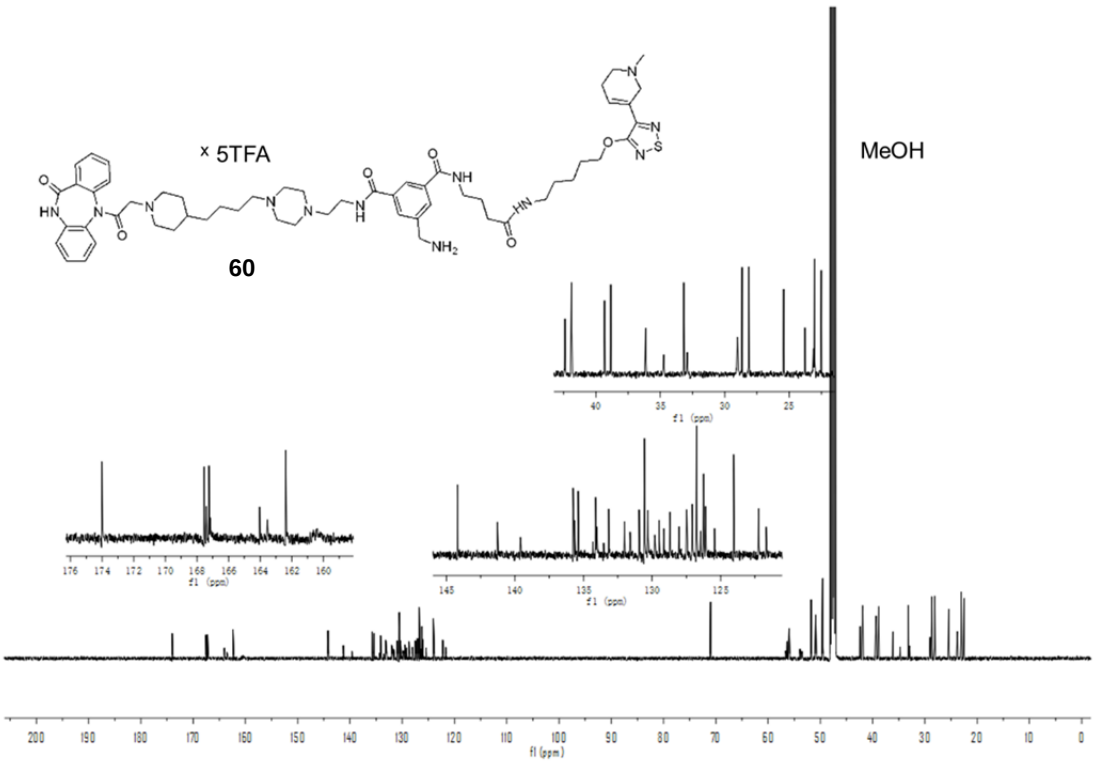
SI Figure 41. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **59**.



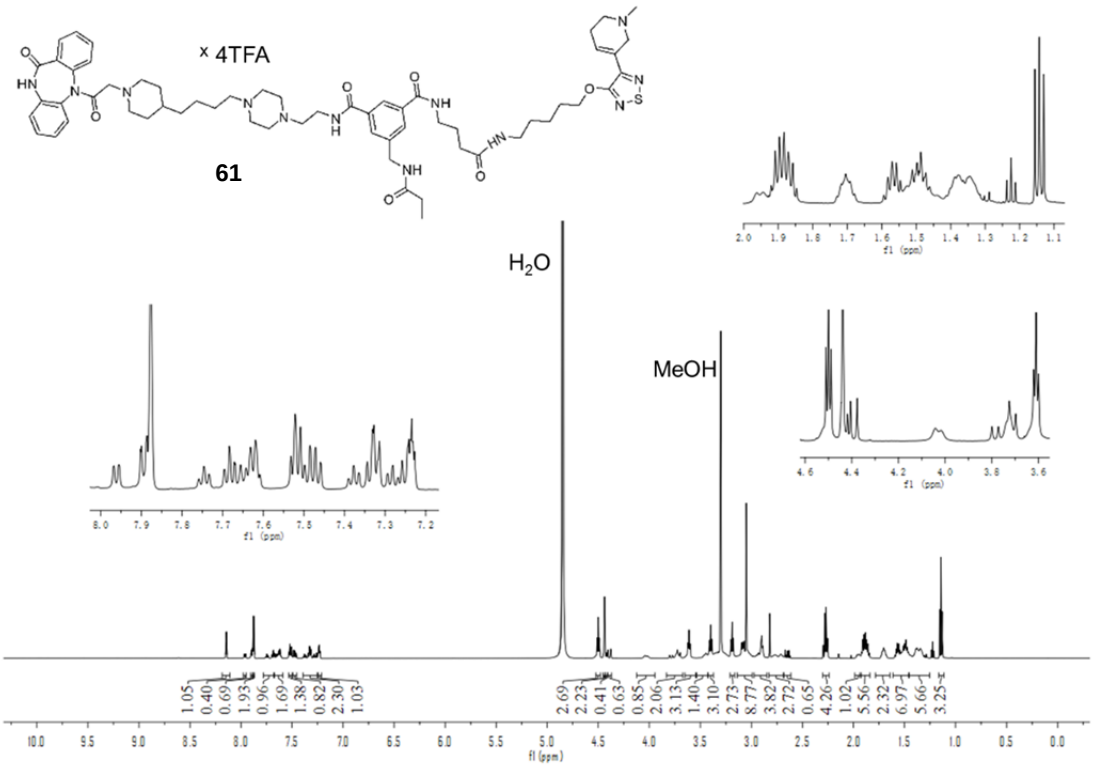
SI Figure 42. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **59**.



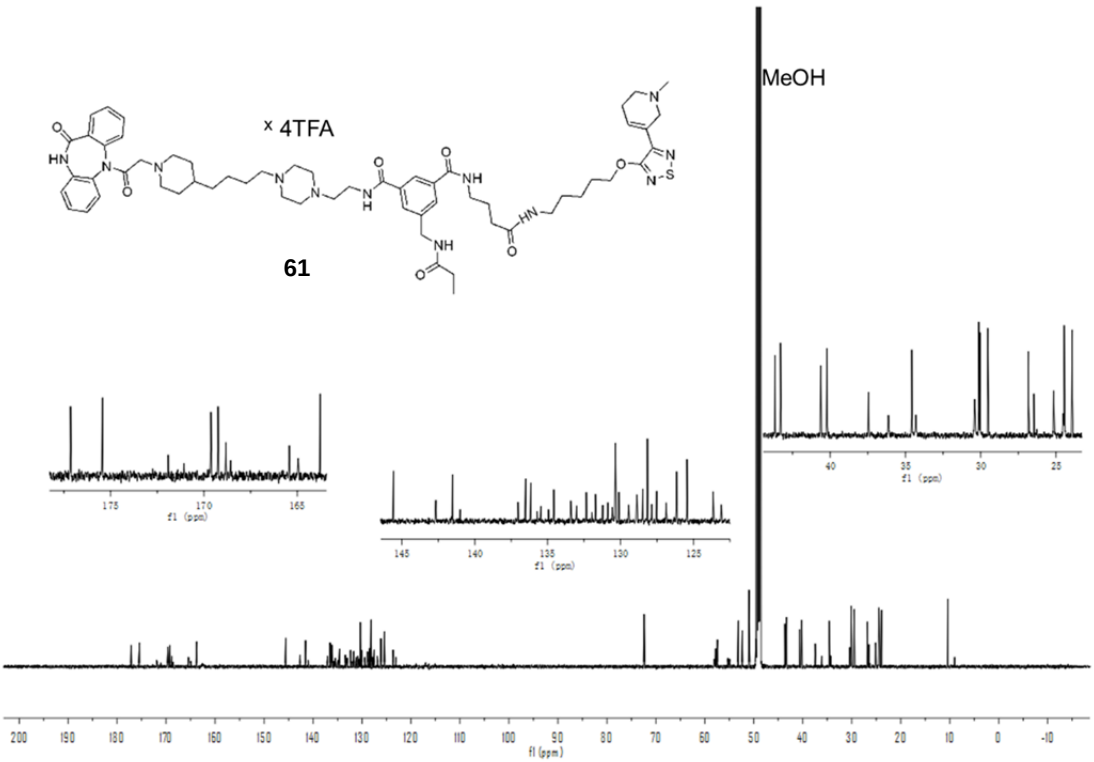
SI Figure 43. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **60**.



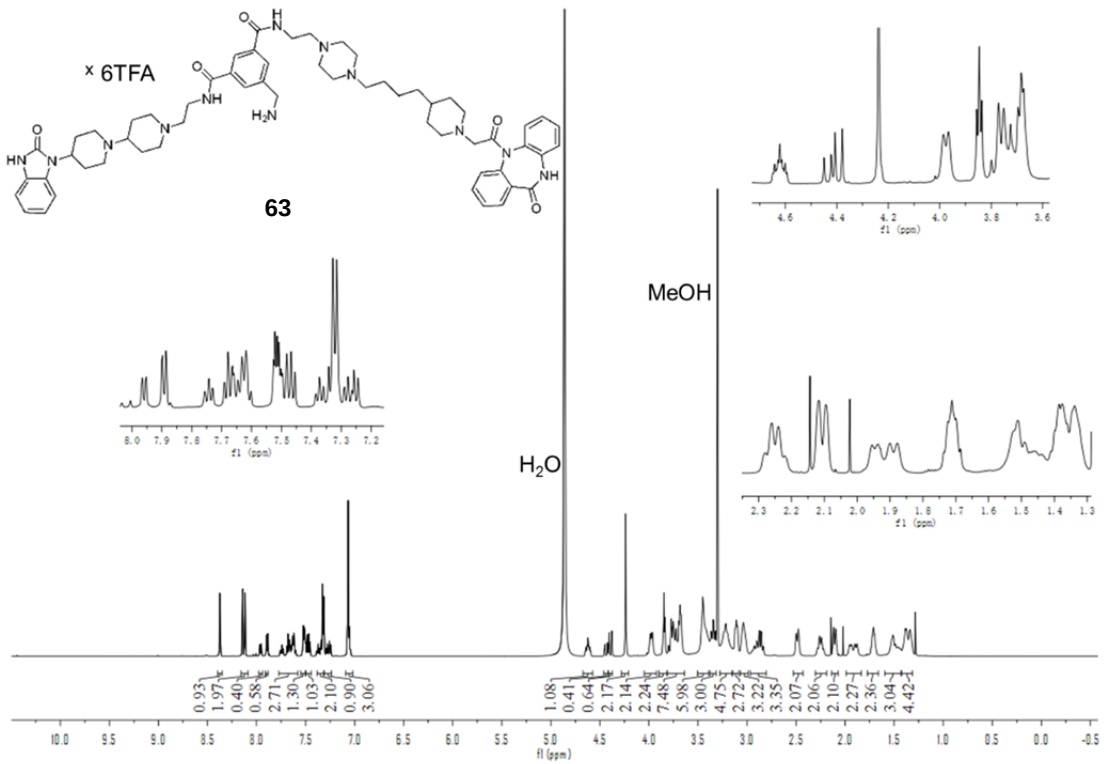
SI Figure 44. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **60**.



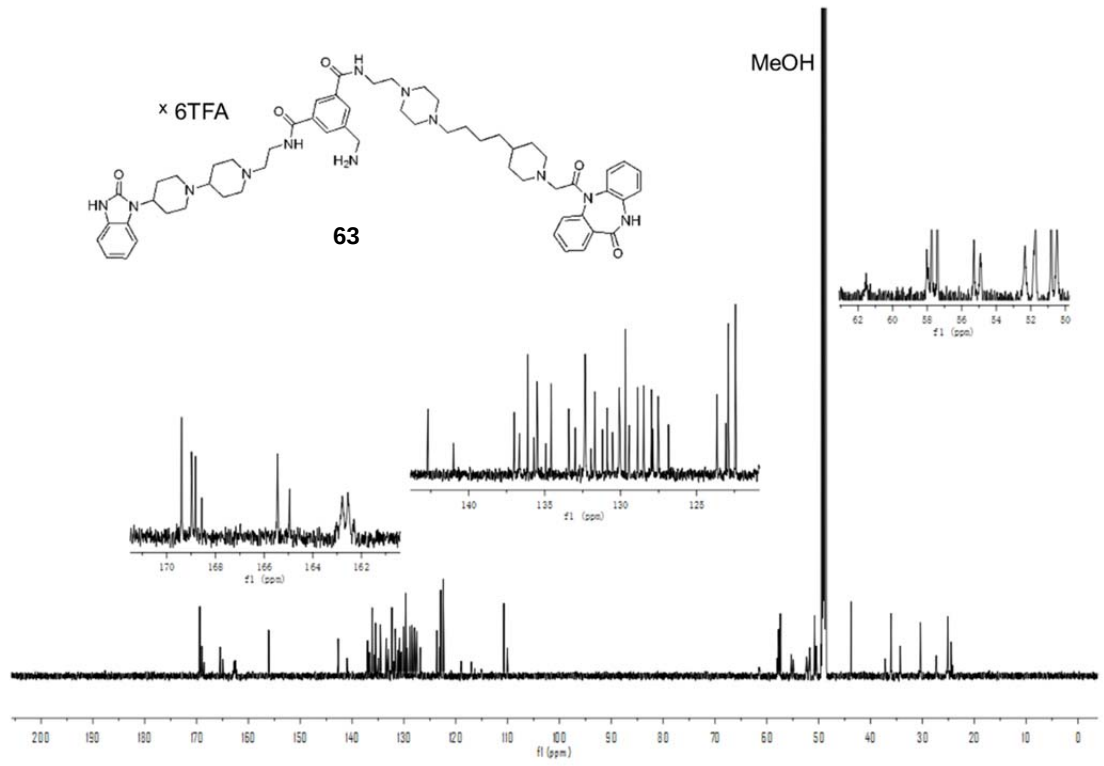
SI Figure 45. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **61**.



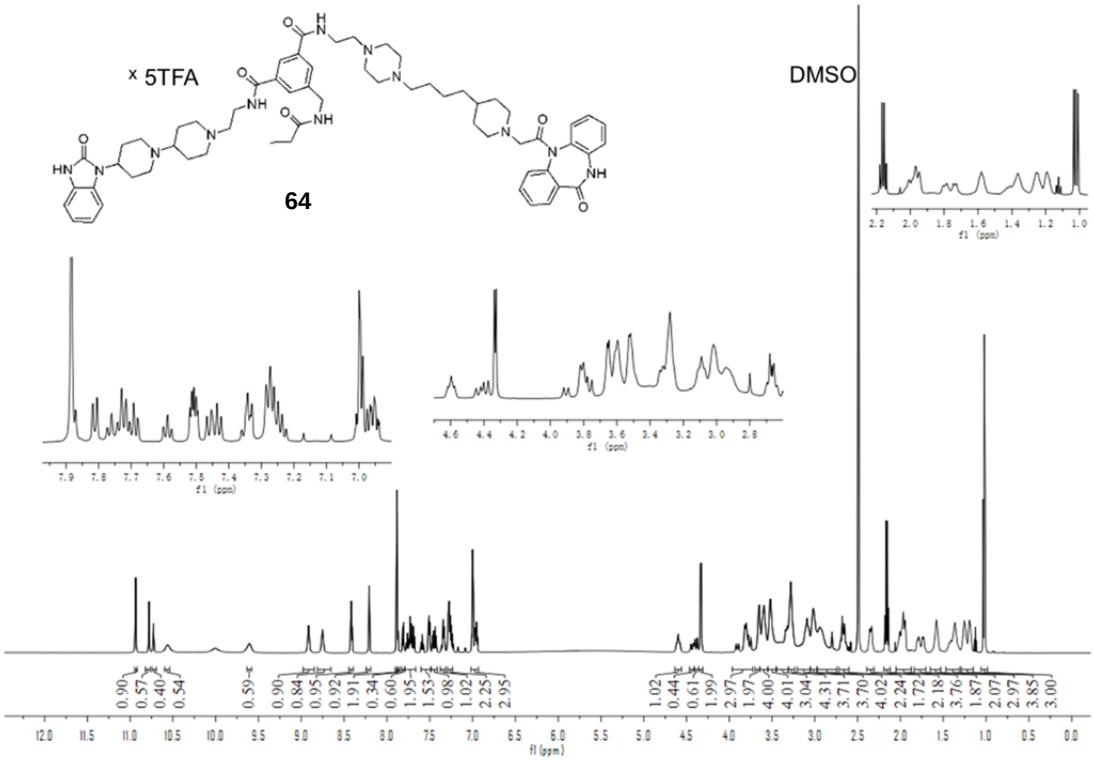
SI Figure 46. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **61**.



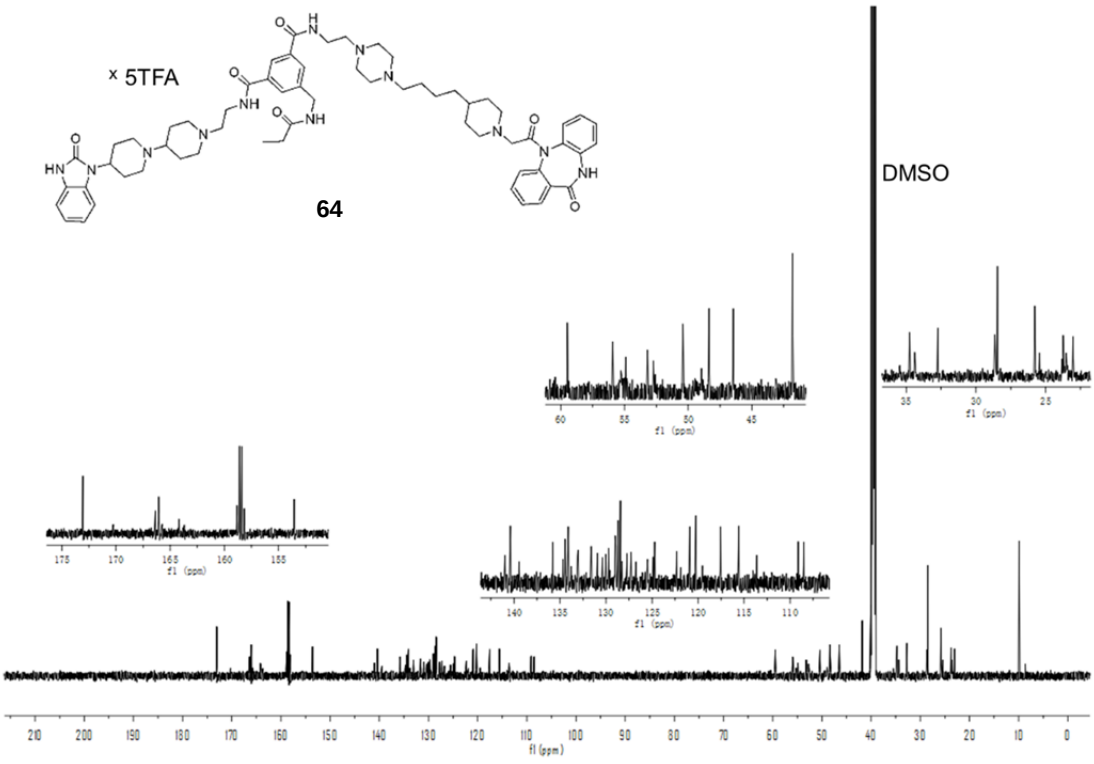
SI Figure 47. [1]H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **63**.



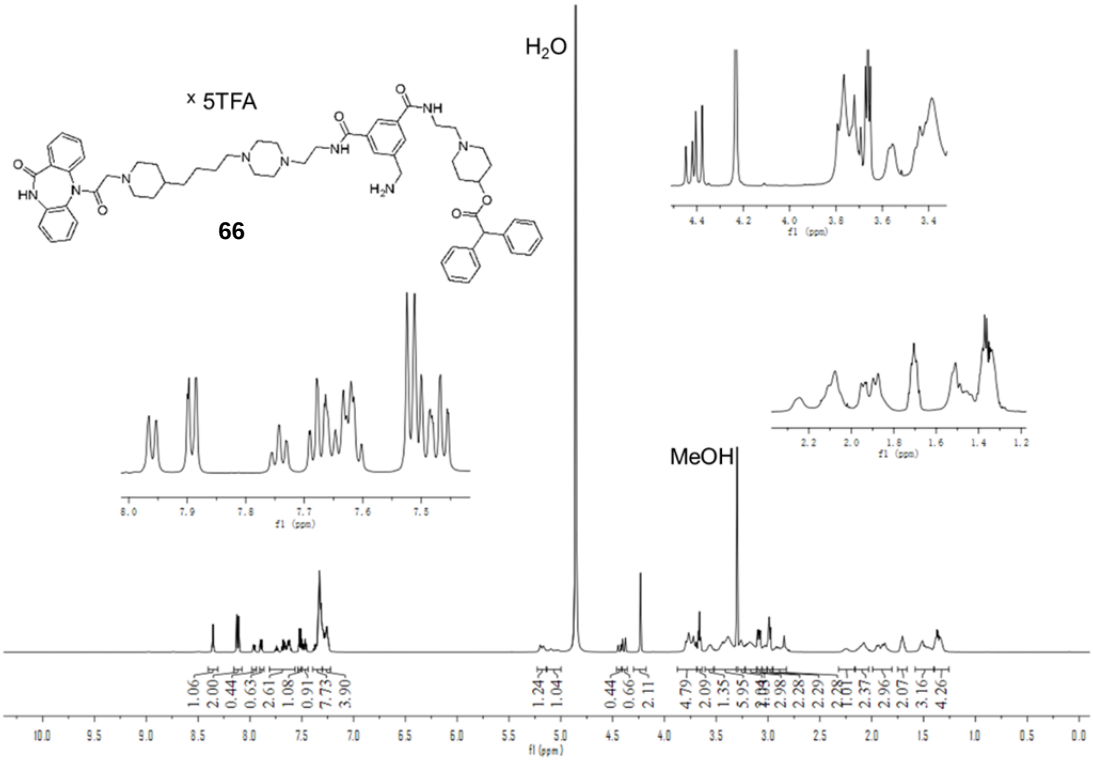
SI Figure 48. [13]C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **63**.



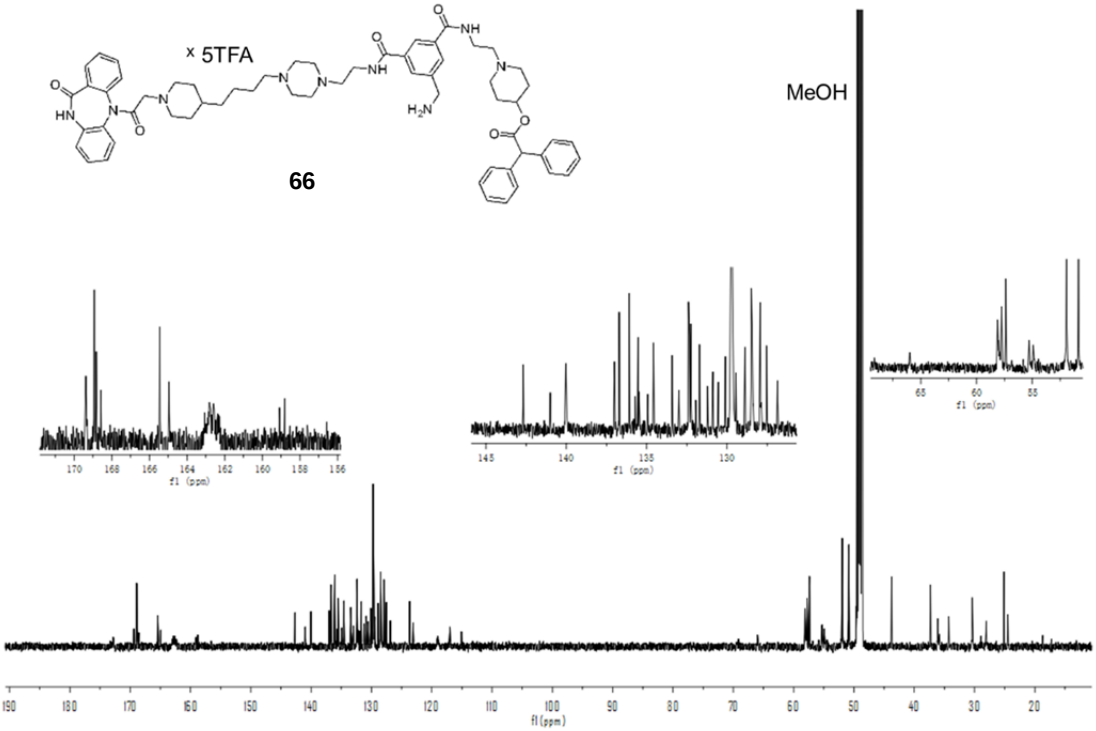
SI Figure 49. ^{1}H-NMR spectrum (600 MHz, [D_6]DMSO) of compound **64**.



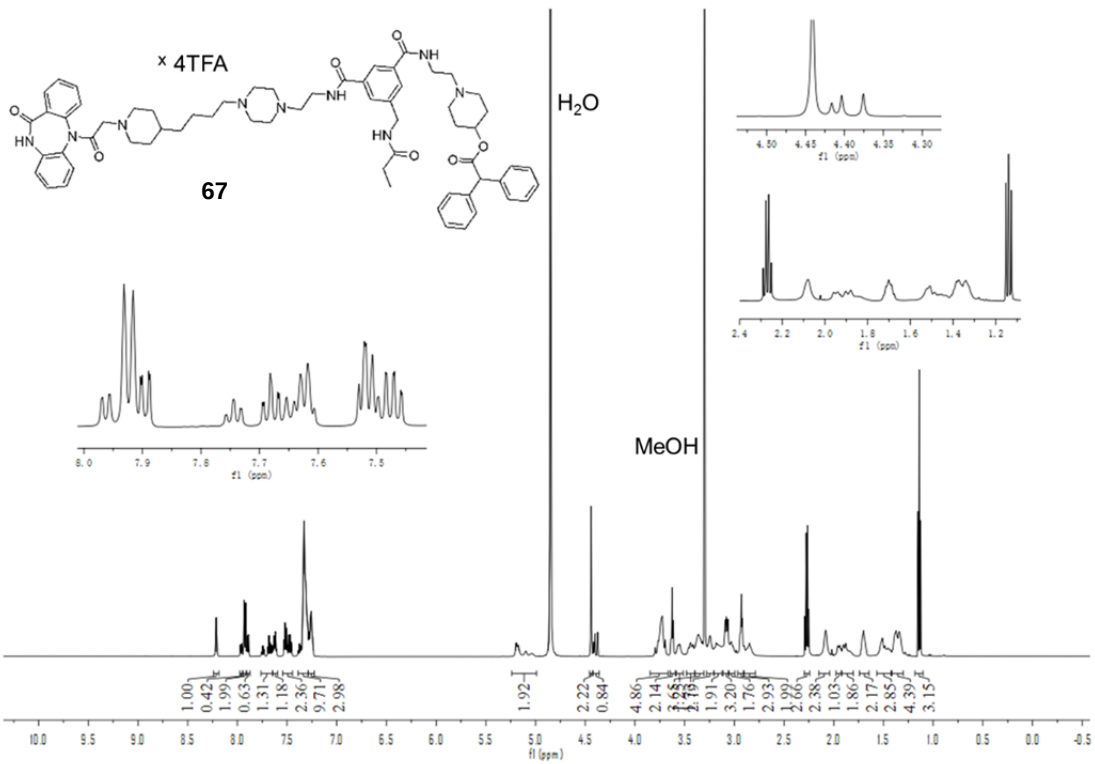
SI Figure 50. ^{13}C-NMR spectrum (150 MHz, [D_6]DMSO) of compound **64**.



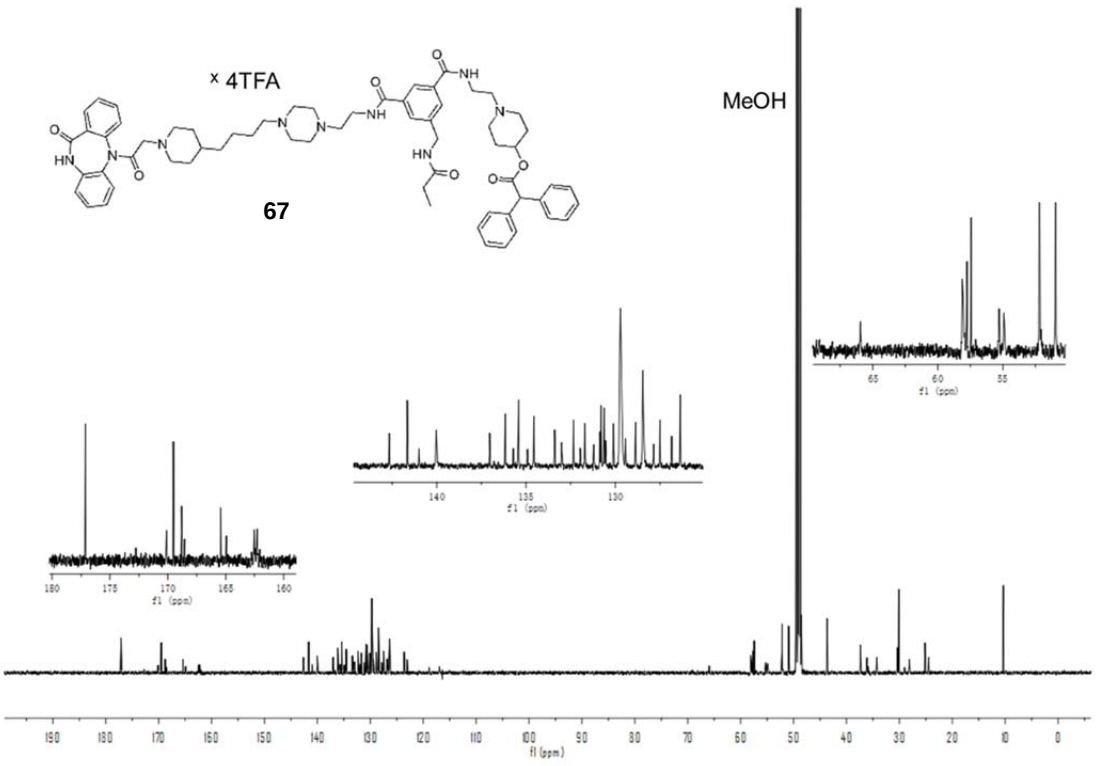
SI Figure 51. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **66**.



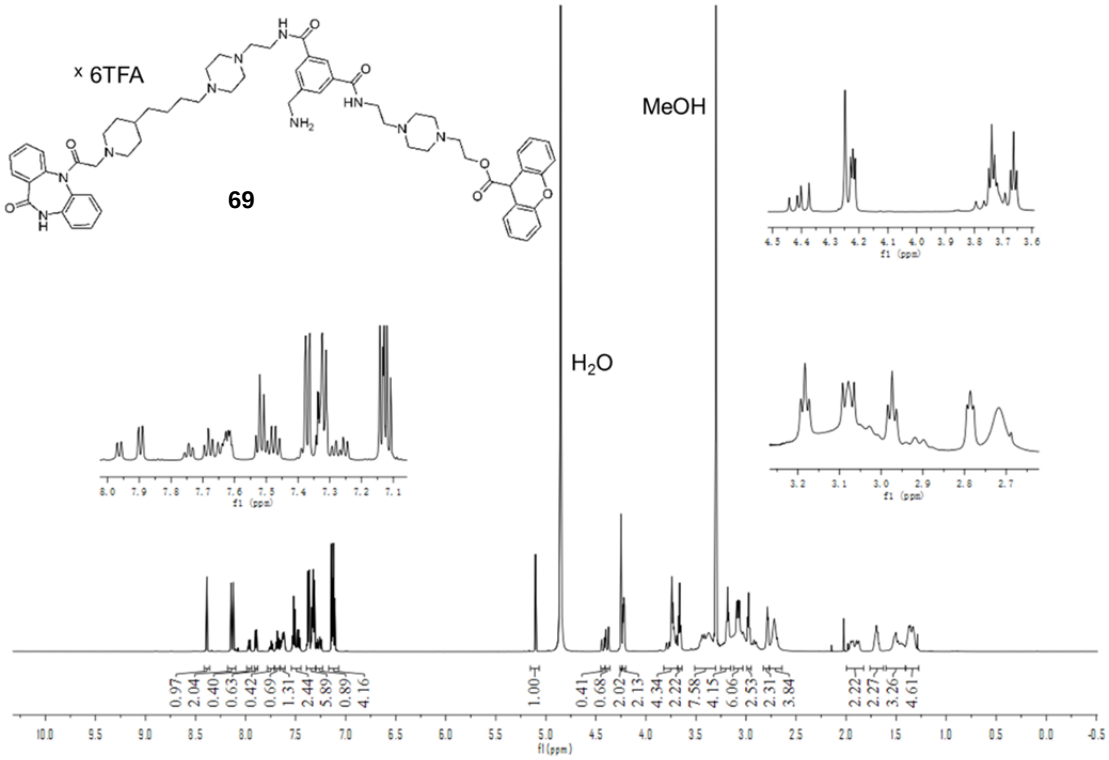
SI Figure 52. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **66**.



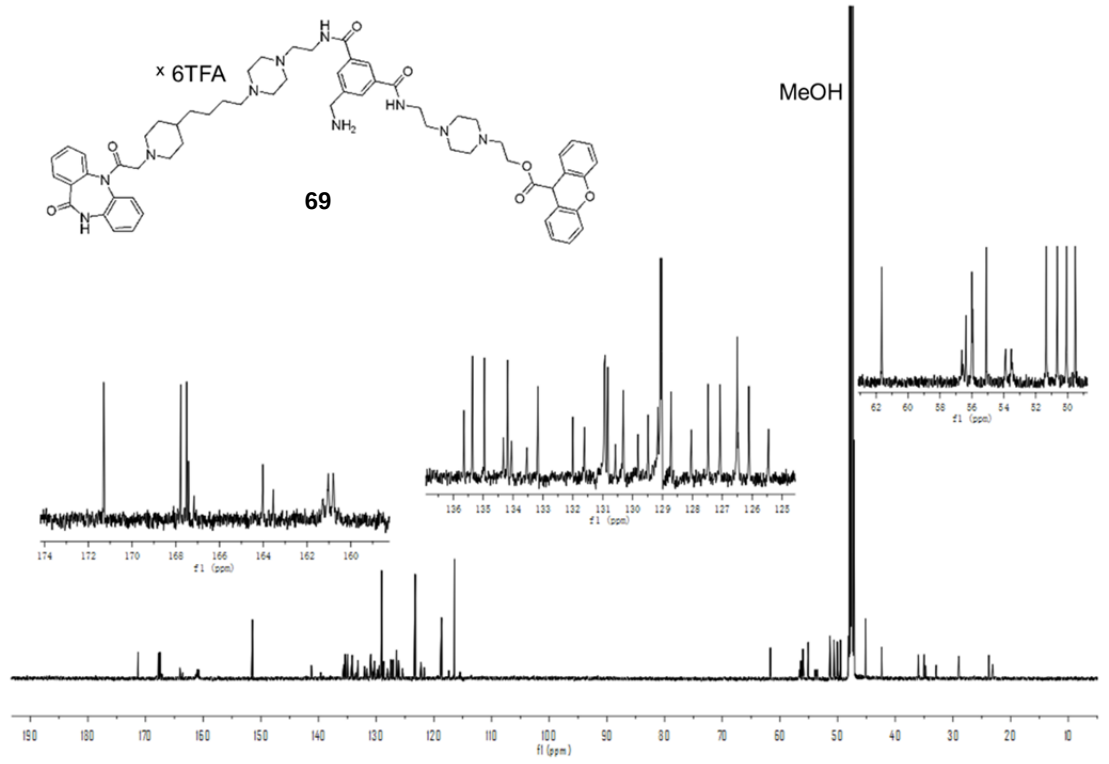
SI Figure 53. ^{1}H-NMR spectrum (600 MHz, [D$_4$]MeOH) of compound **67**.



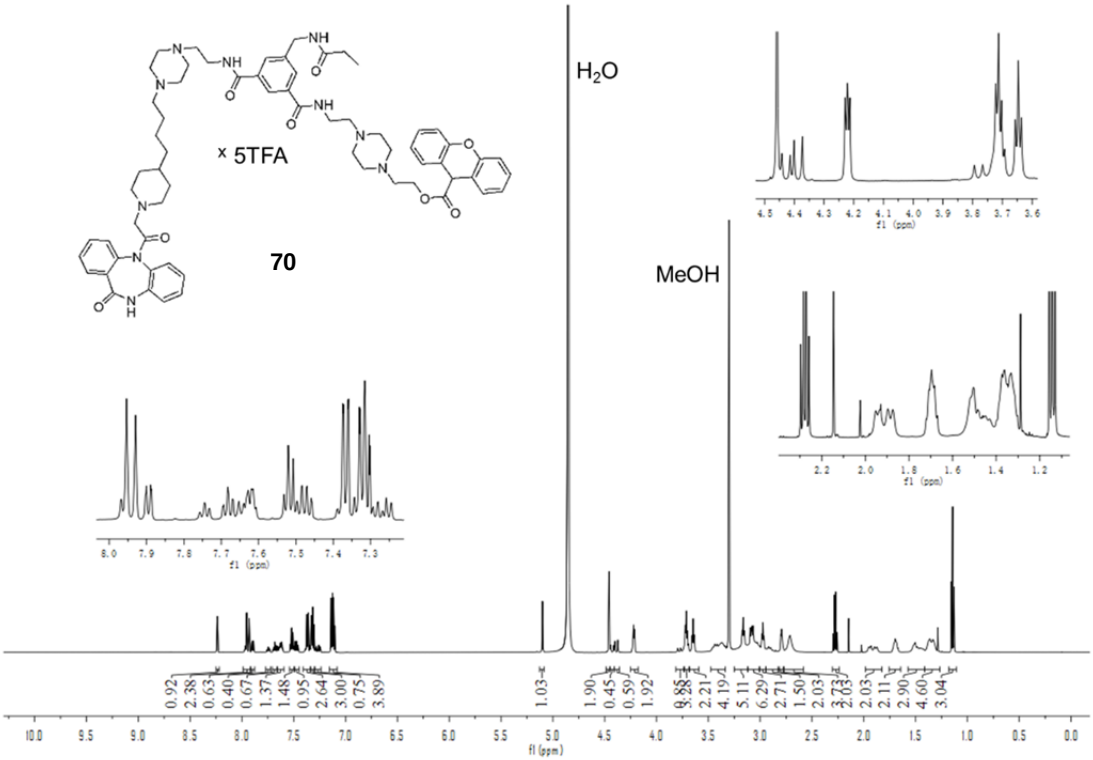
SI Figure 54. ^{13}C-NMR spectrum (150 MHz, [D$_4$]MeOH) of compound **67**.



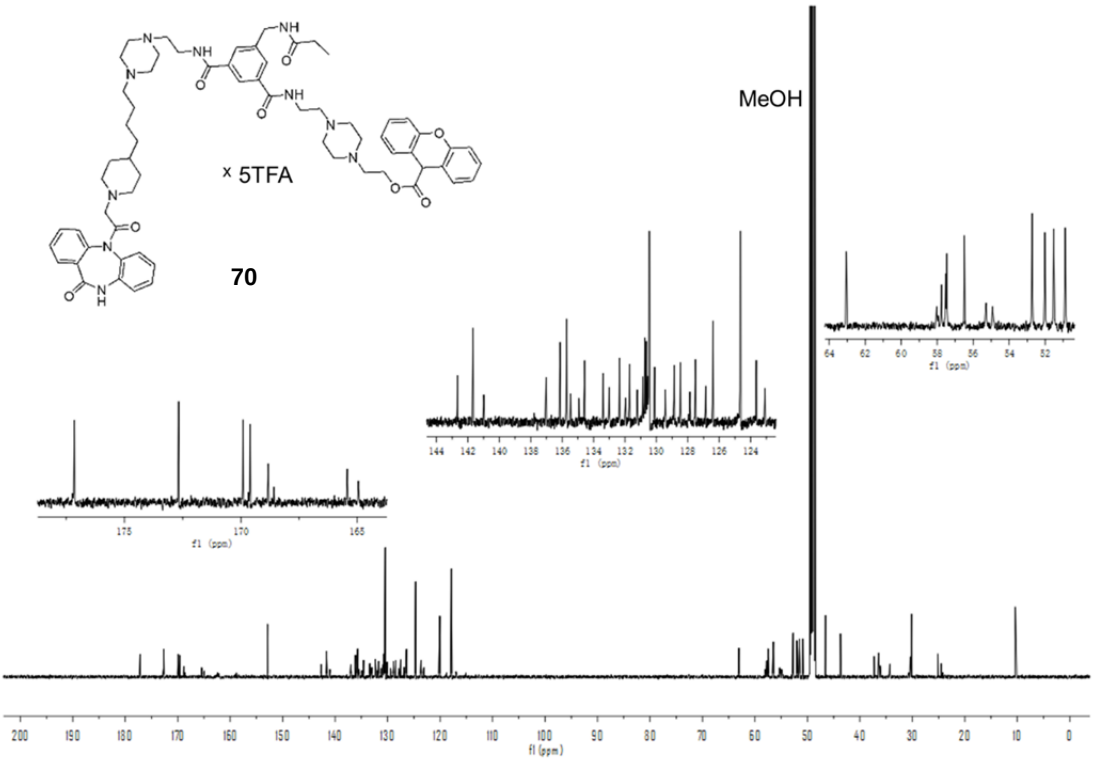
SI Figure 55. [1]H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **69**.



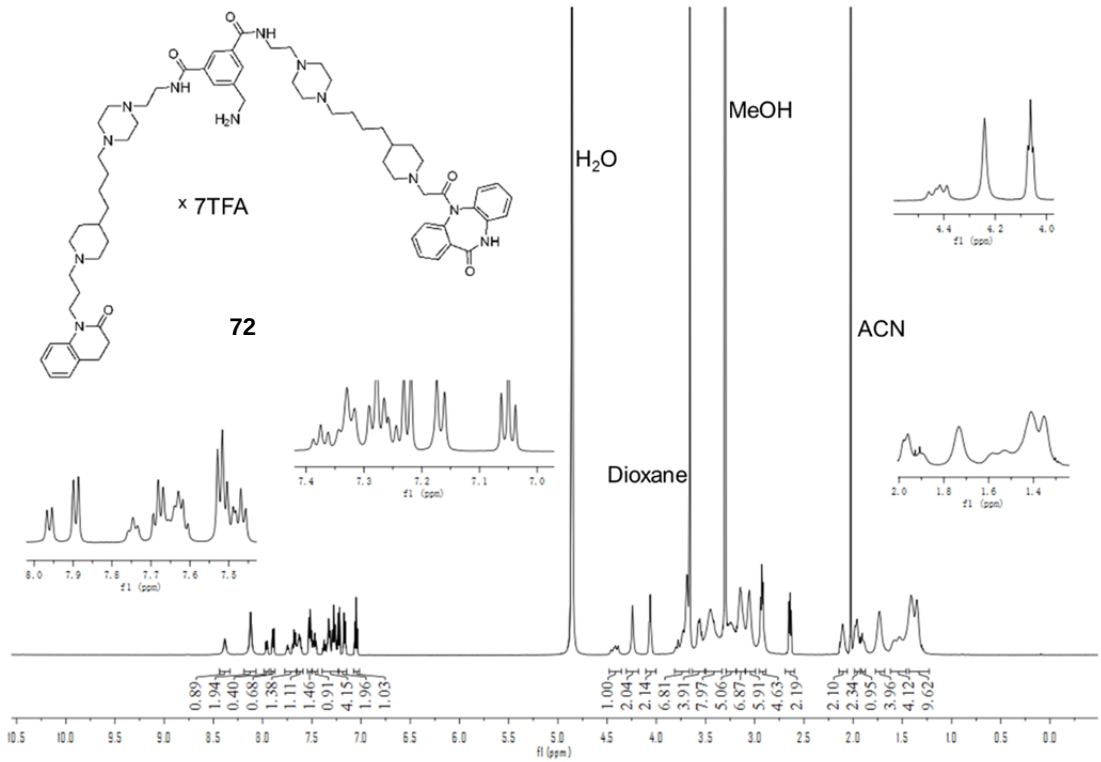
SI Figure 56. [13]C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **69**.



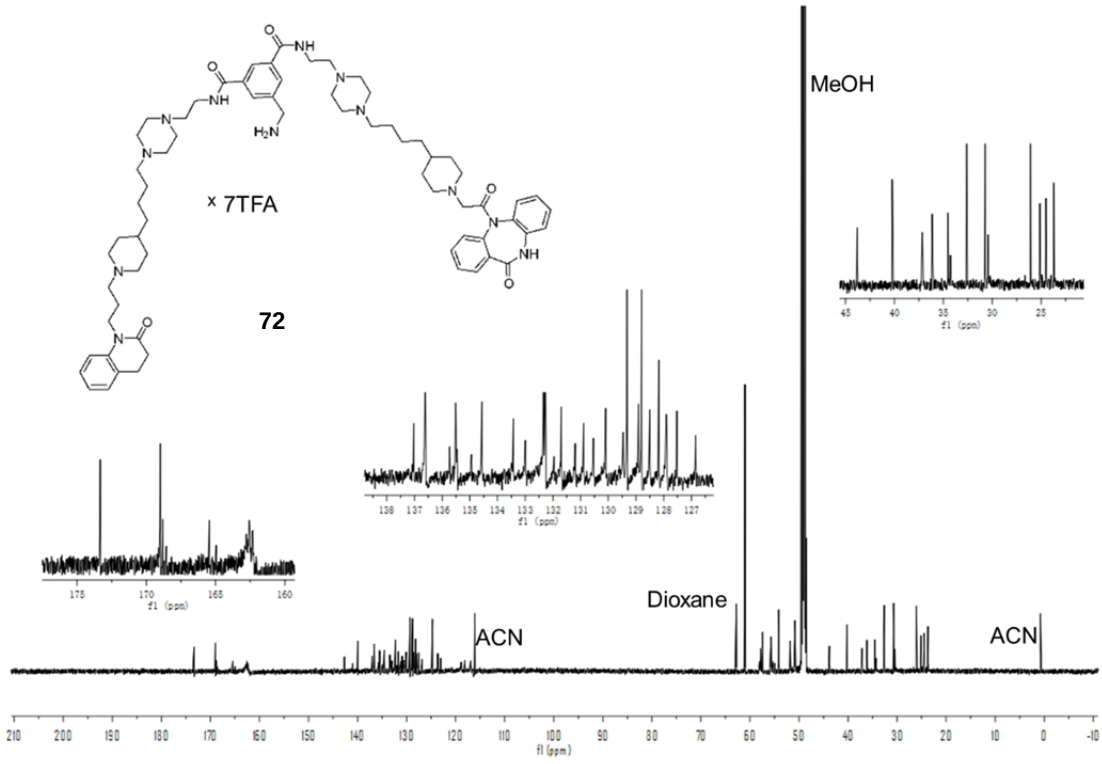
SI Figure 57. [1]H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **70**.



SI Figure 58. [13]C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **70**.

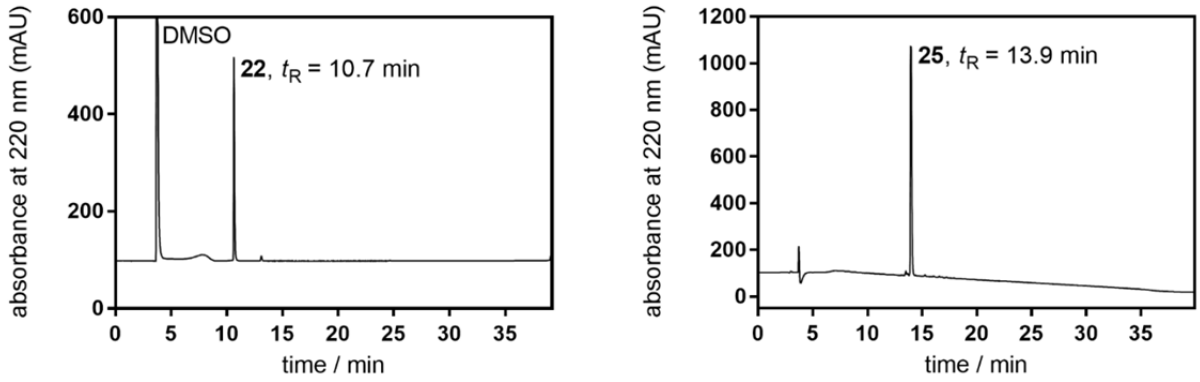


SI Figure 59. ^{1}H-NMR spectrum (600 MHz, [D_4]MeOH) of compound **72**.

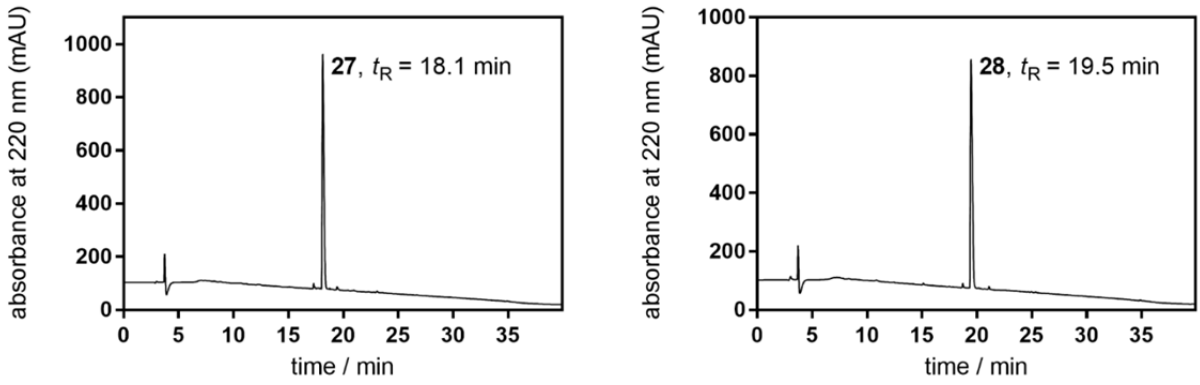


SI Figure 60. ^{13}C-NMR spectrum (150 MHz, [D_4]MeOH) of compound **72**.

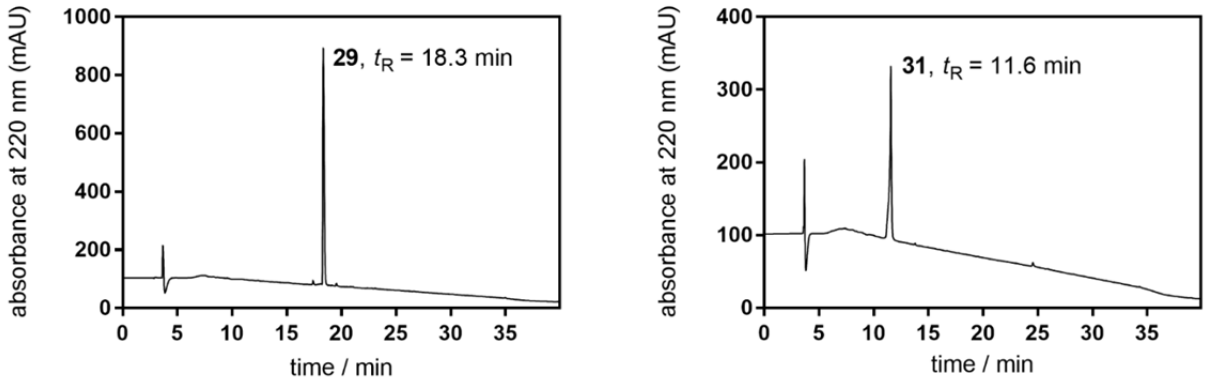
6. RP-HPLC chromatograms of compounds 22, 25, 27-29, 31, 34, 35, 38, 39, 43, 44, 46, 48, 50-52, 55, 58-61, 63, 64, 66, 67, 69, 70, 72 (SI Figures 61-75)



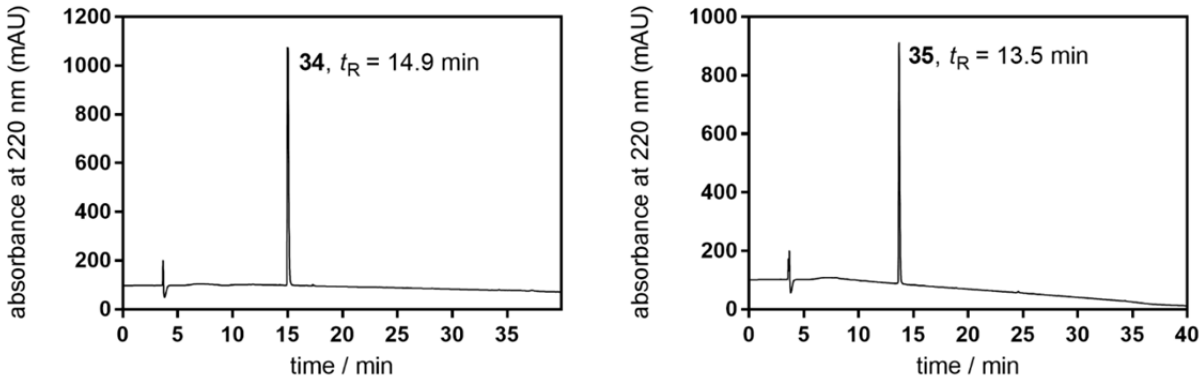
SI Figure 61. RP-HPLC analysis (purity control) of **22** and **25**.



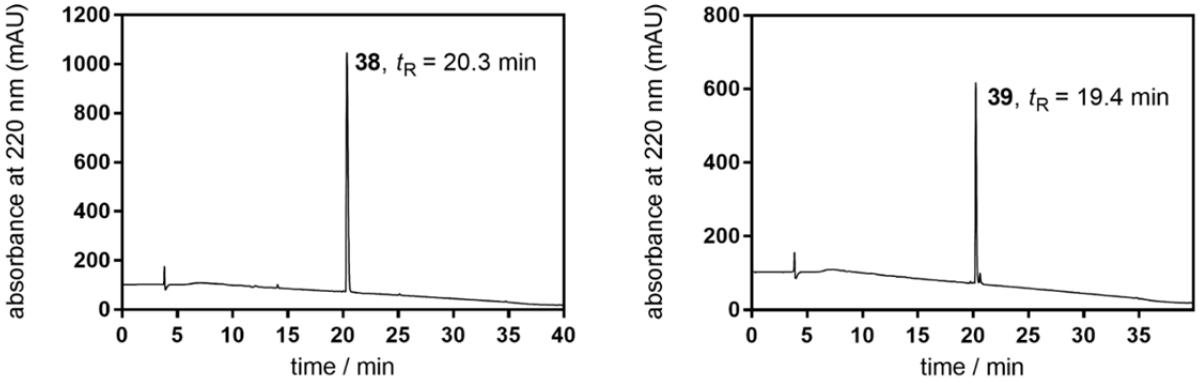
SI Figure 62. RP-HPLC analysis (purity control) of **27** and **28**.



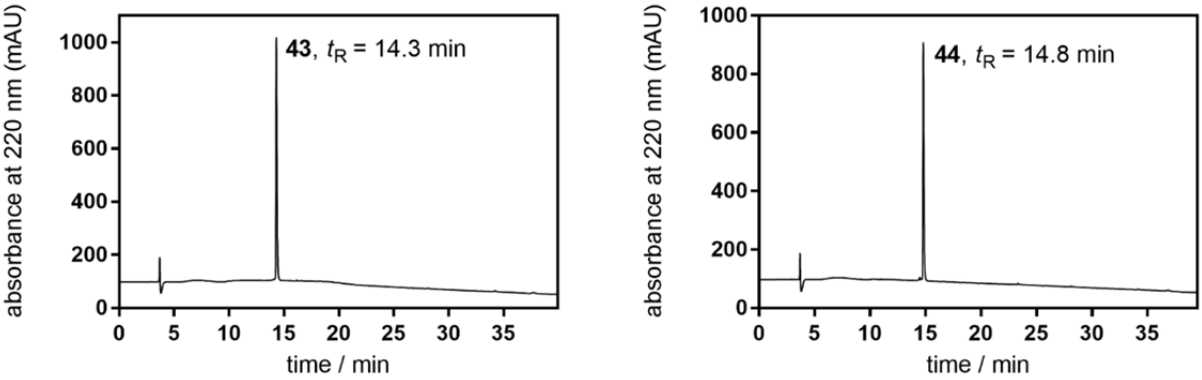
SI Figure 63. RP-HPLC analysis (purity control) of **29** and **31**.



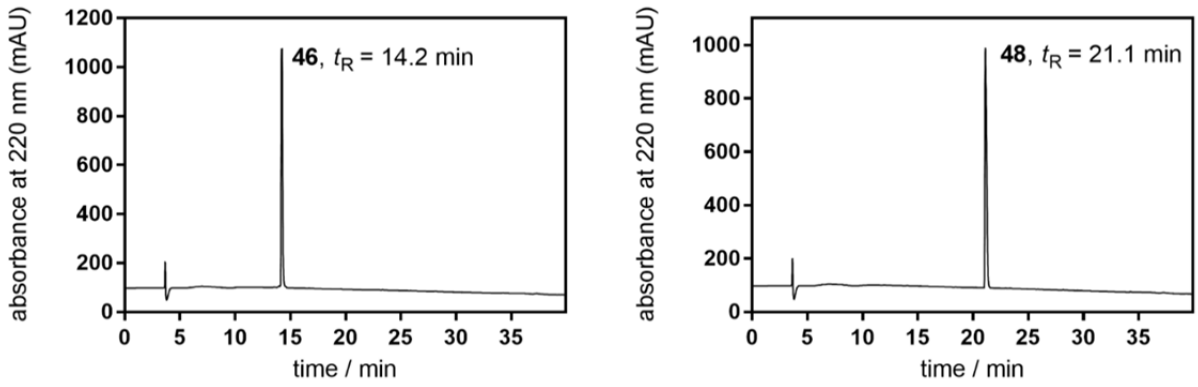
SI Figure 64. RP-HPLC analysis (purity control) of **34** and **35**.



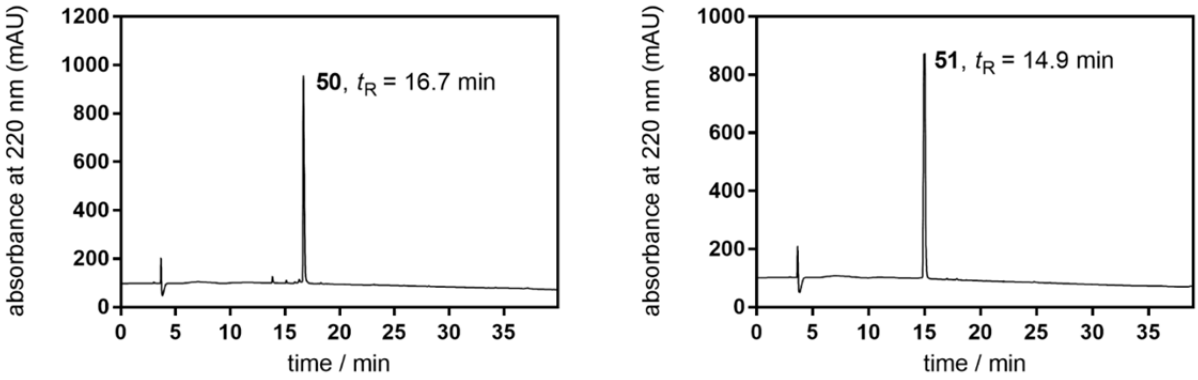
SI Figure 65. RP-HPLC analysis (purity control) of **38** and **39**.



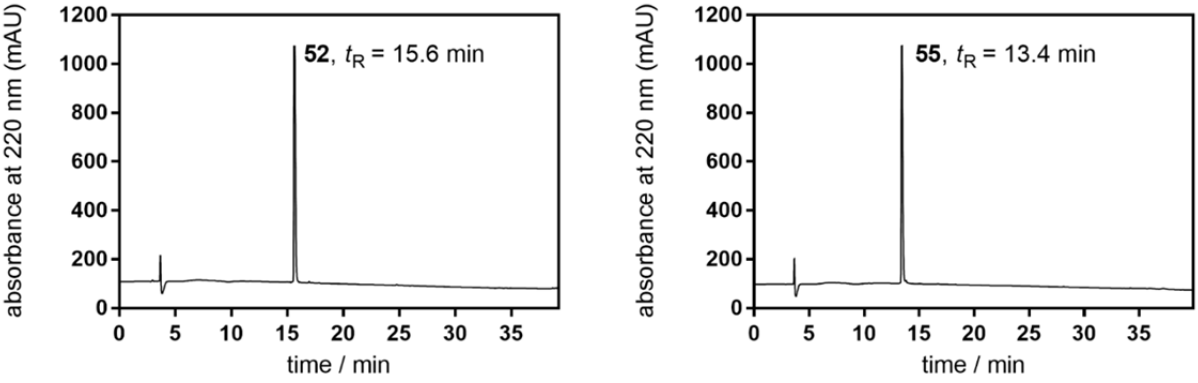
SI Figure 66. RP-HPLC analysis (purity control) of **43** and **44**.



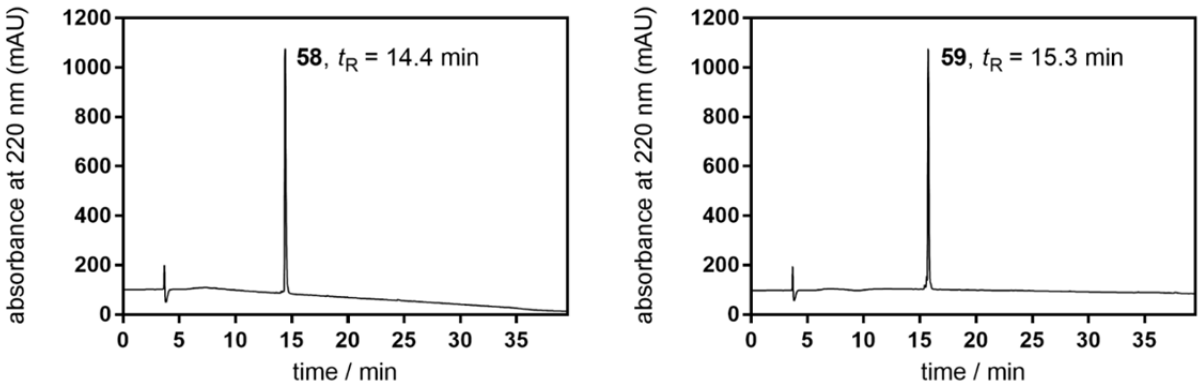
SI Figure 67. RP-HPLC analysis (purity control) of **46** and **48**.



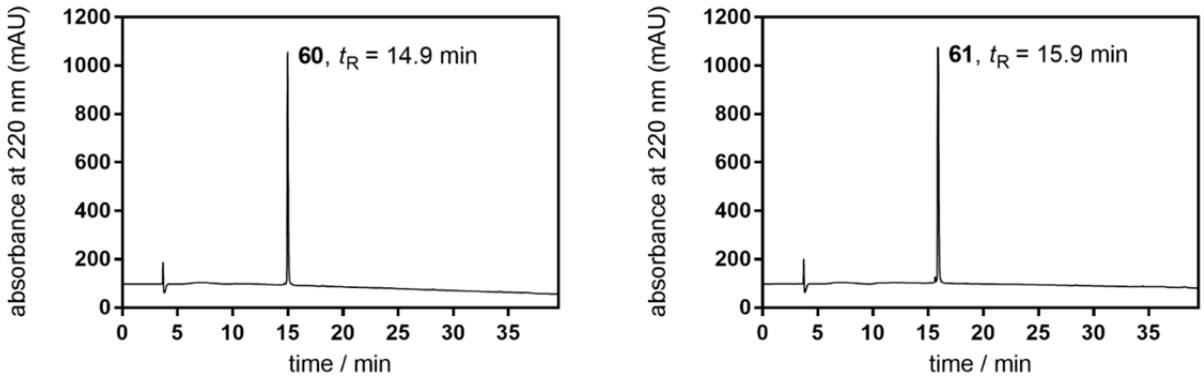
SI Figure 68. RP-HPLC analysis (purity control) of **50** and **51**.



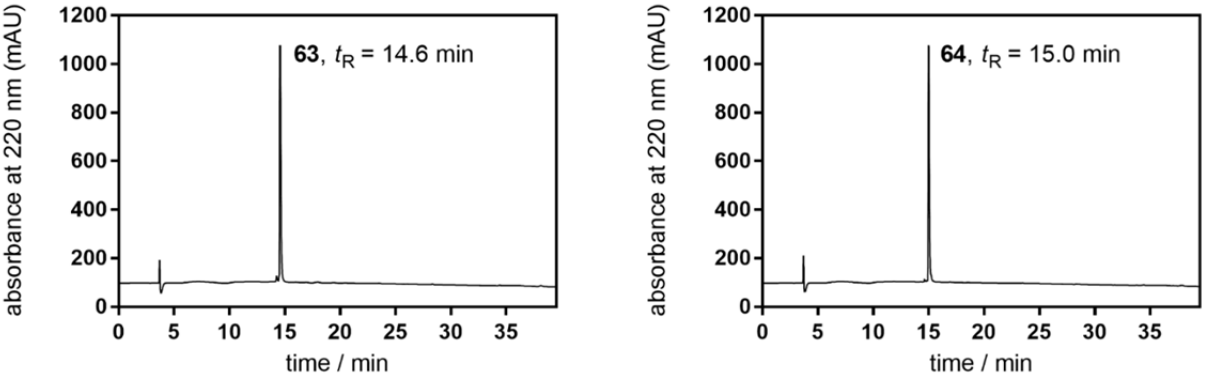
SI Figure 69. RP-HPLC analysis (purity control) of **52** and **55**.



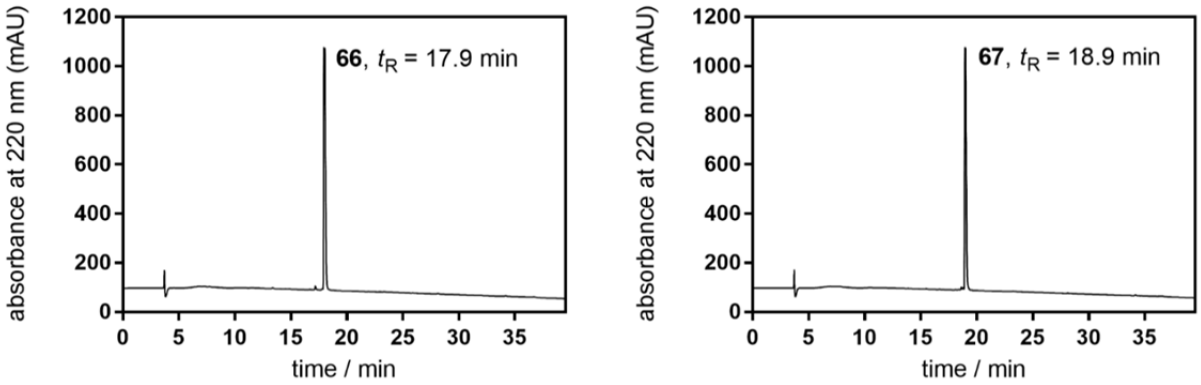
SI Figure 70. RP-HPLC analysis (purity control) of **58** and **59**.



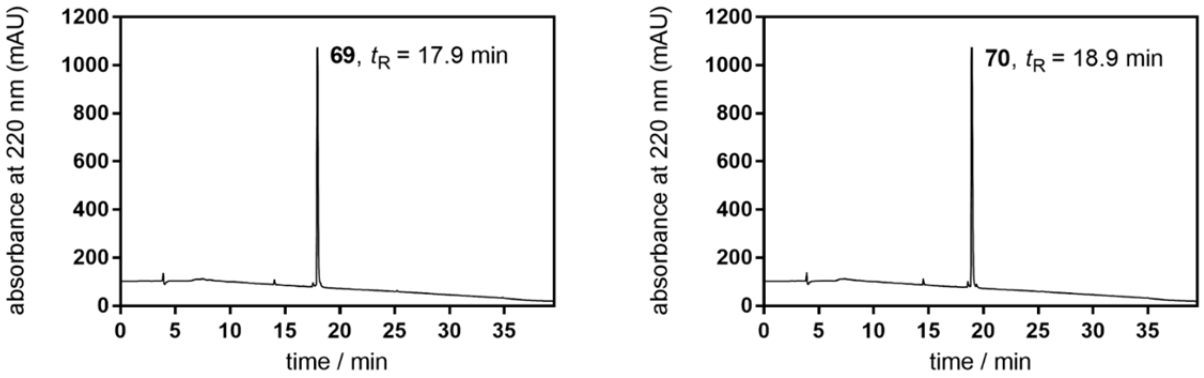
SI Figure 71. RP-HPLC analysis (purity control) of **60** and **61**.



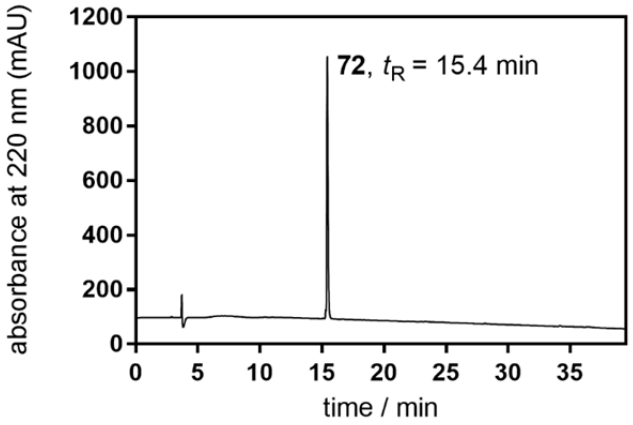
SI Figure 72. RP-HPLC analysis (purity control) of **63** and **64**.



SI Figure 73. RP-HPLC analysis (purity control) of **66** and **67**.



SI Figure 74. RP-HPLC analysis (purity control) of **69** and **70**.



SI Figure 75. RP-HPLC analysis (purity control) of **72**

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