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Chemistry & Drug Discovery

Supporting Information

Quinoline Carboxamide-Type ABCG2 Modulators: Indole and Quinoline Moieties as Anilide Replacements

Stefanie Bauer,[a] Cristian Ochoa-Puentes,[b] Qiu Sun,[b] Manuel Bause,[b] Günther Bernhardt,[a] Burkhard König,*[b] and Armin Buschauer*[a]

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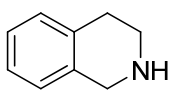
Contents

1 Synthesis of tetrahydroisoquinolines 20-23

Chemicals and solvents were purchased from commercial suppliers and used without further purification.

1.1 Experimental details and analytical data

Compound **20** and **21** are commercially available; the synthesis of **22** has already been reported.[1]



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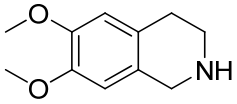

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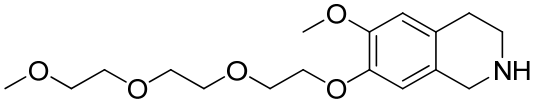
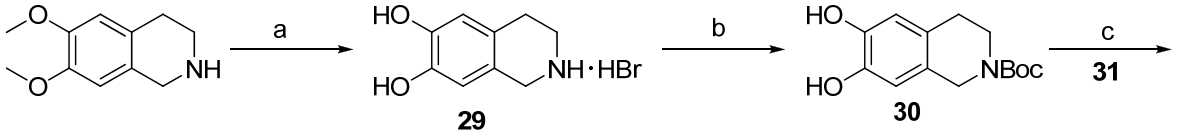


22

Synthesis of compound **23**:



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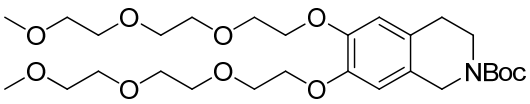

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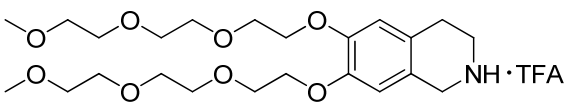
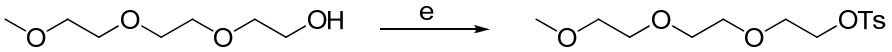


23

with



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Scheme 1: Synthesis of **23**. *Reagents and conditions:* (a) HBr/CH_3COOH, reflux. (b) Boc_2O, Et_3N, DCM 0 °C. (c) **31**, K_2CO_3, THF, reflux. (d) TFA, DCM, rt. (e) TosCl, NaOH, H_2O/THF, rt.

1,2,3,4-Tetrahydroisoquinoline-6,7-diol hydrobromide 29
Compound **29** has already been described.[2] 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (21.8 mmol) was refluxed in a mixture of HBr (24 mL, 48% in H_2O) and CH_3COOH (96 mL) for 8 h. The solvent mixture was removed by distillation. The product was used without purification. Yield: 21.8 mmol (100%). ^{1}H NMR (400 MHz, CD_3OD, δ): 2.95 (t, *J* = 6.3 Hz, 2 H, CH_2), 3.31 (quint, *J* = 1.7 Hz, 1 H, NH), 3.42 (d, *J* = 6.4 Hz, 2 H, CH_2), 4.18 (s, 2 H, CH_2), 6.59 (s, 1 H, CH_{ar}), 6.62 (s, 1 H, CH_{ar}).

***tert*-Butyl 6,7-dihydroxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 30**
Compound **30** was prepared according to known procedures[2] from **2** (21.8 mmol), Di-*tert*-butyldicarbonate (0.95 eq, 20.7 mmol), and triethylamine (5 eq, 109 mmol). Flash column chromatography (PE:EA 1:1) of the sticky brown crude product yielded a slightly yellow solid. Yield: 12.9 mmol (63 %). R_f (PE:EA 1:1): 0.58. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.48 (s, 9 H), 2.66 (t, *J* = 5.6 Hz, 2 H), 3.58 (s, 2 H), 4.41 (s, 2 H), 6.55 (s, 1 H), 6.58 (s, 1 H).

2-(2-(2-Methoxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate 31
Compound **31** was prepared according to known procedures.[3] It was obtained as colorless oil and

used without further purification. Yield: 88.1 mmol (76 %). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.42 (s, 3 H), 3.34 (s, 3 H), 3.48-3.52 (m, 2 H), 3.55-3.60 (m, 6 H), 3.66 (t, *J* = 4.8, 3 H), 4.13 (t, *J* = 4.8, 3 H), 7.32 (d, *J* = 8.2, 2 H), 7.77 (d, *J* = 8.3, 2 H).

tert-Butyl 6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 32

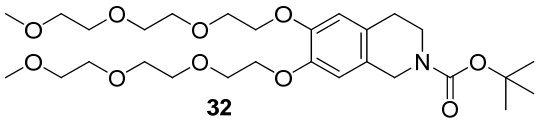
Compound **30** (12.9 mmol), potassium hydroxide (2.4 eq, 31.0 mmol), and **31** (2.4 eq, 31.0 mmol) were dissolved in tetrahydrofurane and refluxed overnight. The solvent was evaporated and the residue was taken up in ethyl acetate, washed with water and brine, and concentrated. Flash column chromatography (EA) of the crude product yielded **32** as yellow oil. Yield: 9.5 mmol (73 %). R_f (EA): 0.26; R_f ($CHCl_3$:MeOH 19:1): 0.33. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.41 (s, 9 H, ^{t}Bu), 2.65 (t, *J* = 5.3 Hz, 2 H, $NCH_2CH_2C_q$), 3.30 (s, 6 H, OCH_3), 3.46-3.49 (m, 4 H, PEG), 3.51-3.56 (m, 2 H, $NCH_2CH_2C_q$), 3.56-3.61 (m, 8 H, PEG), 3.65-3.68 (m, 4 H, PEG), 3.77 (t, *J* = 5.1 Hz, 4 H, PEG), 4.06 (t, *J* = 5.04 Hz, 4 H, PEG), 4.39 (s, 2 H, NCH_2C_q), 6.57 (s, 1 H, $NCH_2C_qCH_{ar}$), 6.60 (s, 1 H, $NCH_2CH_2C_qCH_{ar}$). ^{13}C NMR (101 MHz, $CDCl_3$, δ): 28.42 (CH_2), 28.49 (CH_3 ^{t}Bu), 40.60 (CH_2), 41.90 (CH_2), 44.86 (CH), 45.53 (CH_2), 59.01 (CH_3), 69.02 (CH_2 PEG), 69.08 (CH_2 PEG), 69.61 (CH_2 PEG), 70.53 (CH_2 PEG), 70.67 (CH_2 PEG), 70.78 (CH_2 PEG), 71.92 (CH_2 PEG), 79.72 (C_q tBu), 112.74 (CH_{ar}), 115.07 (CH_{ar}), 126.24 (C_q), 127.55 (C_q), 147.49 (C_q), 147.54 (C_q), 154.89 (*C*=O). FTIR (cm^{-1}): v 2933.7 (m, br), 2877.8 (m, br), 1695.4 (m), 1516.0 (w), 1456.3 (w), 1415.7 (w), 1365.6 (w), 1259.5 (m), 1161.1 (m), 1101.4 (m), 632.7 (s), 536.2 (s), 495.7 (s), 403.1 (s). MS–ESI (*m/z*): $[M + H]^+$ calcd. for $C_{28}H_{47}NO_{10}$ 558.3; found 558.1.

6,7-Bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline 2,2,2-trifluoroacetate 23

Compound **31** (9.0 mmol) was dissolved in DCM and trifluoroacetic acid (10 eq, 90 mmol) and stirred overnight at room temperature. The solvent was evaporated to yield **23** as a gray solid, which was used without further purification. Yield: 9.0 mmol (100 %). ^{1}H NMR (400 MHz, CD_3OD, δ): 3.00 (t, *J* = 6.2 Hz, 2 H, $NCH_2CH_2C_q$), 3.35 (s, 6 H, OCH_3), 3.49 (t, *J* = 6.4 Hz, 2 H, $NCH_2CH_2C_q$), 3.52-3.56 (m, 4 H, PEG), 3.63-3.68 (m, 8 H, PEG), 3.71-3.74 (m, 4 H, PEG), 3.82-3.85 (m, 4 H, PEG), 4.07-4.13 (m, 4 H, PEG), 4.25 (s, 2 H, NCH_2C_q), 6.68 (s, 1 H, $NCH_2C_qCH_{ar}$), 6.73 (s, 1 H, $NCH_2CH_2C_qCH_{ar}$). ^{13}C NMR (101 MHz, CD_3OD, δ): 25.64 (CH_2), 43.05 (CH_2), 45.59 (CH_2), 59.17 (CH_3), 70.23 (CH_2 PEG), 70.34 (CH_2 PEG), 70.92 (CH_2 PEG), 71.37 (CH_2 PEG), 71.67 (CH_2 PEG), 71.76 (CH_2 PEG), 72.96 (CH_2 PEG), 113.86 (CH_{ar}), 115.77 (CH_{ar}), 121.95 (C_q), 125.73 (C_q), 149.28 (C_q), 150.02 (C_q). FTIR (cm^{-1}): v 3063.0 (w, br), 2935.7 (m, br), 2879.7 (m, br), 1776.4 (m), 1612.5 (w), 1525.7 (m), 1458.2 (w), 1352.1 (w), 1263.4 (w), 1215.2 (m), 1168.9 (s), 1118.7 (s), 1051.2 (s), 962.5 (m), 858.3 (m), 790.8 (m), 700.2 (s), 609.5 (w), 586.4 (w), 461.0 (m), 424.3 (m). HRMS–ESI (*m/z*): $[M + H]^+$ calcd. for $C_{23}H_{40}NO_8$ 458.2748; found 458.2757. MP: 46.7 °C (45.4 – 48.0 °C).

1.2 ^{1}H and ^{13}C NMR spectra

***tert*-Butyl 6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate 32**



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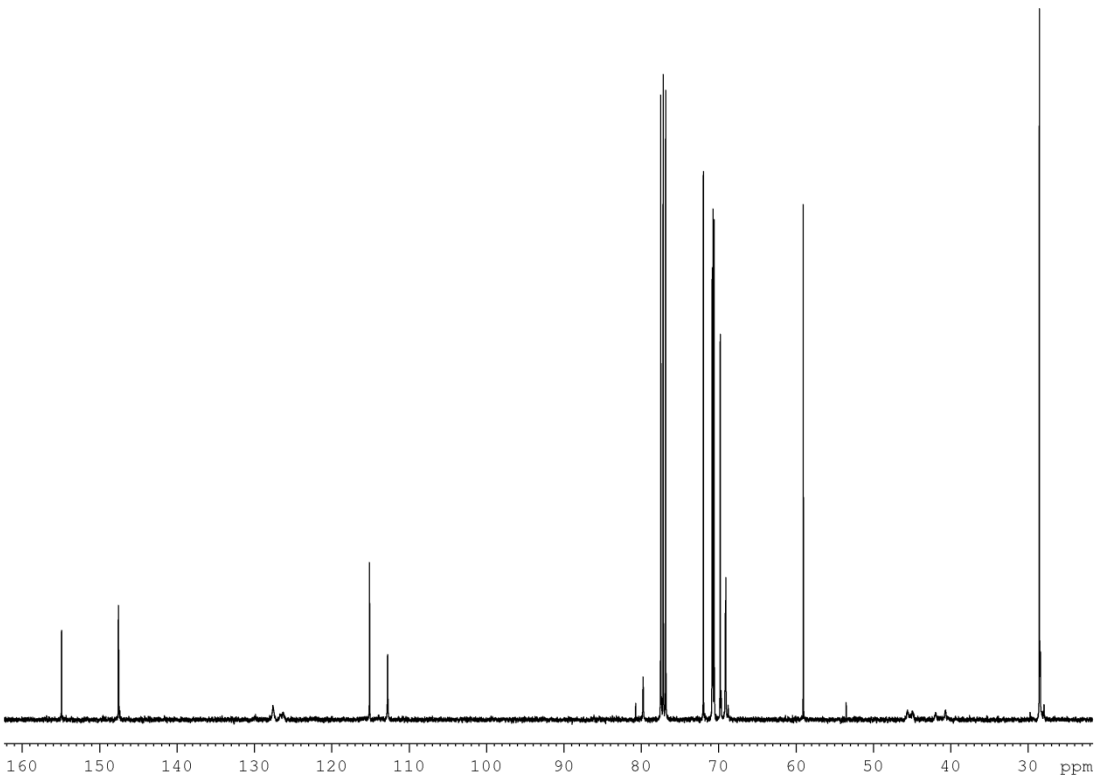
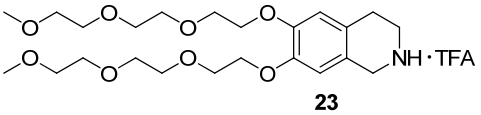


6,7-Bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-1,2,3,4-tetrahydroisoquinoline 2,2,2-trifluoroacetate 23



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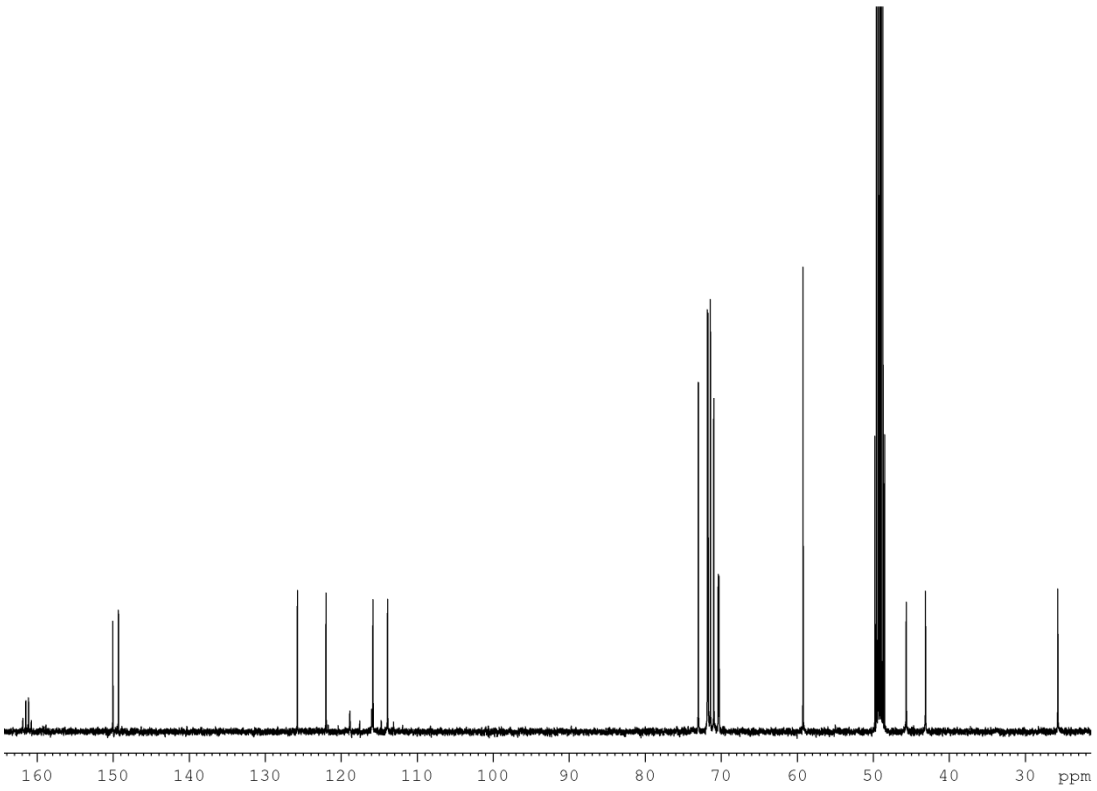


2 Synthesis of compounds 24a-h and 25a-h

2.1 Experimental details and analytical data

2-(4-Amino-3-iodophenyl)ethanol 4
Ethyl 2-(4-amino-3-iodophenyl)acetate **2**[4] (100 mg, 0.32 mmol) was dissolved in anhydrous THF, the solution was cooled in an ice bath and BH_3·THF complex (0.97 mL, 0.97 mmol, 3 equiv) was added dropwise. After the addition, the reaction was stirred at rt during 3 h and quenched with MeOH, diluted with water and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. After evaporating the solvent, the compound was purified by recrystallization from PE:AcOEt 1:1. Yield 77%, white solid, mp. 81.4-82.0 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ= 7.47 (d, ^4J=1.9 Hz, 1H, ArH), 6.98 (dd, ^3J=8.1, ^4J=2.0 Hz, 1H, ArH), 6.73 (d, ^3J=8.1 Hz, 1H, ArH), 3.65 (t, ^3J=7.0 Hz, 2H, CH_2), 2.64 (t, ^3J=7.0 Hz, 2H, CH_2). ^{13}C NMR (CD_3OD, 75 MHz): δ= 147.4 ($C_{quat,}$), 140.1 (+), 131.6 ($C_{quat,}$), 131.0 (+), 116.1 (+), 84.6 ($C_{quat,}$), 64.3 (–), 38.8 (–). HRMS (EI-MS) calcd. for $C_8H_{10}INO$ $[MH]^+$: 262.9807; found: 262.9809. IR (KBr) [cm^{-1}]: v = 3372, 3267, 2947, 2860, 1601, 1495, 665, 584.

4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-iodoaniline 6
Imidazole (140 mg, 2.09 mmol, 1.1 equiv) was added to a mixture of 2-(4-amino-3-iodophenyl)ethanol **4** (500 mg, 1.9 mmol, 1 equiv) and TBDMS -Cl (310 mg, 2.09 mmol, 1.1 equiv) in 10 mL of anhydrous DCM. The reaction was stirred at rt for 4 h, water was added and the organic phase was separated, washed with brine and dried over $MgSO_4$. After evaporating the solvent, the compound was purified by flash chromatography (PE:AcOEt 10:1, R_f = 0.22). Yield 99%, light yellow solid, mp. 81.4-82.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.51 (d, ^4J=1.7 Hz, 1H, ArH), 6.98 (dd, ^3J=8.1, ^4J=1.8 Hz, 1H, ArH), 6.67 (d, ^3J=8.1 Hz, 1H, ArH), 3.98 (s, 2H, NH_2), 3.73 (t, ^3J=6.9 Hz, 2H, CH_2), 2.67 (t, ^3J=6.9 Hz, 2H, CH_2), 0.89 (s, 9H, 3 CH_3), -0.00 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 144.9 ($C_{quat,}$), 139.3 (+), 131.0 ($C_{quat,}$), 130.1 (+), 114.5 (+), 84.1 ($C_{quat,}$), 64.5 (–), 38.0 (–), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). HRMS (EI-MS) calcd. for $C_{14}H_{25}INOSi$ $[M+H]^+$: 378.0745; found: 378.0750. IR (KBr) [cm^{-1}]: v = 3448, 3207, 2951, 2856, 1616, 1498, 665.

General procedure for the preparation of the methanesulfonamides 7 and 8.
Methanesulfonyl chloride (0.36 mmol) was added dropwise to a solution of the aromatic amines **5** or **6**[5] (0.36 mmol) in 5 mL of pyridine at 0 °C. The mixture was stirred at room temperature overnight. Water and AcOEt were added, the organic phase was separated, washed with 1 N HCl, 1 N $NaHCO_3$ and dried over $MgSO_4$. After evaporating the solvent, the compound was recrystallized from PE:DCM 1:1 (compound **8**) or used without any further purification (compound **7**).

N-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-iodophenyl)methanesulfonamide 7
Yield 80%, white solid, mp. 100.3-101.8 °C, ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.81-7.78 (m, 1H, ArH), 7.59 (d, ^3J=8.3 Hz, 1H, ArH), 7.31 (dd, ^3J=8.4, ^4J=1.6 Hz, 1H, ArH), 6.57 (s, 1H, NH), 4.67 (s, 2H, CH_2), 2.99 (s, 3H, CH_3), 0.94 (s, 9H, 3 CH_3), 0.11 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.1 ($C_{quat,}$), 136.8 (+), 136.1 ($C_{quat,}$), 127.5 (+), 122.6 (+), 92.4 ($C_{quat,}$), 63.4 (–), 40.0 (+), 25.9 (+), 18.4 ($C_{quat,}$), -5.2 (+). HRMS (EI-MS) calcd. for $C_{14}H_{24}INO_3SSi$ $[MH]^+$: 441.0291; found: 441.0290. IR (KBr) [cm^{-1}]: v = 3273, 2953, 1327, 1149, 1089, 775.

N-(4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-iodophenyl)methanesulfonamide 8
Yield 83%, viscous orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.75 (d, ^4J=1.8 Hz, 1H, ArH), 7.58 (d, ^3J=8.3 Hz, 1H, ArH), 7.25 (dd, ^3J=8.3, ^4J=1.5 Hz, 1H, ArH), 6.62 (s, 1H, NH), 3.82 (t, ^3J=6.4 Hz, 2H, CH_2), 3.01 (s, 3H, CH_3), 2.78 (t, ^3J=6.4 Hz, 2H, CH_2), 0.89 (s, 9H, 3 CH_3), -0.00 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (+), 139.5 ($C_{quat,}$), 135.6 ($C_{quat,}$), 130.7 (+), 122.8 (+), 92.5 ($C_{quat,}$), 63.7 (–), 39.9 (+), 38.1 (–), 25.8 (+), 18.2 ($C_{quat,}$), -5.4 (+). HRMS (EI-MS) calcd. for $C_{15}H_{27}INO_3SSi$ $[M+H]^+$: 456.0520; found: 456.0513. IR (KBr) [cm^{-1}]: v =2926, 2856, 1332, 1161, 632.

Methyl 2-amino-4-((trimethylsilyl)ethynyl)benzoate 10
A mixture of methyl 2-amino-4-bromobenzoate **9** (100 mg, 0.43 mmol), trimethylsilylacetylene (73 µL, 0.52 mmol, 1.2 equiv.), CuI (8.1 mg, 430 µmol, 10% mol) and $Pd(PPh_3)_2Cl_2$ (15 mg, 21.5 µmol, 5%mol) in 5 mL of THF/TEA 2/1 was stirred and heated at 60 °C for 6 h. Water and DCM were added, the organic layer separated and washed with 1N HCl, 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:1.

Yield 73%, Yellow solid, mp. 69-73.1 °C, R_f = 0.27. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.72 (d, ^3J=8.3 Hz, 1H, ArH), 6.73 (d, ^4J=1.4 Hz, 1H, ArH), 6.67 (dd, ^3J=8.3, ^4J=1.5 Hz, 1H, ArH), 5.68 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 0.20 (s, 9H, 3 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 168.2 (C=O,), 150.1 ($C_{quat,}$), 131.2 (+), 128.6 ($C_{quat,}$), 119.9 (+), 119.7 (+), 110.6 ($C_{quat,}$), 104.5 ($C_{quat,}$), 96.5 ($C_{quat,}$), 51.7 (+), -0.01 (+). MS (CI-MS NH_3): m/z (%)= 247.1 (75) $[MH]^{+\cdot}$. IR (KBr) [cm^{-1}]: v = 3460, 3354, 2949, 2160, 1689, 1244, 837, 758.

Methyl 2-amino-4-ethynylbenzoate 11

A solution of methyl 2-amino-4-((trimethylsilyl)ethynyl)benzoate **10** (77 mg, 0.31 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.31 mL, 0.31 mmol, 1M in THF) was added and the reaction was stirred for 10 min. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:1. Yield 74%, Yellow solid, mp. 75.1-76.8 °C, R_f = 0.22. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.82 (d, ^3J=8.3 Hz, 1H, ArH), 6.81 (d, ^4J=1.5 Hz, 1H, ArH), 6.76 (dd, ^3J=8.2, ^4J=1.5 Hz, 1H, ArH), 5.77 (s, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 168.0 (C=O), 149.9 ($C_{quat,}$), 131.2 (+), 127.5 ($C_{quat,}$), 120.0 (+), 119.7 (+), 110.8 ($C_{quat,}$), 83.0 ($C_{quat,}$), 79.0 (+), 51.6 (+). MS (EI-MS): m/z (%)= 175.1 (100) $[MH]^{+\cdot}$. IR (KBr) [cm^{-1}]: v = 3479, 3375, 3244, 2949, 1689, 1244, 1099, 769.

General procedure for the synthesis of compounds 12 and 13

A mixture of methyl 2-amino-4-ethynylbenzoate **11** (0.57 mmol), Methanesulfonamides **7** or **8** (0.57 mmol), CuI (10.8 mg, 57 µmol, 10% mol) and $Pd(PPh_3)_2Cl_2$ (20 mg, 28.5 µmol, 5%mol) in 5 mL of DMF/TEA 2/1 was stirred and heated at 90 °C for 24 h. Water was added and the compound was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The compound was purified by flash chromatography PE:AcOEt 10:3.

Methyl 2-amino-4-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)benzoate 12

Yield 69%, Yellow solid, mp. 112-114.8 °C, R_f = 0.29. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.03 (d, ^3J=8.6 Hz, 1H, ArH), 7.87 (d, ^3J=8.2 Hz, 1H, ArH), 7.54 (d, ^4J=0.8 Hz, 1H, ArH), 7.31 (dd, ^3J=8.6, ^4J=1.6 Hz, 1H, ArH), 6.87-6.80 (m, 2H, ArH), 6.73 (s, 1H, ArH), 5.49 (bs, 2H, NH_2), 4.83 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.69 (s, 3H, SO_2CH_3), 0.95 (s, 9H, 3 OCH_3), 0.12 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3 (C=O), 149.6 ($C_{quat,}$), 141.5 ($C_{quat,}$), 138.2 ($C_{quat,}$), 137.5 ($C_{quat,}$), 137.4 ($C_{quat,}$), 130.5 (+), 130.3 ($C_{quat,}$), 123.9 (+), 118.6 (+), 118.2 (+), 117.9 (+), 115.7 (+), 113.9 (+), 110.7, 64.8 (–), 51.6 (+), 38.9 (+), 26.0 (+), 18.4 ($C_{quat,}$), -5.1 (+). MS (EI-MS): m/z (%)= 530 (100) $[M+NH_4]^+$, 489 (10) $[MH]^+$. IR (KBr) [cm^{-1}]: v = 3496, 3381, 2953, 2858, 1678 775.

Methyl 2-amino-4-(5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)benzoate 13

Yield 54%, Yellow solid, mp. 132-134 °C, R_f = 0.36. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.01 (d, ^3J=8.5 Hz, 1H, ArH), 7.90 (d, ^3J=8.1 Hz, 1H, ArH), 7.44 (d, ^4J=1.0 Hz, 1H, ArH), 7.26 (dd, ^3J=8.9, ^4J=1.9 Hz, 1H, ArH), 6.91-6.84 (m, 2H, ArH), 6.73 (s, 1H, ArH), 5.83 (bs, 2H, NH_2), 3.91-3.83 (m, 5H, OCH_3, CH_2), 2.94 (t, ^3J=6.9 Hz, 2H, CH_2), 2.70 (s, 3H, SO_2CH_3), 0.89 (s, 9H, 3 CH_3), 0.00 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 168.3 (C=O), 149.7 ($C_{quat,}$), 141.4 ($C_{quat,}$), 137.5 ($C_{quat,}$), 137.0 ($C_{quat,}$), 136.0 ($C_{quat,}$), 130.5 (+), 130.4 ($C_{quat,}$), 126.9 (+), 121.5 (+), 118.1 (+), 117.9 (+), 115.6 (+), 113.8 (+), 110.7 ($C_{quat,}$), 64.6 (–), 51.6 (+), 39.3 (–), 38.7 (+), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). HRMS (EI-MS) calcd. for $C_{25}H_{35}N_2O_5SSi$ $[M+H]^+$: 503.2030; found: 503.2035. IR (KBr) [cm^{-1}]: v = 3495, 3379, 2951, 2854, 1689, 773.

General procedure for the preparation of compounds 14 and 15

To a mixture of **12** or **13** (0.38 mmol) and TEA (1.66 mmol, 3 equiv.) in anhydrous DCM, quinoline-2-carbonyl chloride (0.45 mmol, 1.2 equiv.) was added. The mixture was stirred and heated at 40 °C overnight. 1N HCl was added and the compound was extracted with DCM, washed with 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 10:3.

Methyl 4-(5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 15

Yield 92%, Yellow solid, mp. 81-83 °C, R_f = 0.45. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.39 (s, 1H, NHCO), 9.30 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.33 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz,

1H, ArH), 7.90 (d, ^3J=8.2 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.4 Hz, 1H, ArH), 7.69-7.62 (m, 1H, ArH), 7.46 (d, ^4J=1.1 Hz, 1H, ArH), 7.41 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.27 (dd, ^3J=8.5, ^4J=1.7 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.88 (t, ^3J=6.8 Hz, 2H, CH_2), 2.95 (t, ^3J=6.8 Hz, 2H, CH_2), 2.84 (s, 3H, SO_2CH_3), 0.89 (s, 9H, 3 CH_3), 0.00 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.0 ($C_{quat,}$), 140.4 ($C_{quat,}$), 138.0 ($C_{quat,}$), 137.7 (+), 137.1 ($C_{quat,}$), 136.0 ($C_{quat,}$), 130.4 ($C_{quat,}$), 130.3 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 127.1 (+), 125.3 (+), 121.6 (+), 120.6 (+), 118.8 (+), 116.1 ($C_{quat,}$), 115.5 (+), 114.5 (+), 64.6 (–), 52.5 (+), 39.3 (–), 39.2 (+), 25.9 (+), 18.3 ($C_{quat,}$), -5.3 (+). HRMS (EI-MS) calcd. for $C_{35}H_{40}N_3O_6SSi$ $[M+H]^+$: 658.2402; found: 658.2402. IR (KBr) [cm^{-1}]: v = 2953, 2856, 1685, 771.

Methyl 4-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 14

Yield 76%, Yellow solid, mp. 165-167 °C, R_f = 0.50. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.34 (s, 1H, NHCO), 9.25 (d, ^4J=1.6 Hz, 1H, ArH), 8.34-8.29 (m, 3H, ArH), 8.13 (d, ^3J=8.3 Hz, 1H, ArH), 8.01 (d, ^3J=8.6 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.79 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.65-7.59 (m, 1H, ArH), 7.54 (s, 1H, ArH), 7.37 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.31 (dd, ^3J=8.6, ^4J=1.4 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 4.82 (s, 2H, CH_2), 4.03 (s, 3H, OCH_3), 2.81 (s, 3H, SO_2CH_3), 0.93 (s, 9H, 3 CH_3), 0.09 (s, 6H, 2 CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.1 ($C_{quat,}$), 140.4 ($C_{quat,}$), 138.2 ($C_{quat,}$), 137.9 ($C_{quat,}$), 137.7 (+), 137.5 ($C_{quat,}$), 130.3 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 125.3 (+), 124.0 (+), 120.6 (+), 118.8 (+), 118.7 (+), 116.2 ($C_{quat,}$), 115.6 (+), 114.7 (+), 64.9 (–), 52.5 (+), 39.4 (+), 26.0 (+), 18.4 ($C_{quat,}$), -5.1 (+). HRMS (EI-MS) calcd. for $C_{34}H_{37}N_3NaO_6SSi$ $[M+Na]^+$: 666.2065; found: 666.2066. IR (KBr) [cm^{-1}]: v = 2949, 2852, 1705, 1676, 767.

Synthesis of compounds 16 and 17. General procedure.

A solution of **14** or **15** (0.15 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.15 mmol, 1M in THF) was added and the reaction was stirred for 10 min. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography PE:AcOEt 2:3.

Methyl 4-(5-(2-hydroxyethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)-benzoate 17

Yield 61%, Yellow solid, mp. 198-200 °C, R_f = 0.32. ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.39-8.32 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.03 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.70-7.62 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.29-7.24 (m, 1H, ArH), 6.86 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.93 (t, ^3J=6.5 Hz, 2H, CH_2), 2.99 (t, ^3J=6.5 Hz, 2H, CH_2), 2.89 (s, 3H, SO_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.1 ($C_{quat,}$), 140.3 ($C_{quat,}$), 137.9 ($C_{quat,}$), 137.7 (+), 137.1 ($C_{quat,}$), 135.1 ($C_{quat,}$), 130.6 ($C_{quat,}$), 130.4 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 126.6 (+), 125.3 (+), 121.5 (+), 120.7 (+), 118.8 (+), 116.2 ($C_{quat,}$), 115.8 (+), 114.2 (+), 63.8 (–), 52.5 (+), 39.7 (+), 39.0 (–). HRMS (EI-MS) calcd. for $C_{29}H_{26}N_3O_6S$ $[M+H]^+$: 544.1537; found: 544.1541. IR (KBr) [cm^{-1}]: v = 2937, 2883, 1683, 769.

Methyl 4-(5-(hydroxymethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)-benzoate 16

Yield 73%, Yellow solid, mp. 172.6-174 °C, R_f = 0.25. ^{1}H NMR (DMSO, 300 MHz): δ= 13.12 (s, 1H, NHCO), 9.12 (d, ^4J=1.6 Hz, 1H, ArH), 8.62 (d, ^3J=8.5 Hz, 1H, ArH), 8.25 (d, ^3J=8.5 Hz, 1H, ArH), 8.18 (d, ^3J=8.4 Hz, 1H, ArH), 8.09 (m, 2H, ArH), 7.92 (m, 2H, ArH), 7.75 (td, ^3J=7.1, ^4J=0.8 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.43 (td, ^3J=8.3, ^4J=1.5 Hz, 2H, ArH), 7.05 (s, 1H, ArH), 5.32 (s, 1H, OH), 4.64 (s, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.22 (s, 3H, SO_2CH_3). ^{13}C NMR (75 MHz, DMSO) δ: 166.8 (C=O), 162.7 (C=O), 149.1 ($C_{quat,}$), 145.6 ($C_{quat,}$), 140.0 ($C_{quat,}$), 139.0 ($C_{quat,}$), 138.7 ($C_{quat,}$), 138.3 (+), 137.8 ($C_{quat,}$), 136.6 ($C_{quat,}$), 130.7 (+), 130.3 (+), 129.5 ($C_{quat,}$), 129.2 (+), 128.9 ($C_{quat,}$), 128.5 (+), 128.0 (+), 124.3 (+), 124.1 (+), 120.5 (+), 119.0 (+), 118.4 (+), 115.6 ($C_{quat,}$), 114.7 (+), 113.6 (+), 62.6 (–), 52.6 (+), 40.1 (+). HRMS (EI-MS) calcd. for $C_{28}H_{24}N_3O_6S$ $[M+H]^+$: 530.1380; found: 530.1382. IR (KBr) [cm^{-1}]: v = 3267, 1681, 1249, 765.

Synthesis of compounds 18 and 19. General procedure.
A mixture of **16** or **17** (0.18 mmol) and TEA (0.47 mmol, 2.5 equiv.) in 10 mL of anhydrous DCM was stirred and cooled in an ice bath. Mesyl chloride (0.18 mmol) was added dropwise and the reaction was stirred at rt overnight. Water was added, the organic layer separated and washed with 1N HCl, 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography (diethyl ether:PE 10:1). Compound **18** was used in the next step without any further purification.

Methyl 4-(1-(methylsulfonyl)-5-(2-((methylsulfonyl)oxy)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 19
Yield 81%, Yellow solid, mp. 220-222 °C, R_f = 0.40. ^{1}H NMR ($CDCl_3$, 300 MHz)= δ: 13.39 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.40-8.32 (m, 3H, ArH), 8.18 (d, ^3J=8.3 Hz, 1H, ArH), 8.06 (d, ^3J=8.6 Hz, 1H, ArH), 7.92 (d, ^3J=8.2 Hz, 1H, ArH), 7.84 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.71-7.64 (m, 1H, ArH), 7.49 (d, ^4J=1.2 Hz, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.27 (dd, ^3J=8.6, ^4J=1.7, 1H, ArH), 6.86 (s, 1H, ArH), 4.49 (t, ^3J=6.8 Hz, 2H, CH_2), 4.09 (s, 3H, OCH_3), 3.19 (t, ^3J=6.8 Hz, 2H, CH_2), 2.93 (s, 3H, SO_2CH_3), 2.92 (s, 3H, SO_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 ($C_{quat,}$), 146.6 ($C_{quat,}$), 141.3 ($C_{quat,}$), 140.4 ($C_{quat,}$), 137.7 ($C_{quat,}$), 137.7 (+), 137.3 ($C_{quat,}$), 132.8 ($C_{quat,}$), 130.5 ($C_{quat,}$), 130.5 (+), 130.3 (+), 130.2 (+), 129.4 ($C_{quat,}$), 128.3 (+), 127.6 (+), 126.4 (+), 125.2 (+), 121.6 (+), 120.8 (+), 118.8 (+), 116.3 ($C_{quat,}$), 115.9 (+), 113.8 (+), 70.2 (–), 52.5 (+), 40.0 (+), 37.5 (+), 35.5 (–). HRMS (EI-MS) calcd. for $C_{30}H_{28}N_3O_8S_2$ $[M+H]^+$: 622.1312; found: 622.1315. IR (KBr) [cm^{-1}]: v = 2949, 1683, 769.

General procedure for the synthesis of indole derivatives 24a-h
A mixture **18** or **19** (56 µmol), DIPEA (67µmol, 1.2 equiv.) and the tetrahydroisoquinolines **20-23** in CH_3CN was refluxed overnight. The solvent was evaporated, 1N HCl was added and the compound was extracted with AcOEt. The organic layer was washed with 1N $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography.

Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24e
Yield 62%, yellow solid, mp. 121-123 °C, R_f = 0.21 (DCM/MeOH 100/3). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.38 (s, 1H, NHCO), 9.29 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.34 (m, 3H, ArH), 8.17 (d, ^3J=8.2 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=7.7 Hz, 1H, ArH), 7.85-7.82 (m, 1H, ArH), 7.67-7.65 (m, 1H, ArH), 7.49 (d, ^4J=0.9 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.30 (dd, ^3J=8.5, ^4J=1.6 Hz, 1H, ArH), 7.16-7.10 (m, 3H, ArH), 7.07-7.04 (m, 1H, ArH), 6.87 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.77 (s, 2H, CH_2), 3.05 (dd, ^3J=9.5, ^3J=6.6 Hz, 2H, CH_2), 2.96 (t, ^3J=5.8 Hz, 2H, CH_2), 2.88 (s, 3H, SO_2CH_3), 2.86-284 (m, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.9 (C_q), 146.6 (C_q), 140.9 (C_q), 140.3 (C_q), 137.9 (C_q), 137.6 (+), 137.0 (C_q), 136.9 (C_q), 134.2 (C_q), 130.5 (+), 130.3 (+), 130.3 (+), 130.2 (C_q), 129.3 (C_q), 128.6 (+), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 126.1 (+), 125.6 (+), 125.3 (+), 121.0 (+), 120.6 (C_q), 118.7 (+), 116.1 (C_q), 115.6 (+), 114.3 (+), 77.2 (–), 77.0 (–), 76.7 (–), 60.4 (–), 56.1 (–), 52.4 (+), 50.9 (–), 39.5 (+), 33.7 (–), 29.0 (–). HRMS (EI-MS) calcd. for $C_{38}H_{35}N_4O_5S$ $[M+H]^+$: 659.2323; found: 659.2329. IR (KBr) [cm^{-1}]: v = 2931, 1685, 1519, 773. HPLC: t_R 14.89 min, purity 94%.

Methyl 4-(5-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24a
Yield 79%, yellow solid, mp. 135-137 °C, R_f = 0.23 (DCM/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.37 (s, 1H, NHCO), 9.29 (d, ^4J=1.6 Hz, 1H, ArH), 8.37-8.34 (m, 3H, ArH), 8.18 (d, ^3J=8.2 Hz, 1H, ArH), 8.06 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.83 (ddd, ^3J=8.3, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.68-7.64 (m, 2H, ArH), 7.47 (dd, ^3J=8.6, ^4J=1.6 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.15-7.09 (m, 3H, ArH), 7.00 (d, ^3J=6.9 Hz, 1H, ArH), 6.88 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.82 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 2.96-2.92 (m, 5H, SO_2CH_3, CH_2), 2.81 (t, ^3J = 5.9 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.7 (C=O), 149.8 (C_q), 146.5 (C_q), 140.9 (C_q), 140.3 (C_q), 137.9 (C_q), 137.6 (+), 137.5 (C_q), 134.8 (C_q), 134.6 (C_q), 134.2 (C_q), 130.3 (+), 130.2 (+), 130.2 (C_q), 130.2 (+), 129.3 (C_q), 128.6 (+), 128.2 (+), 127.6 (+), 126.7 (+), 126.5 (+), 126.1 (+), 125.5 (+), 125.2 (+), 121.6 (+), 120.7 (+), 118.7 (+), 116.1 (C_q), 115.4 (+), 114.1 (+), 62.4 (–), 56.0 (–), 52.4 (+), 50.6 (–), 39.8 (+), 29.0 (–). HRMS (EI-MS) calcd. for $C_{37}H_{33}N_4O_5S$ $[M+H]^+$: 645.2166; found: 645.2161. IR (KBr) [cm^{-1}]: v = 1683, 1504, 775. HPLC: t_R 27.60 min, purity 95%.

Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24f

Yield 86%, yellow solid, mp. 124-126 °C, R_f = 0.24 (DCM/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.5 Hz, 1H, ArH), 8.40-8.31 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.02 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.86-7.80 (m, 1H, ArH), 7.68-7.63 (m, 1H, ArH), 7.48 (s, 1H, ArH), 7.40 (dd, ^3J=8.3, ^4J=1.6 Hz, 1H, ArH), 7.29 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.56 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2), 3.04 (dd, ^3J=9.7, ^3J=6.0 Hz, 2H, CH_2), 2.88-2.82 (m, 9H, SO_2CH_3, 6 CH_2).^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (C_q), 147.5 (C_q), 147.2 (C_q), 146.6 (C_q), 141.0 (C_q), 140.4 (C_q), 137.9 (C_q), 137.7 (C_q), 137.0 (+), 136.9 (C_q), 130.5 (C_q), 130.4 (+), 130.3 (+), 130.2 (+), 129.4 (C_q), 128.3 (+), 127.6 (+), 126.6 (+), 126.3 (C_q), 126.1 (C_q), 125.3 (+), 121.1 (+), 120.6 (+), 118.8 (+), 116.2 (C_q), 115.7 (+), 114.3 (+), 111.3 (+), 109.4 (+), 60.3 (–)55.9 (+), 55.9 (+), 55.7 (–), 52.5 (+), 51.0 (–), 39.6 (+), 33.8 (–), 28.6 (–). HRMS (EI-MS) calcd. for $C_{40}H_{39}N_4O_7S$ $[M+H]^+$: 719.2534; found: 719.2532. IR (KBr) [cm^{-1}]: v = 2931, 1683, 1518, 773. HPLC: t_R 14.56 min, purity 98%.

Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24b

Yield 52%, light yellow solid, mp. 140-142 °C, R_f = 0.29 ($CHCl_3$/MeOH 100/3). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.38 (s, 1H, NHCO), 9.28 (d, ^4J=1.5 Hz, 1H, ArH), 8.39-8.32 (m, 3H, ArH), 8.18 (d, ^3J=8.2 Hz, 1H, ArH), 8.06 (d, ^3J=8.5 Hz, 1H, ArH), 7.91 (d, ^3J=7.9 Hz, 1H, ArH), 7.86-7.81 (m, 1H, ArH), 7.69-7.64 (m, 2H, ArH), 7.46 (dd, ^3J=8.5, ^4J=1.1 Hz, 1H, ArH), 7.40 (dd, ^3J=8.2, ^4J=1.6 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.61 (s, 1H, ArH), 6.50 (s, 1H, ArH), 4.08 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83-3.80 (m, 5H, OCH_3, CH_2), 3.61 (s, 2H, CH_2), 2.94 (s, 3H, SO_2CH_3), 2.88-2.84 (m, 2H, CH_2), 2.83-2.79 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (C_q), 147.5 (C_q), 147.2 (C_q), 146.6 (C_q), 140.9 (C_q), 140.3 (C_q), 137.9 (C_q), 137.6 (+), 137.5 (C_q), 130.4 (+), 130.3 (+), 130.2 (C_q), 130.2 (+), 129.3 (C_q), 128.3 (+), 127.6 (+), 126.8 (+), 126.0 (C_q), 125.2 (+), 121.7 (+), 120.7 (+), 118.7 (+), 116.2 (C_q), 115.5 (+), 114.1 (+), 111.4 (+), 109.4 (+), 62.4 (–), 55.8 (+), 52.4 (+), 50.7 (–), 39.9 (+), 29.6 (–), 28.5 (–). HRMS (EI-MS) calcd. for $C_{39}H_{37}N_4O_7S$ $[M+H]^+$: 705.2377; found: 705.2376. IR (KBr) [cm^{-1}]: v = 1687, 1518, 769. HPLC: t_R 14.60 min, purity 99%.

Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24g

Yield 82%, yellow solid, mp. 93-96 °C, R_f = 0.22 (DCM/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.36 (s, 1H, NHCO), 9.27 (d, ^4J=1.6 Hz, 1H, ArH), 8.35-8.33 (m, 3H, ArH), 8.16 (d, ^3J=8.2 Hz, 1H, ArH), 8.01 (d, ^3J=8.5 Hz, 1H, ArH), 7.90 (d, ^3J=7.4 Hz, 1H, ArH), 7.83-7.81 (m, 1H, ArH), 7.67-7.64 (m, 1H, ArH), 7.48 (d, ^4J=0.6 Hz, 1H, ArH), 7.39 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 7.29 (dd, ^3J = 8.6, ^4J=1.6 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 6.61 (s, 2H, ArH), 4.13 (t, ^3J=5.0 Hz, 2H, CH_2), 4.07 (s, 3H, OCH_3), 3.85 (t, ^3J=5.3 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.73 (m, 2H, CH_2), 3.69-3.63 (m, 6H, 3 CH_2), 3.55-3.53 (m, 2H, CH_2), 3.37 (s, 3H, OCH_3), 3.06-3.03 (m, 2H, CH_2), 2.89-2.84 (m, 9H, SO_2CH_3, 3 CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.8 (C_q), 148.2 (C_q), 146.5 (C_q), 146.4 (C_q), 140.9 (C_q), 140.3 (C_q), 137.9 (C_q), 137.6 (+), 136.9 (C_q), 136.7 (C_q), 130.4 (+), 130.3 (+), 130.2 (+), 130.2 (C_q), 129.3 (C_q), 128.2 (+), 127.6 (+), 126.7 (C_q), 126.5 (+), 125.2 (+), 121.0 (+), 120.6 (+), 118.7 (+), 116.1 (C_q), 115.6 (+), 114.2 (+), 112.2 (+), 111.9 (+), 71.8 (–), 70.7 (–), 70.5 (–), 70.4 (–), 69.6 (–), 68.6 (–), 60.1 (–), 58.9 (+), 55.9 (+), 55.4 (–), 52.4 (+), 50.8 (–), 39.5 (+), 33.5 (–), 28.4 (–). HRMS (EI-MS) calcd. for $C_{46}H_{51}N_4O_{10}S$ $[M+H]^+$: 851.3320; found: 851.3326. IR (KBr) [cm^{-1}]: v = 2922, 1685, 1518, 771. HPLC: t_R 24.22 min, purity 95%.

Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24c

Yield 63%, yellow solid, mp. 115-117 °C, R_f = 0.16 (DCM/MeOH 100/3). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.35 (s, 1H, NHCO), 9.28 (d, ^4J=1.7 Hz, 1H, ArH), 8.36-8.31 (m, 3H, ArH), 8.16 (d, ^3J=8.2 Hz, 1H, ArH), 8.05 (d, ^3J=8.6 Hz, 1H, ArH), 7.88 (d, ^3J=8.2 Hz, 1H, ArH), 7.81 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.66-7.62 (m, 2H, ArH), 7.44 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 7.39 (dd, ^3J=8.2, ^4J=1.7 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 6.60 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.10 (t, ^3J=5.4 Hz, 2H, CH_2), 4.06 (s, 3H, OCH_3), 3.83 (t, ^3J=5.1 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2), 3.71 (dd, ^3J=5.9, ^3J=3.7 Hz, 2H, CH_2), 3.66-3.61 (m, 4H, 2 CH_2), 3.57 (s, 2H, CH_2), 3.54-3.51 (m, 2H, CH_2), 3.35 (s, 3H, OCH_3), 2.93 (s, 3H, SO_2CH_3), 2.83 (t, ^3J=5.6 Hz, 2H, CH_2), 2.76 (t, ^3J=5.7 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.6 (C=O), 149.8 (C_q), 148.1 (C_q), 146.5 (C_q), 146.3 (C_q), 140.8 (C_q), 140.2 (C_q), 137.8 (C_q), 137.5 (+), 137.4 (C_q), 134.8 (C_q), 130.3 (+), 130.2 (+), 130.1 (C_q), 130.1

(+), 129.2 (C_q), 128.2 (+), 127.5 (+), 126.8 (C_q), 126.7 (+), 126.5 (C_q), 125.1 (+), 121.5 (+), 120.6 (+), 118.6 (+), 116.1 (C_q), 115.3 (+), 114.1 (+), 112.2 (+), 111.9 (+), 71.8 (–), 70.6 (–), 70.5 (–), 70.4 (–), 69.5 (–), 68.6 (–), 62.4 (–), 58.9 (+), 55.9 (+), 55.5 (–), 52.4 (+), 50.6 (–), 39.7 (+), 28.6 (–). HRMS (EI-MS) calcd. for $C_{45}H_{49}N_4O_{10}S$ $[M+H]^+$: 837.3164; found: 837.3174. IR (KBr) [cm^{-1}]: ν = 2931, 1681, 1518, 767. HPLC: t_R 23.82 min, purity 99%.

Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24h

Yield 38%, sticky yellow solid, R_f = 0.27 (DCM/MeOH 100/5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.35 (s, 1H, NHCO), 9.26 (d, ^4J=1.6 Hz, 1H, ArH), 8.35-8.29 (m, 3H, ArH), 8.14 (d, ^3J=8.3 Hz, 1H, ArH), 8.00 (d, ^3J=8.6 Hz, 1H, ArH), 7.88 (d, ^3J=8.2 Hz, 1H, ArH), 7.80 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.67-7.59 (m, 1H, ArH), 7.46 (s, 1H, ArH), 7.37 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.30-7.25 (m, 1H, ArH), 6.85 (s, 1H, ArH), 6.65 (s, 1H, ArH), 6.60 (s, 1H, ArH), 4.11 (t, ^3J=5.0 Hz, 4H, 2 CH_2), 4.05 (s, 3H, OCH_3), 3.82 (t, ^3J=5.1 Hz, 4H, 2 CH_2), 3.75-3.70 (m, 4H, 2 CH_2), 3.66-3.62 (m, 10H, 5 CH_2), 3.53 (dd, ^3J=5.9, ^3J=3.3 Hz, 4H, 2 CH_2), 3.36 (s, 6H, 2 OCH_3), 3.03-2.98 (m, 2H, CH_2), 2.86 (s, 3H, SO_2CH_3), 2.88-2.75 (m, 6H, 3 CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.7 (C=O), 149.9 (C_q), 147.5 (C_q), 147.1 (C_q), 146.6 (C_q), 141.0 (C_q), 140.3 (C_q), 137.9 (C_q), 137.7 (+), 137.0 (C_q), 136.9 (C_q), 130.5 (C_q), 130.4 (+), 130.3 (+), 130.2 (+), 129.3 (C_q), 128.3 (+), 127.6 (+), 127.5 (+), 127.2 (C_q), 126.5 (+), 125.2 (+), 121.1 (+), 120.6 (+), 118.8 (+), 116.1 (C_q), 115.6 (+), 115.0 (+), 114.3 (+), 113.3 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.1 (–), 69.0 (–), 60.4 (–), 59.0 (+), 55.7 (–), 52.5 (+), 51.0 (–), 39.5 (+), 33.8 (–), 28.6 (–). HRMS (EI-MS) calcd. for $C_{52}H_{63}N_4O_{13}S$ $[M+H]^+$: 983.4107; found: 983.4109. IR (KBr) [cm^{-1}]: ν = 2926, 2879, 1683, 1518. HPLC: t_R 24.13 min, purity 95%.

Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24d

Yield 80%, sticky yellow solid, R_f = 0.27 ($CHCl_3$/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.37 (s, 1H, NHCO), 9.28 (d, ^4J=1.6 Hz, 1H, ArH), 8.38-8.32 (m, 3H, ArH), 8.17 (d, ^3J=8.3 Hz, 1H, ArH), 8.05 (d, ^3J=8.6 Hz, 1H, ArH), 7.90 (d, ^3J=8.2 Hz, 1H, ArH), 7.82 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.67-7.62 (m, 2H, ArH), 7.44 (dd, ^3J=8.6, ^4J=1.5 Hz, 1H, ArH), 7.39 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 6.87 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.15-4.05 (m, 7H, OCH_3, 2 CH_2), 3.86-3.76 (m, 6H, 3 CH_2), 3.75-3.69 (m, 4H, 2 CH_2), 3.68-3.61 (m, 8H, 4 CH_2), 3.56-3.51 (m, 6H, 3 CH_2), 3.36 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.93 (s, 3H, SO_2CH_3), 2.81-2.75 (m, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (C_q), 147.5 (C_q), 147.1 (C_q), 146.6 (C_q), 140.9 (C_q), 140.3 (C_q), 138.0 (C_q), 137.7 (+), 137.5 (C_q), 135.0 (C_q), 130.4 (+), 130.3 (+), 130.3 (C_q), 130.2 (+), 129.4 (C_q), 128.3 (+), 127.6 (+), 127.2 (C_q), 126.8 (+), 125.2 (+), 121.6 (+), 120.7 (+), 118.8 (+), 116.2 (C_q), 115.5 (+), 115.1 (+), 114.2 (+), 113.2 (+), 71.9 (-), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.7 (–), 69.0 (–), 69.0 (–), 62.6 (–), 59.0 (+), 55.7 (–), 52.5 (+), 50.7 (–), 39.8 (+), 28.6 (–). HRMS (EI-MS) calcd. for $C_{51}H_{61}N_4O_{13}S$ $[M+H]^+$: 969.395; found: 969.3954. IR (KBr) [cm^{-1}]: ν = 2877, 1685, 1518, 769. HPLC: t_R 23.74 min, purity 95%.

General procedure for the synthesis of indole derivatives 25a-h.

A solution of **24** (0.15 mmol) in 5 mL THF was stirred and cooled in an ice bath. TBAF (0.15 mmol, 1M in THF) was added and the reaction was stirred for 72 h at room temperature. The solvent was evaporated, saturated NH_4Cl solution was added and the compound was extracted with DCM. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the compound was purified by flash chromatography.

Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25e

Yield 57%, yellow solid, mp. 116-118 °C R_f = 0.29 (DCM/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 5% CD_3OD, 300 MHz): δ= 13.39 (s, 1H, NHCO), 9.99 (s, 1H, NH), 9.19 (d, ^4J=1.5 Hz, 1H, ArH), 8.36-8.29 (m, 3H, ArH), 8.10 (d, ^3J=8.4 Hz, 1H, ArH), 7.89 (d, ^3J=8.2 Hz, 1H, ArH), 7.81 (ddd, ^3J=8.4, ^3J=7.0, ^4J=1.3 Hz, 1H, ArH), 7.67-7.61 (m, 1H, ArH), 7.51 (dd, ^3J=8.4, ^4J=1.7 Hz, 1H, ArH), 7.46 (s, 1H, ArH), 7.42-7.31 (m, 2H, ArH), 7.13-7.02 (m, 4H, ArH), 6.92 (s, 1H, ArH), 4.05 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2), 3.06-2.93 (m, 4H, 2 CH_2), 2.91-2.76 (m, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$, 5% CD_3OD, 75 MHz) δ: 167.7 (C=O), 163.9 (C=O), 149.9 (C_q), 146.6 (C_q), 141.4 (C_q), 137.8 (C_q), 137.7 (+), 136.6 (C_q), 136.1 (C_q), 134.2 (C_q), 132.2 (C_q), 131.9 (+), 130.2 (+), 129.4 (C_q), 128.6 (+), 128.3 (+), 128.0 (C_q), 127.6 (+), 127.2 (C_q), 126.6 (+), 126.1 (+), 125.6 (+), 124.5 (+), 120.5 (+), 119.6 (+), 118.8 (+), 115.6 (+), 114.8 (C_q), 111.2 (+), 101.9 (+), 56.1 (–), 52.4 (+), 51.0 (–), 40.3 (–), 34.0 (–), 28.3 (–). HRMS (EI-MS) calcd. for

$C_{37}H_{33}N_4O_3$ $[M+H]^+$: 581.2547; found: 581.2545. IR (KBr) [cm^{-1}]: v = 1681, 1519, 771, 740. HPLC: t_R 14.60 min, purity 85%.

Methyl 4-(5-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonyl-amino)benzoate 25a

Yield 34%, yellow solid, mp. 204-206 °C R_f = 0.20 ($CHCl_3$/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.40 (s, 1H, NHCO), 9.36 (d, ^4J=1.6 Hz, 1H, ArH), 8.95 (s, 1H, NH), 8.39-8.30 (m, 3H, ArH), 8.13 (d, ^3J=8.3 Hz, 1H, ArH), 7.91 (d, ^3J=8.1 Hz, 1H, ArH), 7.82 (ddd, ^3J=8.4, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.70-7.64 (m, 1H, ArH), 7.63 (s, 1H, ArH), 7.48 (dd, ^3J=8.4, ^4J=1.7 Hz, 1H, ArH), 7.39 (d, ^3J=8.3 Hz, 1H, ArH), 7.29 (dd, ^3J=8.3, ^4J=1.3 Hz, 1H, ArH), 7.10-7.07 (m, 3H, ArH), 7.02-6.94 (m, 2H, ArH), 4.07 (s, 3H, OCH_3), 3.79 (s, 2H, CH_2), 3.69 (s, 2H, CH_2), 2.92 (t, ^3J=5.5 Hz, 2H, CH_2), 2.80 (t, ^3J=5.7 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7 (C=O), 163.9 (C=O), 146.6 (C_q), 137.7 (+), 136.8 (C_q), 136.6 (C_q), 134.9 (C_q), 134.4 (C_q), 131.9 (+), 131.6 (C_q), 130.2 (+), 129.4 (C_q), 129.3 (C_q), 128.9 (C_q), 128.7 (+), 128.3 (+), 127.6 (+), 126.6 (+), 126.0 (+), 125.5 (+), 125.0 (+), 121.5 (+), 119.7 (+), 118.8 (+), 115.7 (+), 114.9 (+), 111.1 (+), 102.1 (+), 63.2 (–), 56.0 (–), 52.4 (+), 50.5 (–), 29.1 (–). HRMS (EI-MS) calcd. for $C_{36}H_{31}N_4O_3$ $[M+H]^+$: 567.2391; found: 567.240. IR (KBr) [cm^{-1}]: v = 3408, 1683, 1514, 773. HPLC: t_R 25.47 min, purity 95%.

Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)-1H-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25f

Yield 70%, yellow solid, mp. 118-120 °C R_f = 0.24 (DCM/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 5% CD_3OD, 300 MHz): δ= 13.35 (s, 1H, NHCO), 10.18 (s, 1H, NH), 9.14 (d, ^4J=1.4 Hz, 1H, ArH), 8.30-8.27 (m, 3H, ArH), 8.06 (d, ^3J=8.4 Hz, 1H, ArH), 7.85 (d, ^3J=8.1 Hz, 1H, ArH), 7.81-7.75 (m, 1H, ArH), 7.61 (t, ^3J=7.5 Hz, 1H, ArH), 7.51-7.43 (m, 2H, ArH), 7.36 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.3, ^4J=1.2 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.59 (s, 1H, ArH), 6.54 (s, 1H, ArH), 4.02 (s, 3H, OCH_3), 3.82 (s, 6H, 2 OCH_3), 3.70 (s, 2H, CH_2), 3.00 (dd, ^3J=10.6, ^3J=5.4 Hz, 2H, CH_2), 2.85-2.80 (m, 6H, 3 CH_2). ^{13}C NMR ($CDCl_3$, 5% CD_3OD, 75 MHz) δ 167.6 (C=O), 163.7 (C=O), 149.6 (C_q), 147.5 (C_q), 147.2 (C_q), 146.5 (C_q), 140.8 (C_q), 138.1 (C_q), 137.6 (+), 136.6 (C_q), 136.3 (C_q), 131.8 (+), 131.5 (C_q), 130.2 (+), 130.2 (+), 129.3 (C_q), 129.1 (C_q), 128.3 (+), 127.6 (+), 126.1 (C_q), 125.9 (C_q), 124.2 (+), 120.3 (+), 120.0 (+), 118.7 (+), 115.5 (+), 114.7 (C_q), 111.3 (+), 111.3 (+), 109.4 (+), 101.4 (+), 60.8 (–), 55.9 (+), 55.8 (+), 55.5 (–), 52.4 (+), 50.9 (–), 33.8 (–), 28.3 (–). HRMS (EI-MS) calcd. for $C_{39}H_{37}N_4O_5$ $[M+H]^+$: 641.2758; found: 641.2763. IR (KBr) [cm^{-1}]: v = 3520, 1668, 1518, 775. HPLC: t_R 14.99 min, purity 98%.

Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25b

Yield 75%, yellow solid, mp. 168-170 °C R_f = 0.23 ($CHCl_3$/MeOH 100/5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.31 (s, 1H, NHCO), 9.31 (d, ^4J=1.6 Hz, 1H, ArH), 9.13 (s, 1H, NH), 8.30-8.25 (m, 3H, ArH), 8.04 (d, ^3J=8.4 Hz, 1H, ArH), 7.84 (d, ^3J=8.1 Hz, 1H, ArH), 7.80-7.73 (m, 1H, ArH), 7.64-7.57 (m, 2H, ArH), 7.39 (dd, ^3J=8.4, ^4J=1.6 Hz, 1H, ArH), 7.32 (d, ^3J=8.3 Hz, 1H, ArH), 7.25 (dd, ^3J=8.4, ^4J=1.2 Hz, 1H, ArH), 6.92 (d, ^4J=1.5 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 6.47 (s, 1H, ArH), 4.03 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2), 3.57 (s, 2H, CH_2), 2.81 (m, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.6 (C=O), 163.8 (C=O), 149.8 (C_q), 147.4 (C_q), 147.1 (C_q), 146.5 (C_q), 141.3 (C_q), 137.7 (C_q), 137.6 (+), 136.8 (C_q), 136.7 (C_q), 131.8 (+), 130.2 (+), 130.1 (+), 130.0 (C_q), 129.3 (C_q), 128.9 (C_q), 128.2 (+), 127.6 (+), 126.8 (C_q), 126.3 (C_q), 124.9 (+), 121.5 (+), 119.6 (+), 118.7 (+), 115.7 (+), 114.8 (C_q), 111.4 (+), 111.2 (+), 109.5 (+), 102.0 (+), 63.2 (–), 55.9 (+), 55.8 (+), 55.6 (–), 52.4 (+), 50.7 (–), 28.7 (–). HRMS (EI-MS) calcd. for $C_{38}H_{35}N_4O_5$ $[M+H]^+$: 627.2602; found: 627.2608. IR (KBr) [cm^{-1}]: v = 3408, 1683, 1516, 771. HPLC: t_R 14.64 min, purity 97%.

Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25g

Yield 65%, yellow solid, mp. 128-130 °C R_f = 0.20 (DCM/MeOH 100/5). ^{1}H NMR ($CDCl_3$, 5% CD_3OD, 300 MHz): δ= 13.35 (s, 1H, NHCO), 9.96 (s, 1H, NH), 9.18 (d, ^4J=1.2 Hz, 1H, ArH), 8.30-8.27 (m, 3H, ArH), 8.06 (d, ^3J=8.4 Hz, 1H, ArH), 7.86 (d, ^3J=8.2 Hz, 1H, ArH), 7.82-7.75 (m, 1H, ArH), 7.62 (t, ^3J=7.5 Hz, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 7.35 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.3, ^4J=1.2 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.59 (s, 2H, ArH), 4.12 (t, ^3J=5.2 Hz, 2H, CH_2), 4.03 (s, 3H, OCH_3), 3.85 (t, ^3J=5.1 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.74-3.70 (m, 2H, CH_2), 3.67-3.62 (m, 6H, 3 CH_2), 3.54 (dd, ^3J=5.8, ^3J=3.3 Hz, 2H, CH_2), 3.36 (s, 3H, OCH_3), 2.99 (dd, ^3J=10.5, ^3J=5.4 Hz, 2H, CH_2), 2.82 (dd, ^3J=9.9, ^3J=6.0 Hz, 6H, 3 CH_2). ^{13}C NMR ($CDCl_3$, 5% CD_3OD, 75 MHz,) δ: 167.7 (C=O), 163.8 (C=O), 149.7 (C_q), 148.1 (C_q), 146.5 (C_q), 146.4 (C_q), 141.0 (C_q), 138.1 (C_q), 137.6 (+), 136.7 (C_q), 136.4 (C_q), 131.8 (+), 131.7 (C_q), 130.2 (+), 129.3 (C_q), 129.1 (C_q), 128.3 (+), 127.6 (+), 126.8 (C_q), 126.4 (C_q),

124.2 (+), 120.3 (+), 119.9 (+), 118.7 (+), 115.6 (+), 114.7 (C_q), 112.2 (+), 111.9 (+), 111.4 (+), 101.5 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.6 (–), 68.6 (–), 60.9 (–), 59.0 (+), 55.9 (+), 55.6 (–), 52.4 (+), 51.0 (–), 33.9 (–), 28.5 (–). HRMS (EI-MS) calcd. for $C_{45}H_{49}N_4O_8$ $[M+H]^+$: 773.3545; found: 773.3544. IR (KBr) [cm^{-1}]: v = 3533, 2916, 2833, 1681, 1516, 771. HPLC: t_R 14.87 min, purity 90%.

Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25c

Yield 18%, light yellow solid, mp. 110-112 °C R_f = 0.15 ($CHCl_3$/MeOH 100/4). ^{1}H NMR ($CDCl_3$, 600 MHz): δ= 13.34 (s, 1H, NHCO), 9.32 (d, ^4J=1.7 Hz, 1H, ArH), 9.18 (s, 1H, NH), 8.31-8.29 (m, 3H, ArH), 8.08 (d, ^3J=8.3 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.79 (ddd, ^3J=8.3, ^3J=6.9, ^4J=1.3 Hz, 1H, ArH), 7.65-7.61 (m, 1H, ArH), 7.59 (s, 1H, ArH), 7.44 (dd, ^3J=8.3, ^4J=1.7 Hz, 1H, ArH), 7.36 (d, ^3J=8.3 Hz, 1H, ArH), 7.27-7.25 (m, 1H, ArH), 6.95 (d, ^4J=1.5 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 6.52 (s, 1H, ArH), 4.07 (t, ^3J=5.4 Hz, 2H, CH_2), 4.05 (s, 3H, OCH_3), 3.81 (t, ^3J=5.1 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2), 3.70 (dd, ^3J=5.9, ^3J=3.7 Hz, 2H, CH_2), 3.65-3.61 (m, 4H, 2 CH_2), 3.56 (s, 2H, CH_2), 3.53-3.50 (m, 2H, CH_2), 3.35 (s, 3H, OCH_3), 2.82 (t, ^3J=5.5 Hz, 2H, CH_2), 2.76 (t, ^3J=5.6 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 151 MHz) δ: 167.6 (C=O), 163.7 (C=O), 149.8 (C_q), 148.0 (C_q), 146.5 (C_q), 146.3 (C_q), 141.2 (C_q), 137.7 (C_q), 137.6 (+), 136.8 (C_q), 136.6 (C_q), 131.8 (+), 130.1 (+), 130.1 (+), 129.9 (C_q), 129.3 (C_q), 128.8 (C_q), 128.2 (+), 127.5 (+), 127.0 (C_q), 126.8 (C_q), 124.8 (+), 121.4 (+), 119.5 (+), 118.7 (+), 115.7 (+), 114.7 (C_q), 112.2 (+), 111.9 (+), 111.1 (+), 101.9 (+), 71.8 (–), 70.7 (–), 70.5 (–), 70.4 (–), 69.5 (–), 68.5 (–), 63.1 (–), 58.9 (+), 55.9 (+), 55.5 (–), 52.3 (+), 50.5 (–), 28.6 (–). HRMS (EI-MS) calcd. for $C_{44}H_{47}N_4O_8$ $[M+H]^+$: 759.3394; found: 759.3408. IR (KBr) [cm^{-1}]: v = 2900, 2875, 1681, 1516, 771. HPLC: t_R 14.63 min, purity 98%.

Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25h

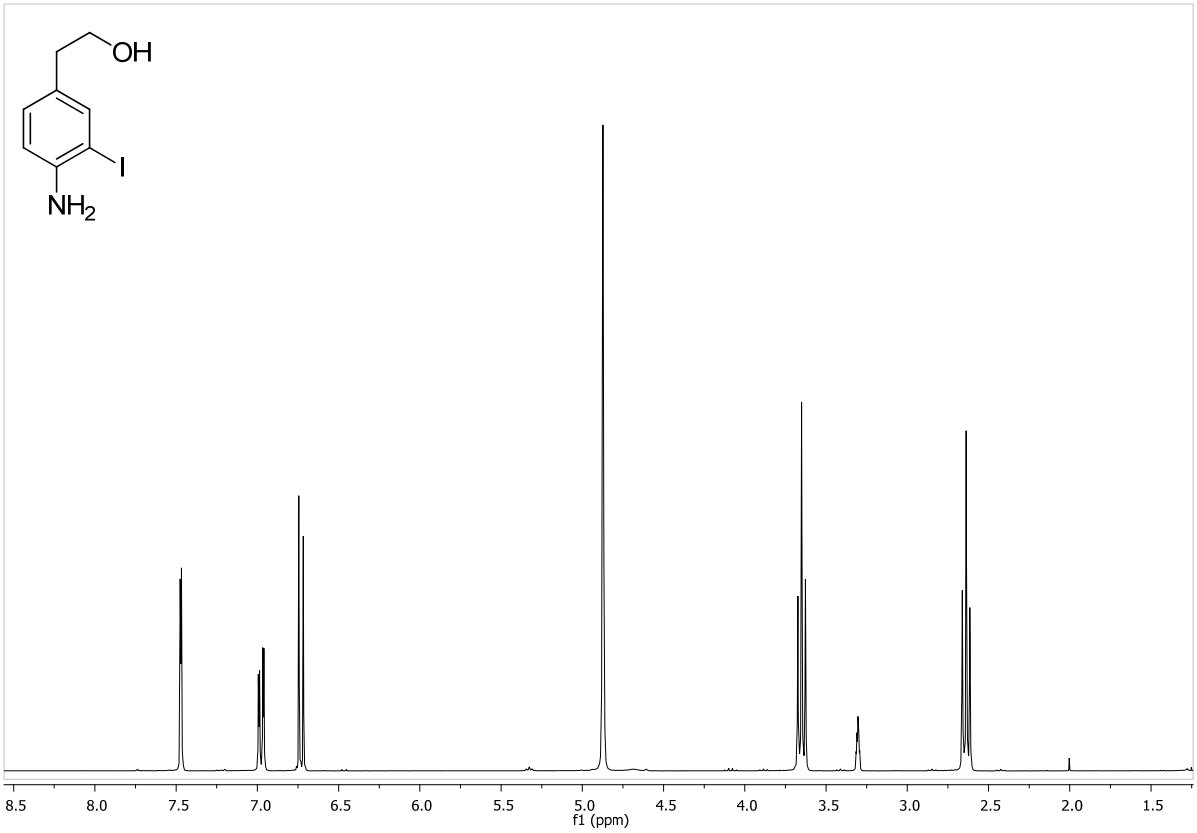
Yield 53%, sticky light yellow oil, R_f = 0.23 (DCM/MeOH 100/5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.33 (s, 1H, NHCO), 9.31 (d, ^4J=1.5 Hz, 1H, ArH), 9.25 (s, 1H, NH), 8.33-8.26 (m, 3H, ArH), 8.07 (d, ^3J=8.4 Hz, 1H, ArH), 7.87 (d, ^3J=8.1 Hz, 1H, ArH), 7.82-7.75 (m, 1H, ArH), 7.66-7.59 (m, 1H, ArH), 7.46-7.43 (m, 2H, ArH), 7.33 (d, ^3J=8.3 Hz, 1H, ArH), 7.07 (dd, ^3J=8.4, ^4J=1.3 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.58 (s, 1H, ArH), 4.11 (t, ^3J=5.0 Hz, 4H, 2 CH_2), 4.04 (s, 3H, OCH_3), 3.82 (t, ^3J=5.1 Hz, 4H, 2 CH_2), 3.75-3.70 (m, 4H, 2 CH_2), 3.69-3.61 (m, 10H, 5 CH_2), 3.54 (dd, ^3J=5.9, ^3J=3.3 Hz, 4H, 2 CH_2), 3.36 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.99 (dd, ^3J=10.1, ^3J=5.6 Hz, 2H, CH_2), 2.83-2.77 (m, 6H, 3 CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7 (C=O), 163.8 (C=O), 149.8 (C_q), 147.4 (C_q), 147.0 (C_q), 146.5 (C_q), 141.3 (C_q), 137.9 (C_q), 137.6 (+), 136.6 (C_q), 136.2 (C_q), 132.0 (C_q), 131.8 (+), 130.2 (+), 129.3 (C_q), 129.2 (C_q), 128.2 (+), 127.6 (+), 127.2 (C_q), 124.3 (+), 120.4 (+), 119.5 (+), 118.7 (+), 115.7 (+), 114.9 (+), 114.7 (C_q), 113.2 (+), 111.3 (+), 101.7 (+), 71.9 (–), 70.7 (–), 70.6 (–), 70.5 (–), 69.7 (–), 69.0 (–), 68.9 (–), 61.0 (–), 59.0 (+), 55.7 (–), 52.4 (+), 51.0 (–), 34.1 (–), 28.6 (–). HRMS (EI-MS) calcd. for $C_{51}H_{61}N_4O_{11}$ $[M+H]^+$: 905.4331; found: 905.4333. IR (KBr) [cm^{-1}]: v = 2870, 1683, 1516, 771. HPLC: t_R 24.75 min, purity 94%.

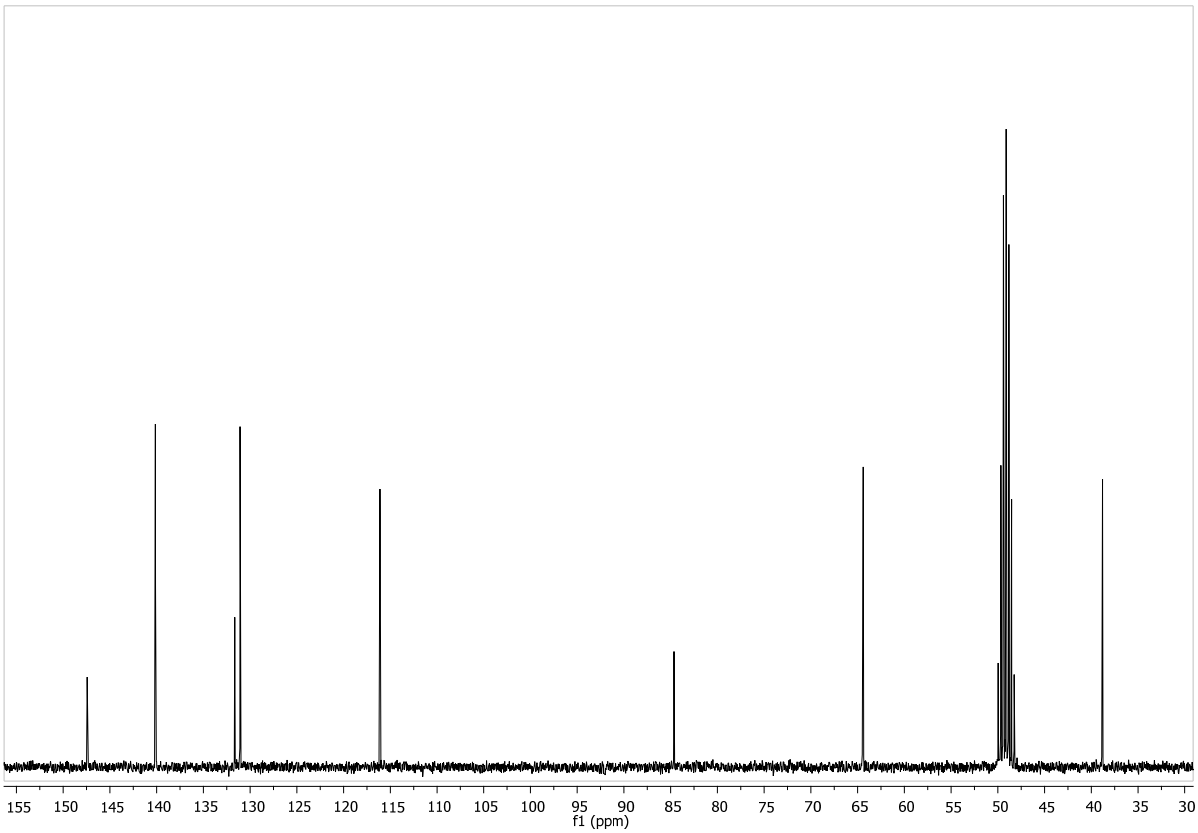
Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25d

Yield 55%, light yellow oil, R_f = 0.18 ($CHCl_3$/MeOH 100/6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 13.37 (s, 1H, NHCO), 9.34 (d, ^4J=1.5 Hz, 1H, ArH), 9.15 (s, 1H, NH), 8.36-8.28 (m, 3H, ArH), 8.11 (d, ^3J=8.4 Hz, 1H, ArH), 7.89 (d, ^3J=8.1 Hz, 1H, ArH), 7.84-7.76 (m, 1H, ArH), 7.66-7.59 (m, 2H, ArH), 7.48 (dd, ^3J=8.4, ^4J=1.5 Hz, 1H, ArH), 7.38 (d, ^3J=8.3 Hz, 1H, ArH), 7.26 (dd, ^3J=8.3, ^4J=1.1 Hz, 1H, ArH), 6.96 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.51 (s, 1H, ArH), 4.12-4.05 (m, 5H, OCH_3, CH_2), 3.82-3.60 (m, 20H, 10 CH_2), 3.55-3.49 (m, 6H, 3 CH_2), 3.36 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.82-2.71 (m, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.7 (C=O), 163.8 (C=O), 149.9 (C_q), 147.3 (C_q), 147.0 (C_q), 146.6 (C_q), 141.4 (C_q), 137.8 (C_q), 137.7 (+), 136.8 (C_q), 136.7 (C_q), 131.9 (+), 130.2 (+), 130.0 (+), 129.4 (C_q), 128.9 (C_q), 128.3 (+), 127.9 (C_q), 127.6 (+), 127.3 (C_q), 124.9 (+), 121.4 (+), 119.6 (+), 118.8 (+), 115.7 (+), 115.1 (+), 114.8 (C_q), 113.1 (+), 111.2 (+), 102.0 (+), 77.2 (–), 71.9 (–), 70.7 (–), 70.7 (–), 70.6 (–), 70.6 (–), 70.5 (–), 70.5 (–), 69.7 (–), 69.7 (–), 68.9 (–), 63.2 (–), 59.0 (+), 55.6 (–), 52.4 (+), 50.6 (–), 28.6 (–). HRMS (EI-MS) calcd. for $C_{50}H_{59}N_4O_{11}$ $[M+H]^+$: 891.4175; found: 891.4178. IR (KBr) [cm^{-1}]: v = 2872, 1685, 1516, 771. HPLC: t_R 14.46 min, purity 97%.

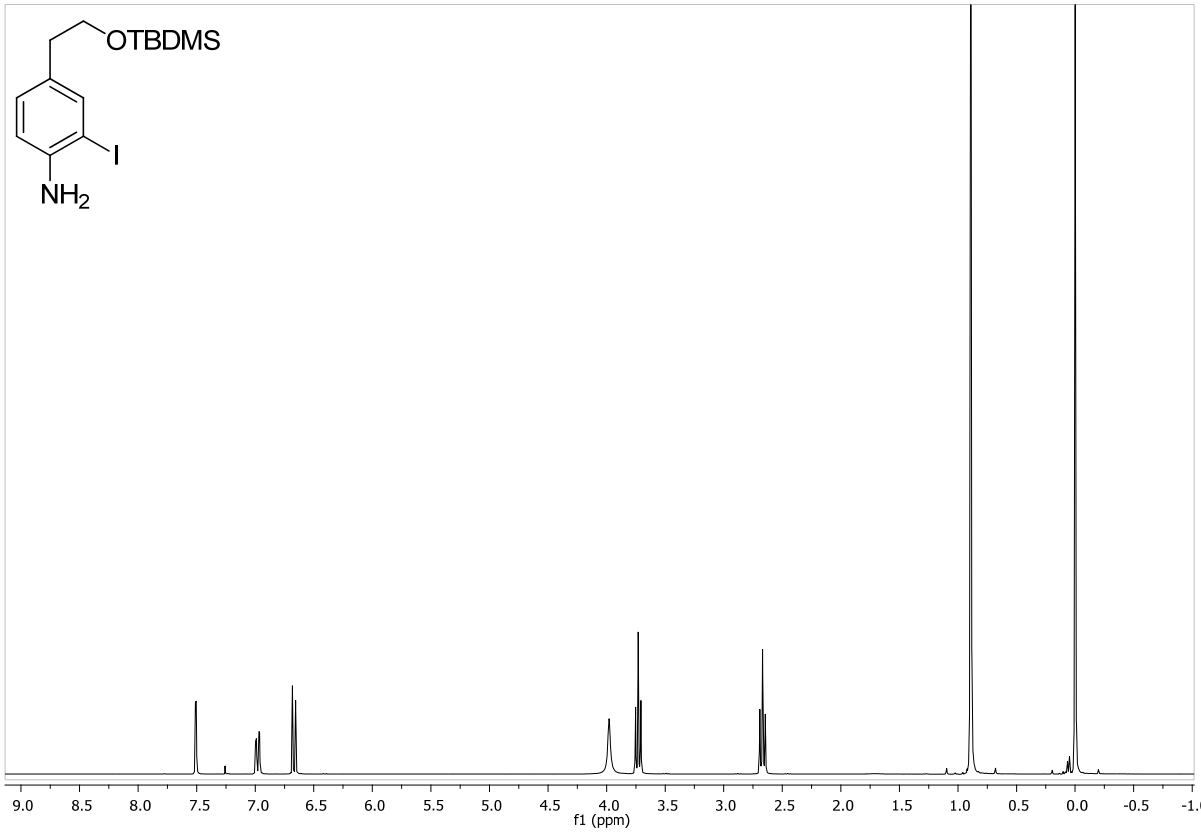
2.2 ^{1}H and ^{13}C NMR spectra

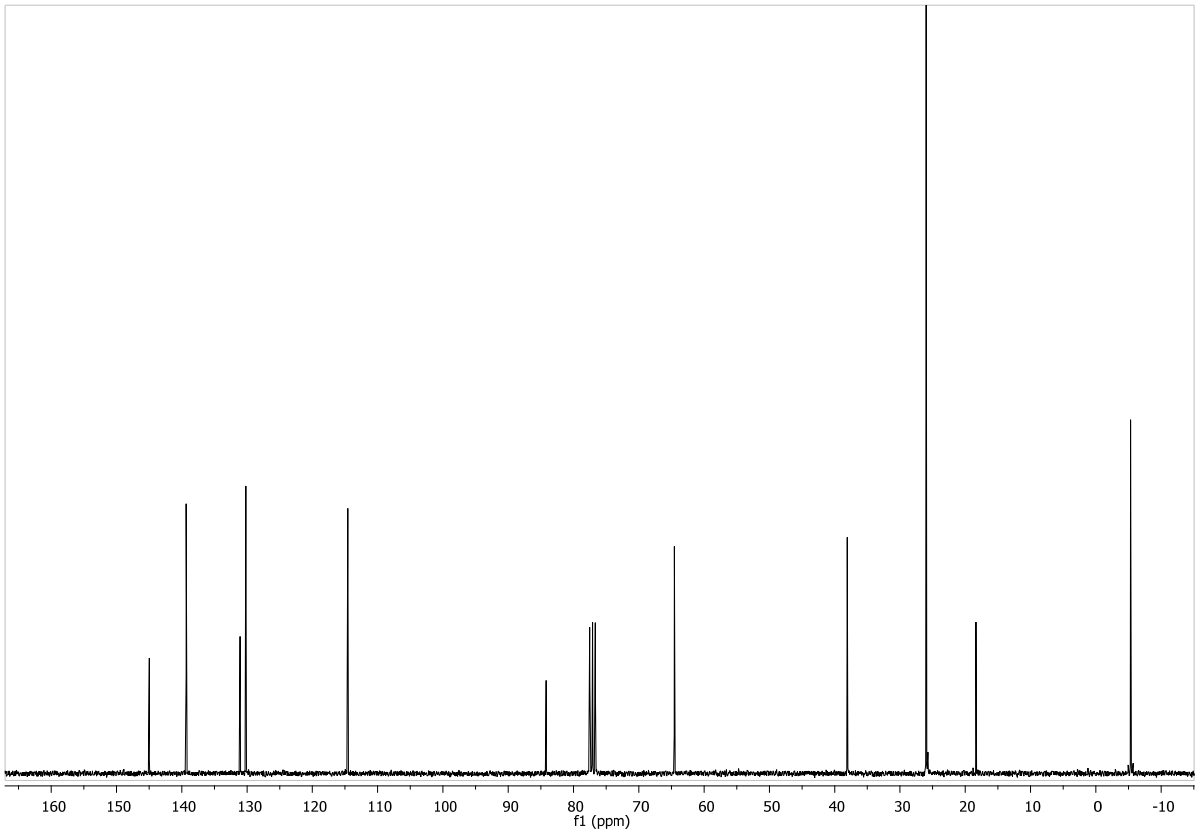
2-(4-Amino-3-iodophenyl)ethanol 4



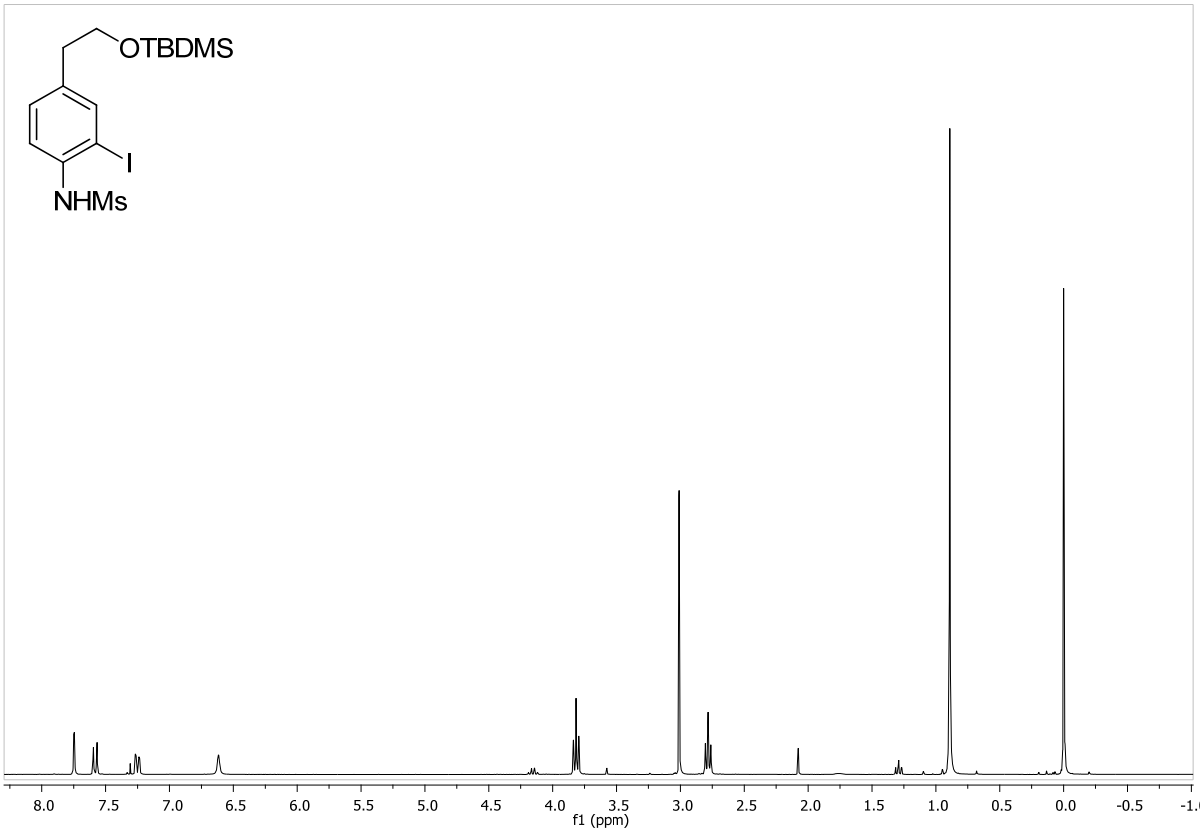


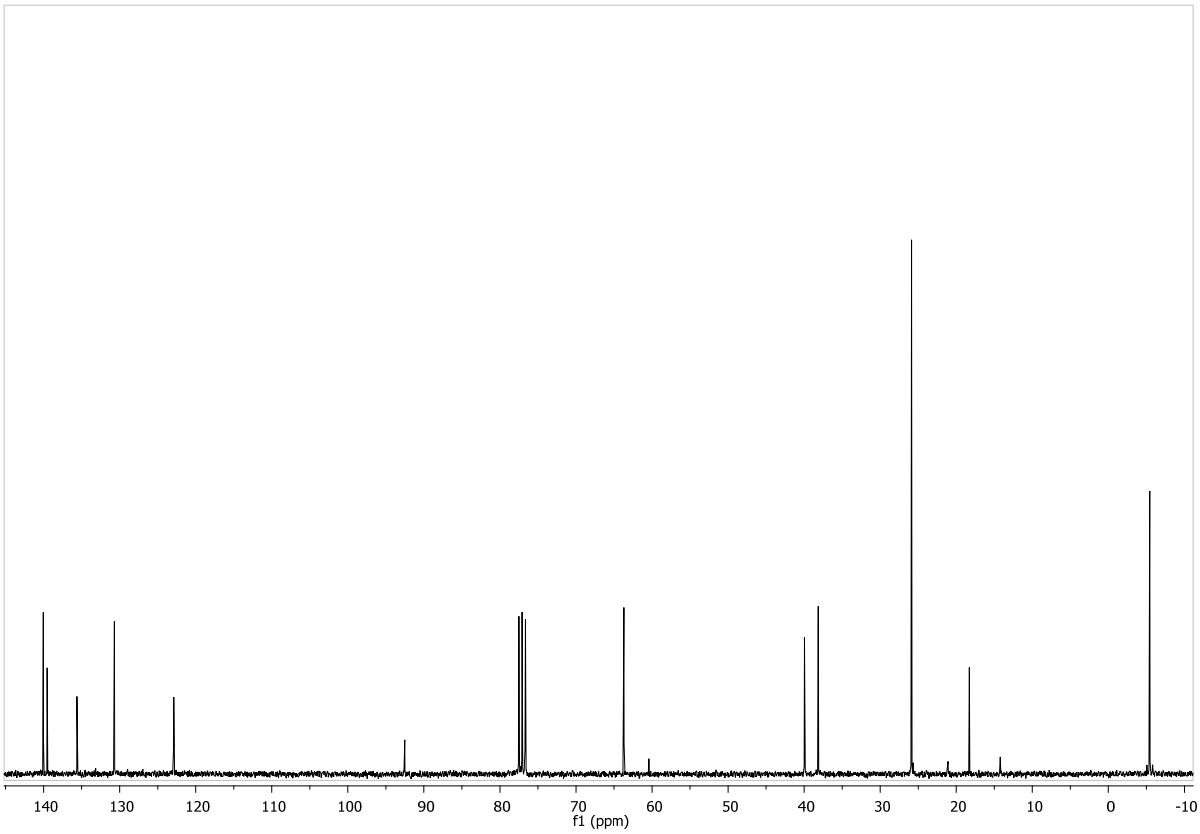
4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-iodoaniline 6



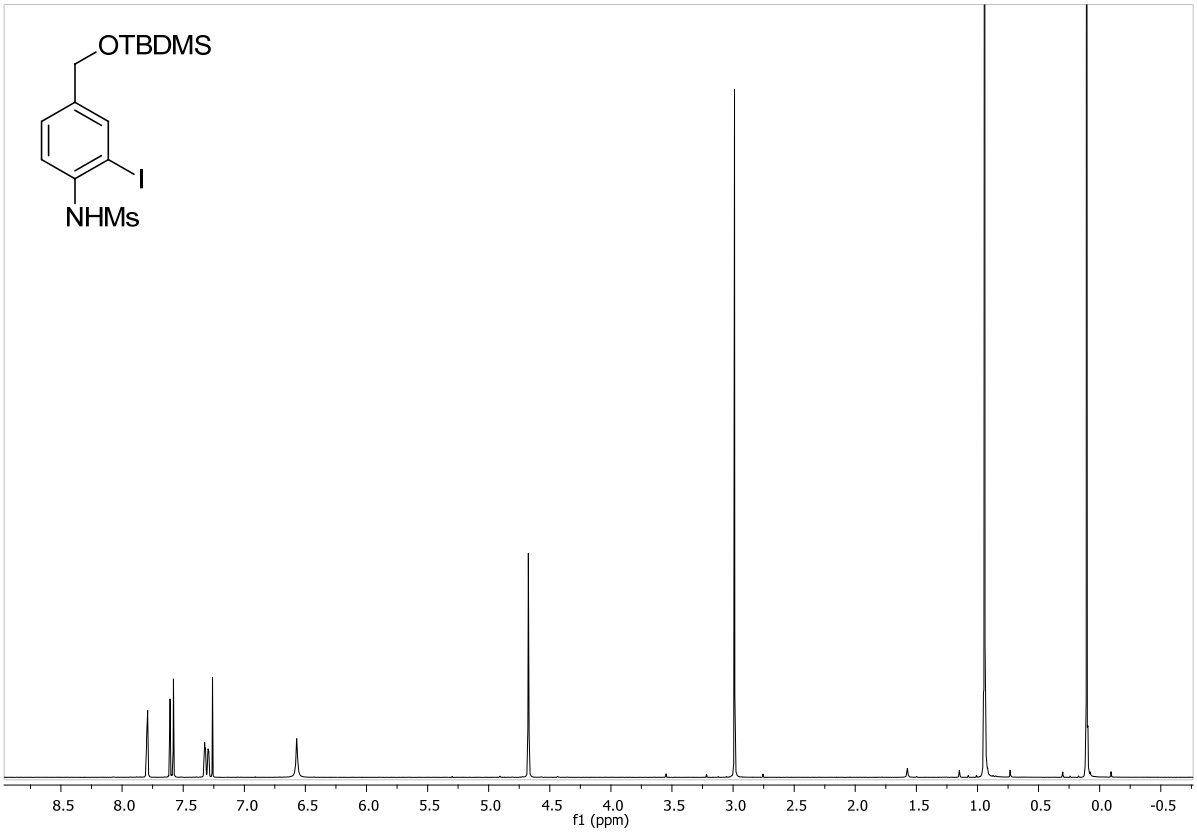


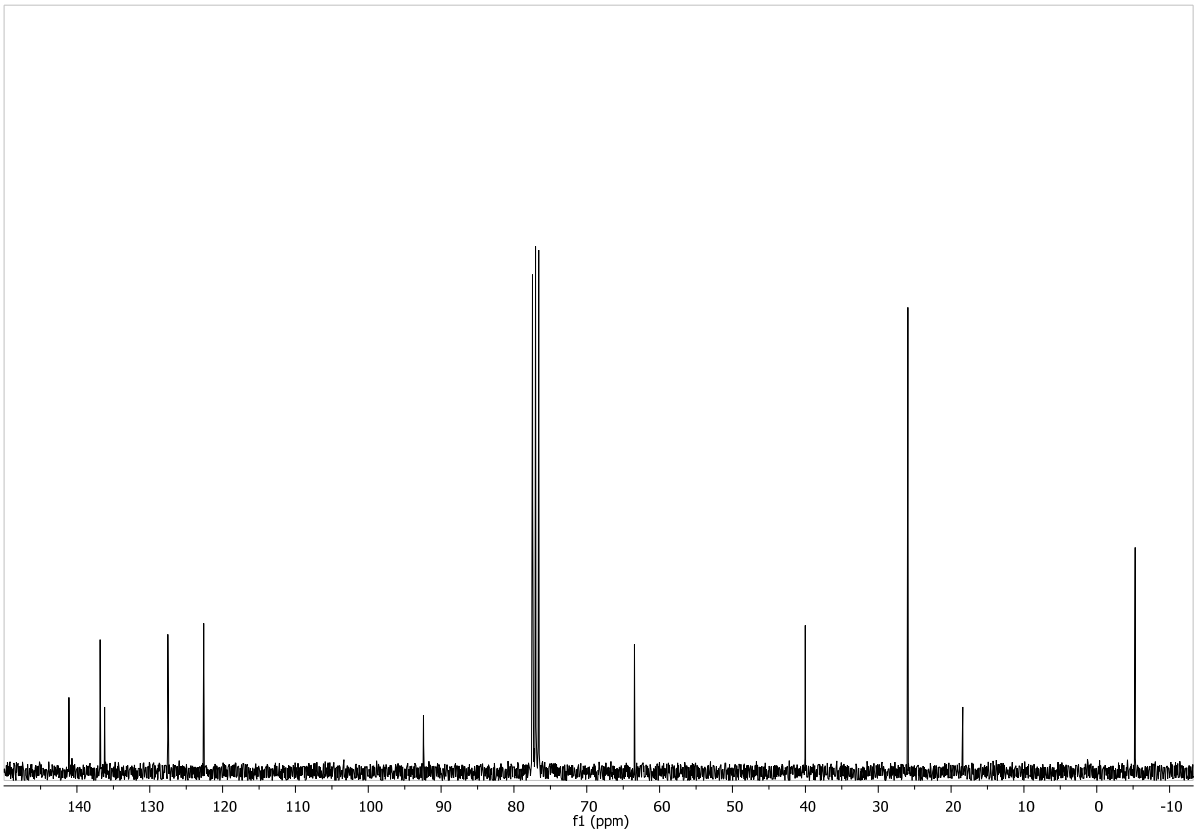
N-(4-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-2-iodophenyl)methanesulfonamide 8



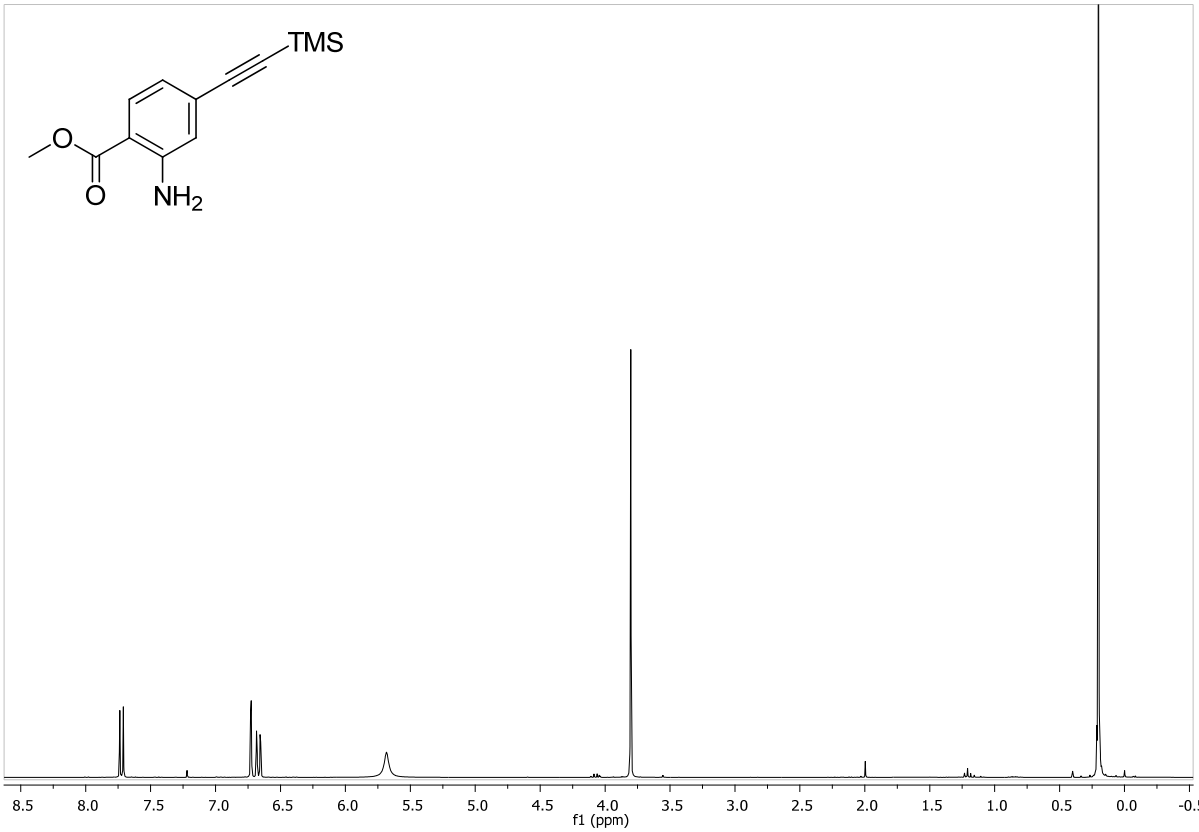


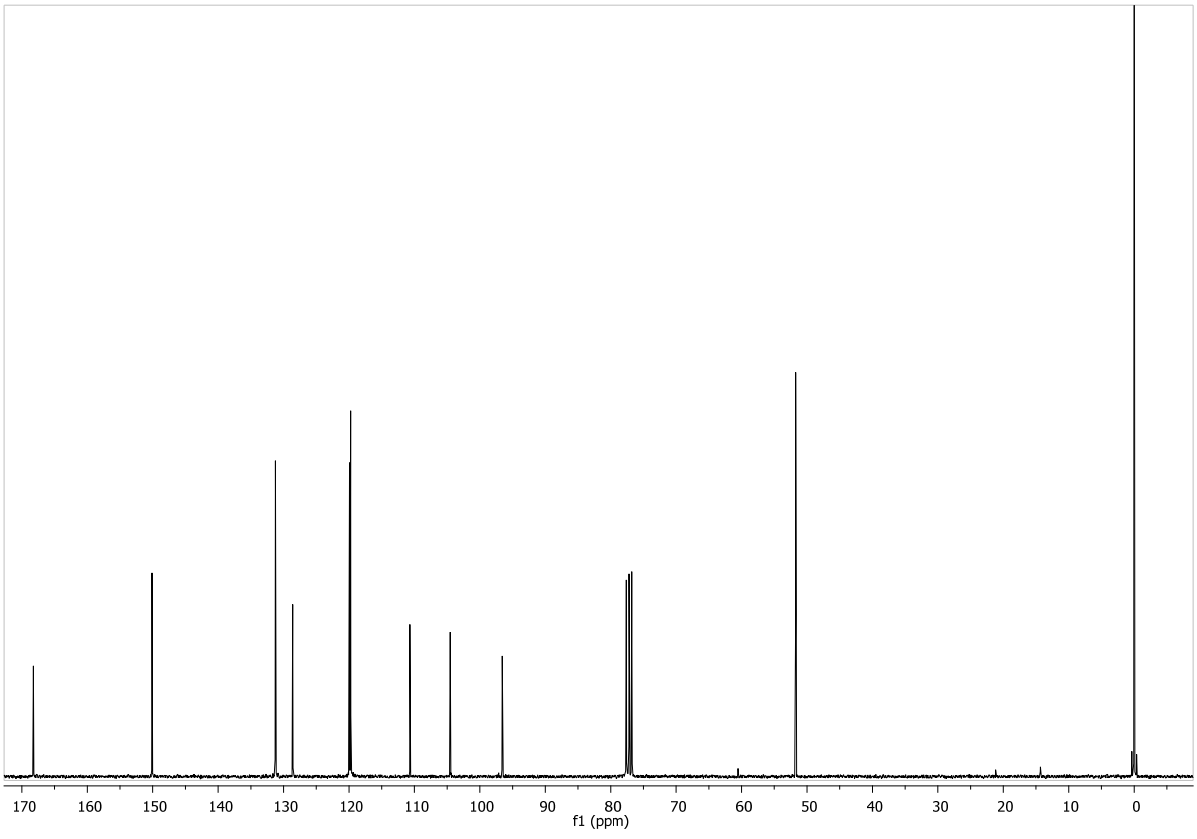
N-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-iodophenyl) methane sulfonamide 7.



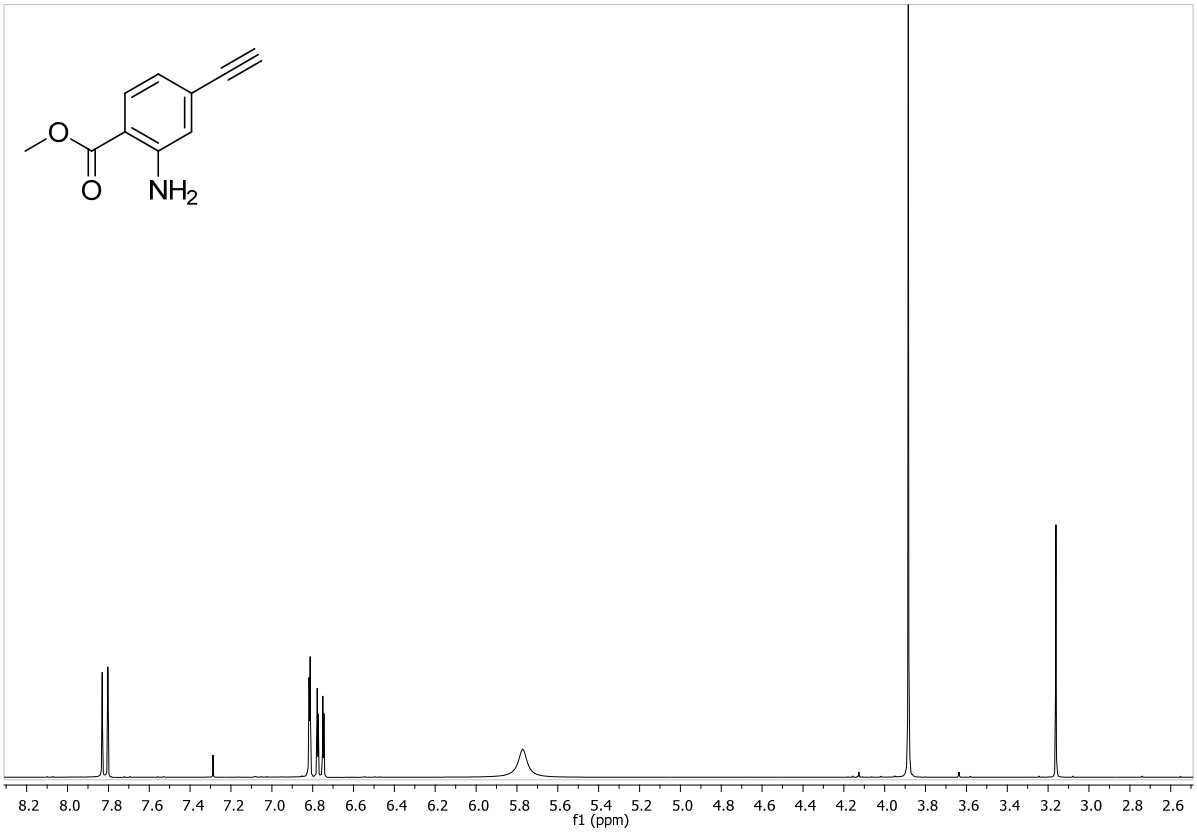


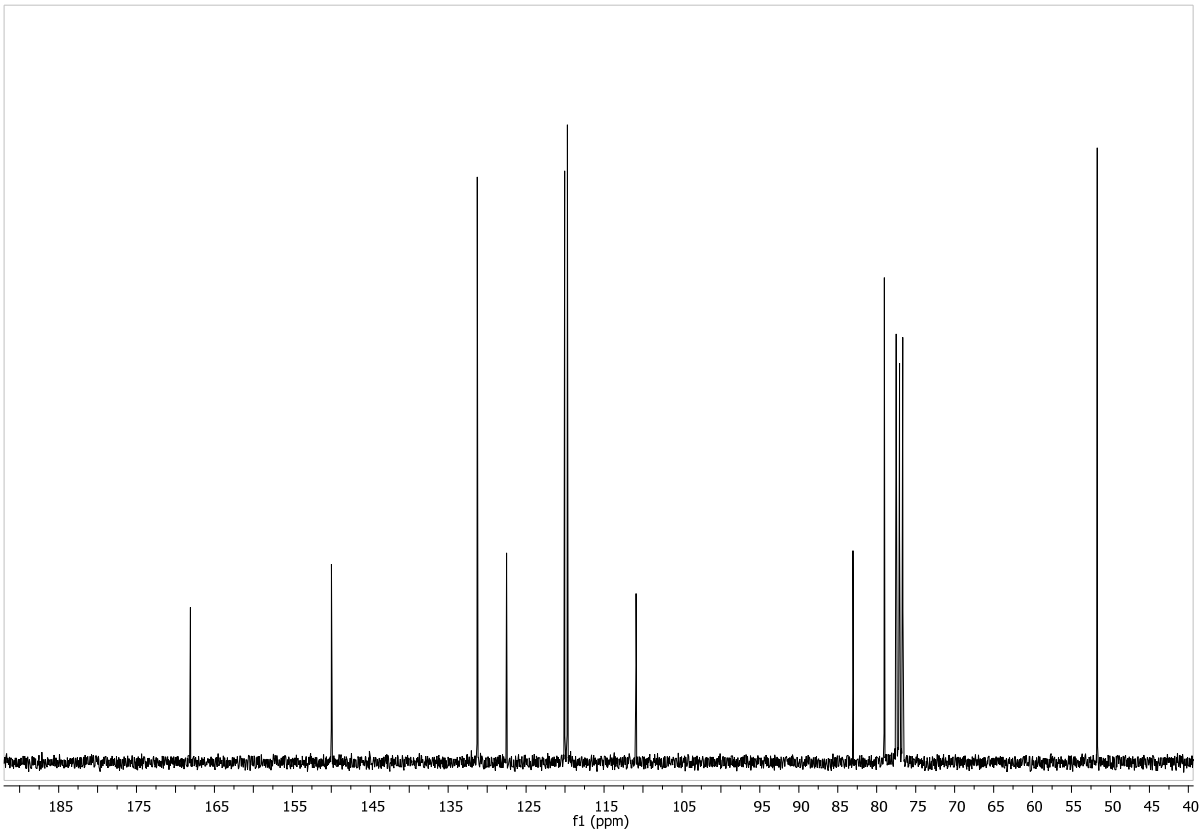
Methyl 2-amino-4-((trimethylsilyl)ethynyl)benzoate 10



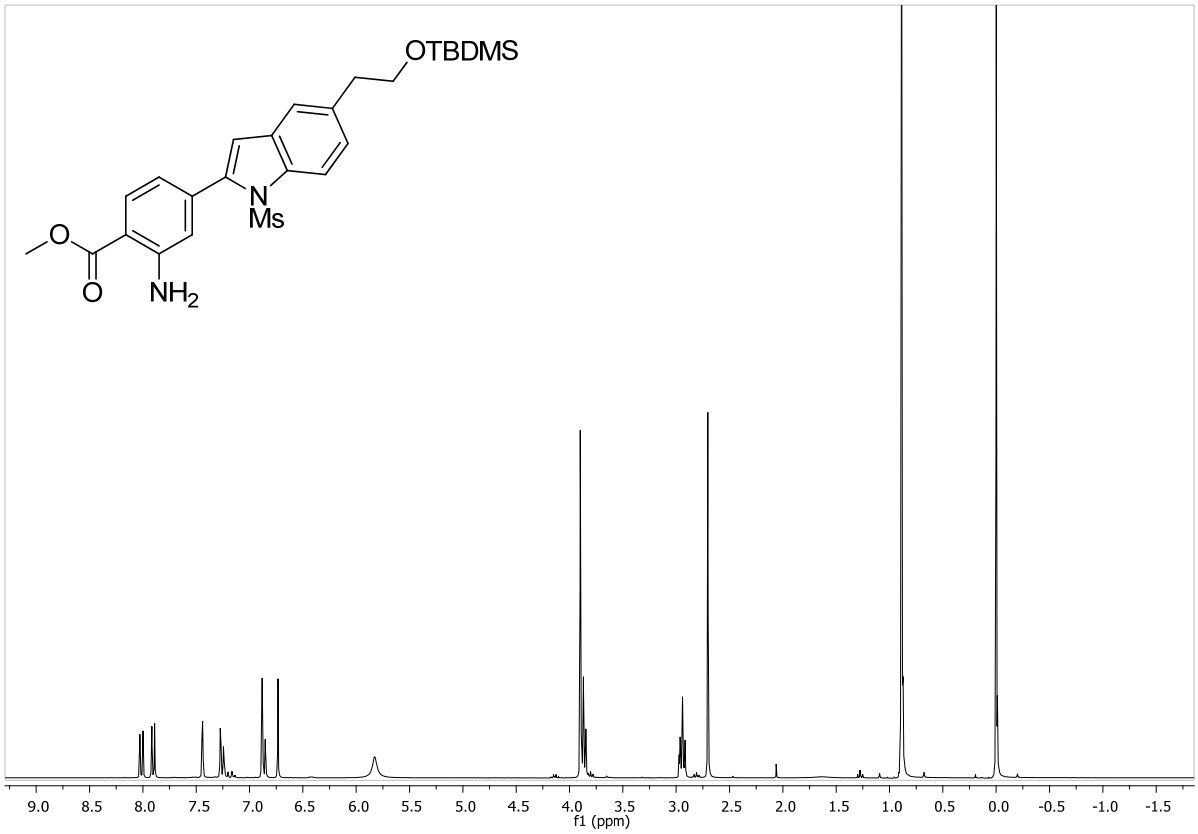


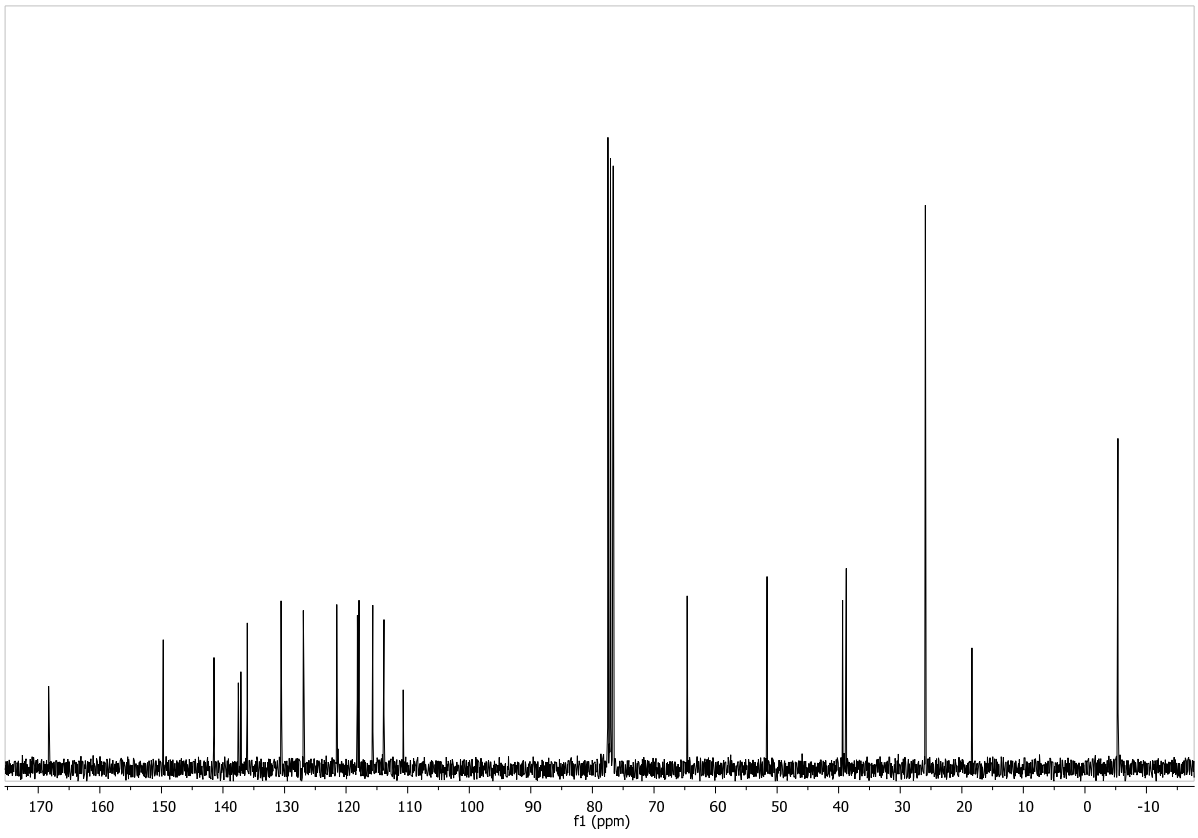
Methyl 2-amino-4-ethynylbenzoate 11



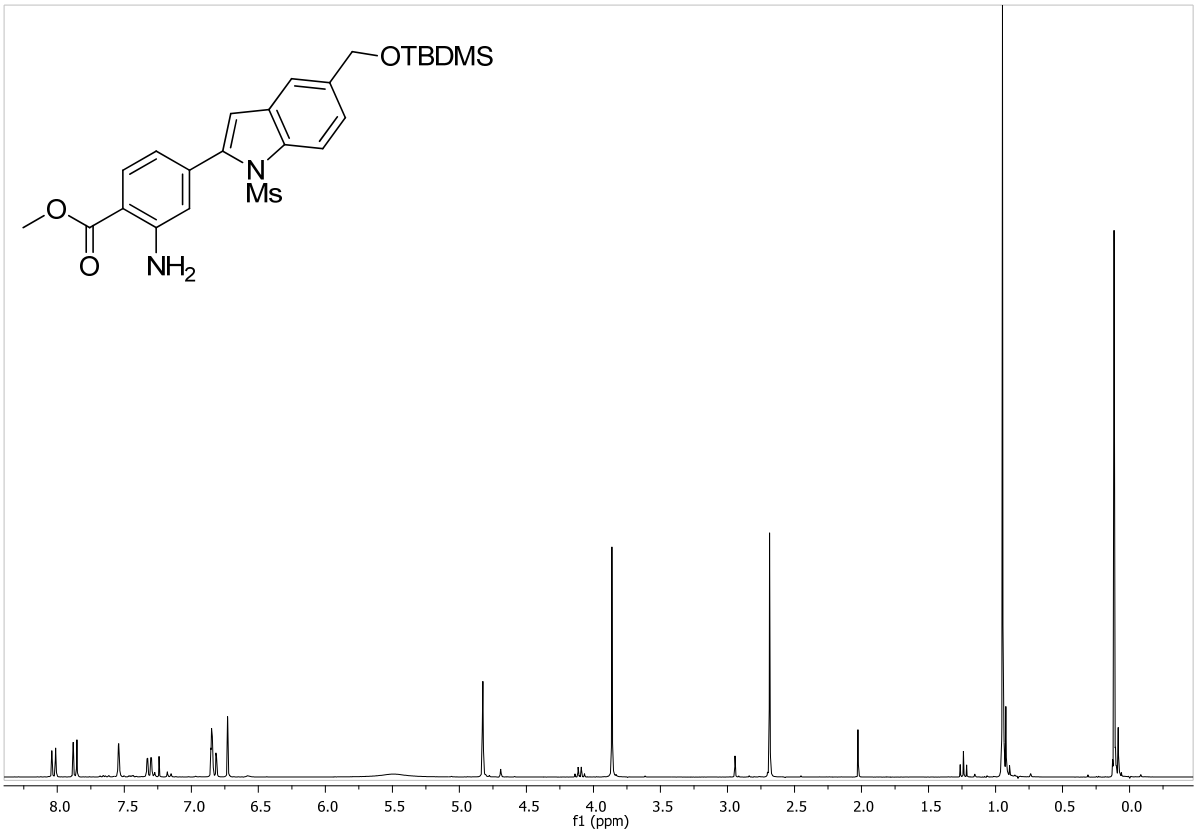


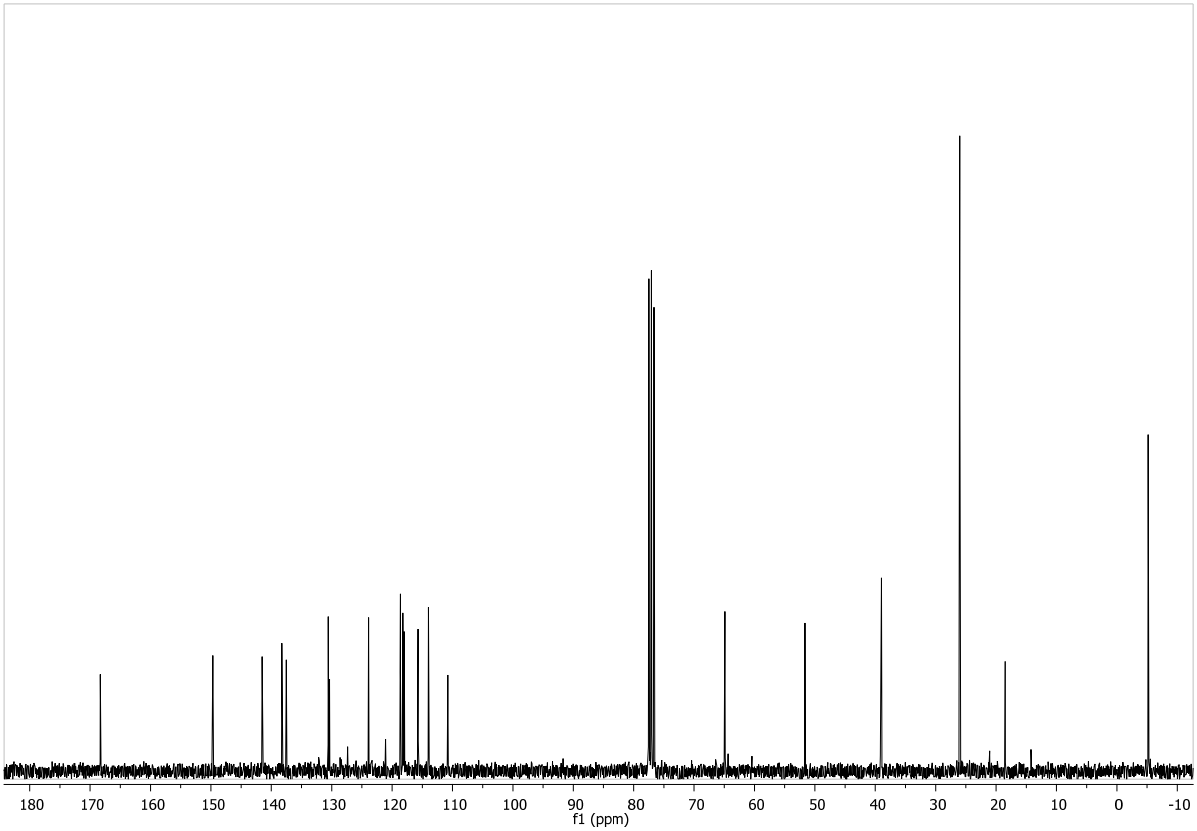
Methyl 2-amino-4-(5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)benzoate 13



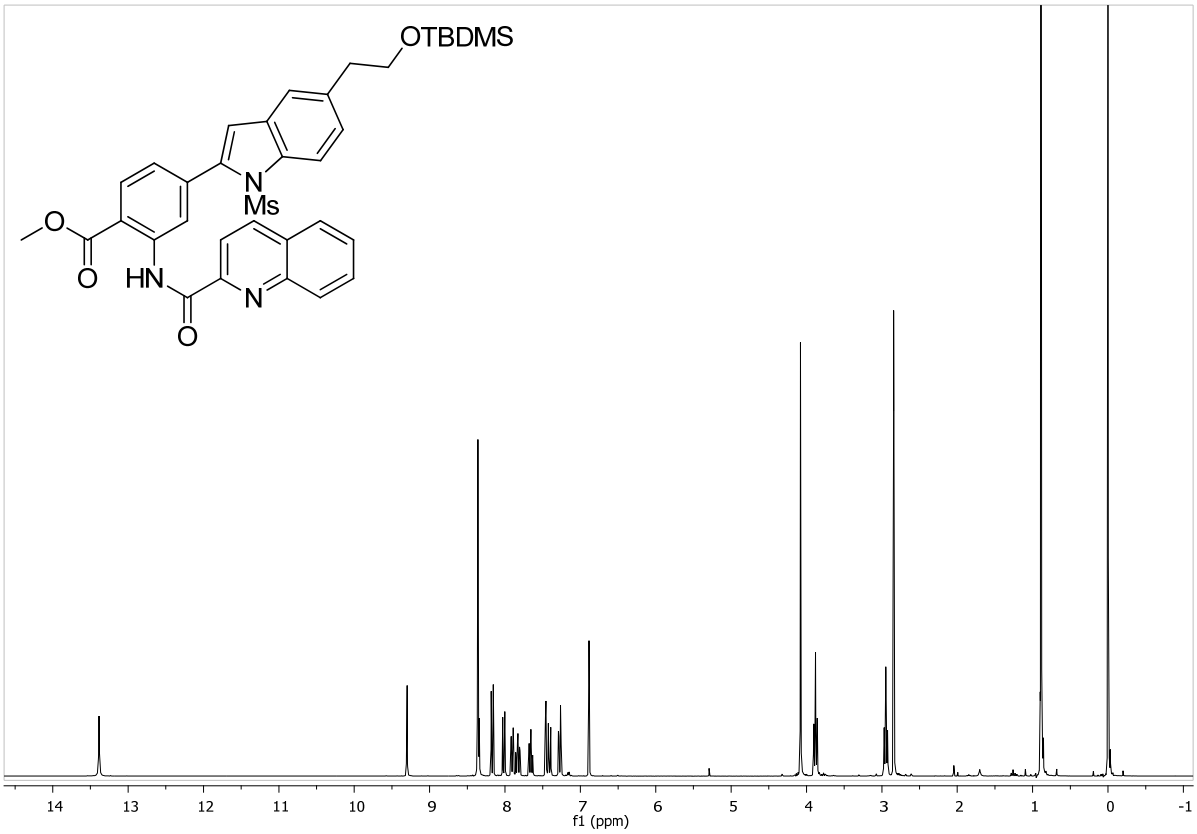


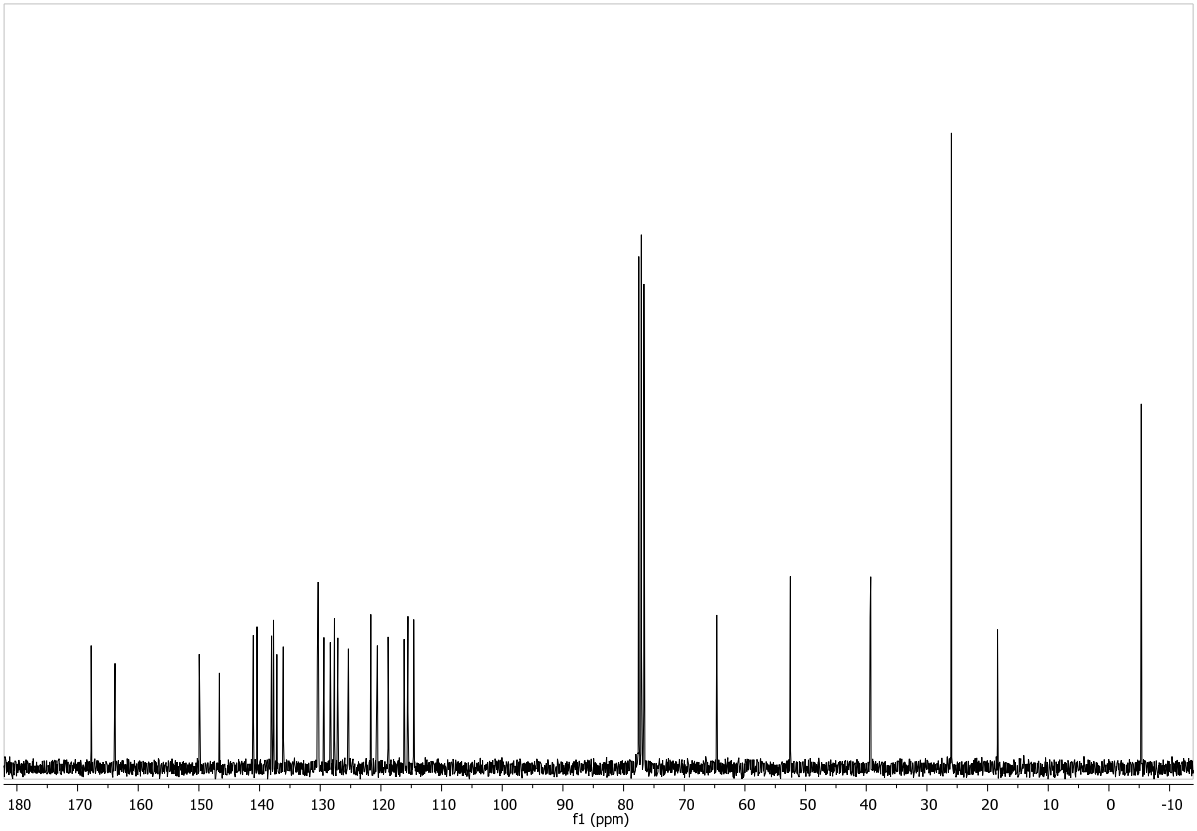
Methyl 2-amino-4-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1H-indol-2-yl)benzoate 12



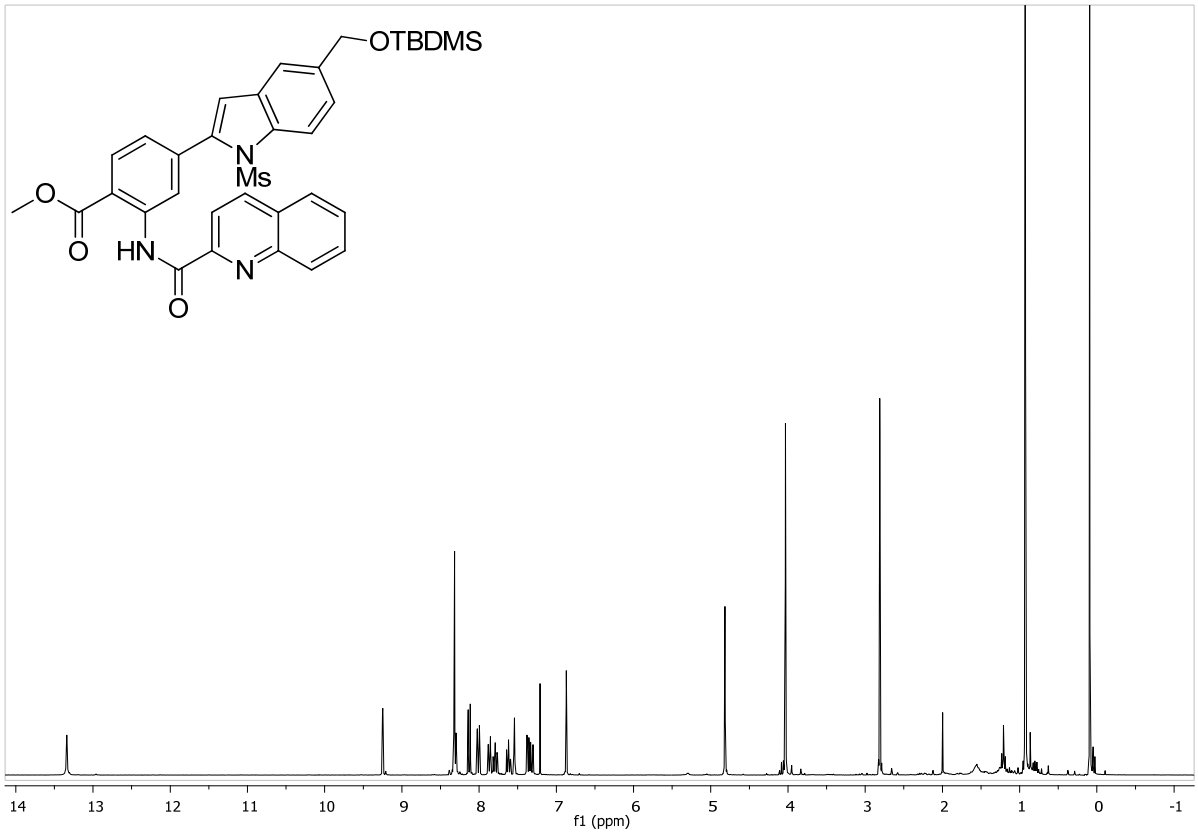


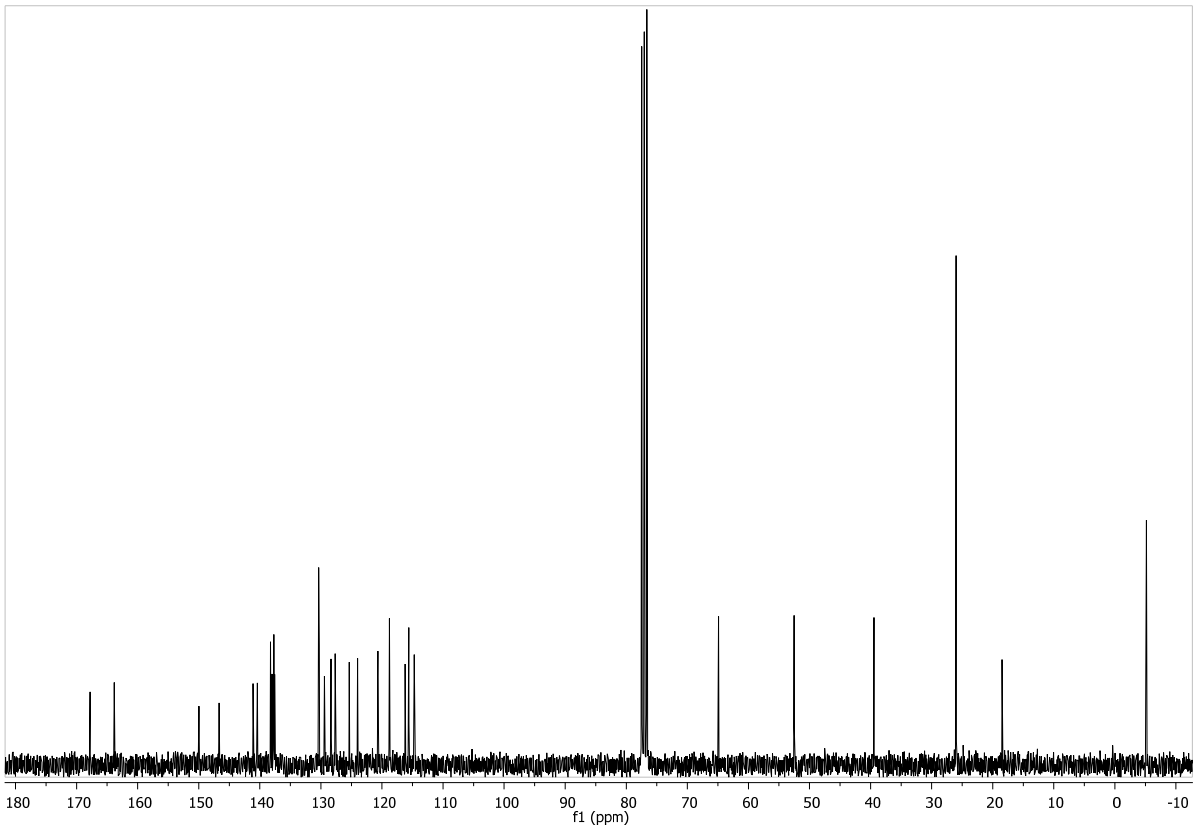
Methyl 4-(5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 15



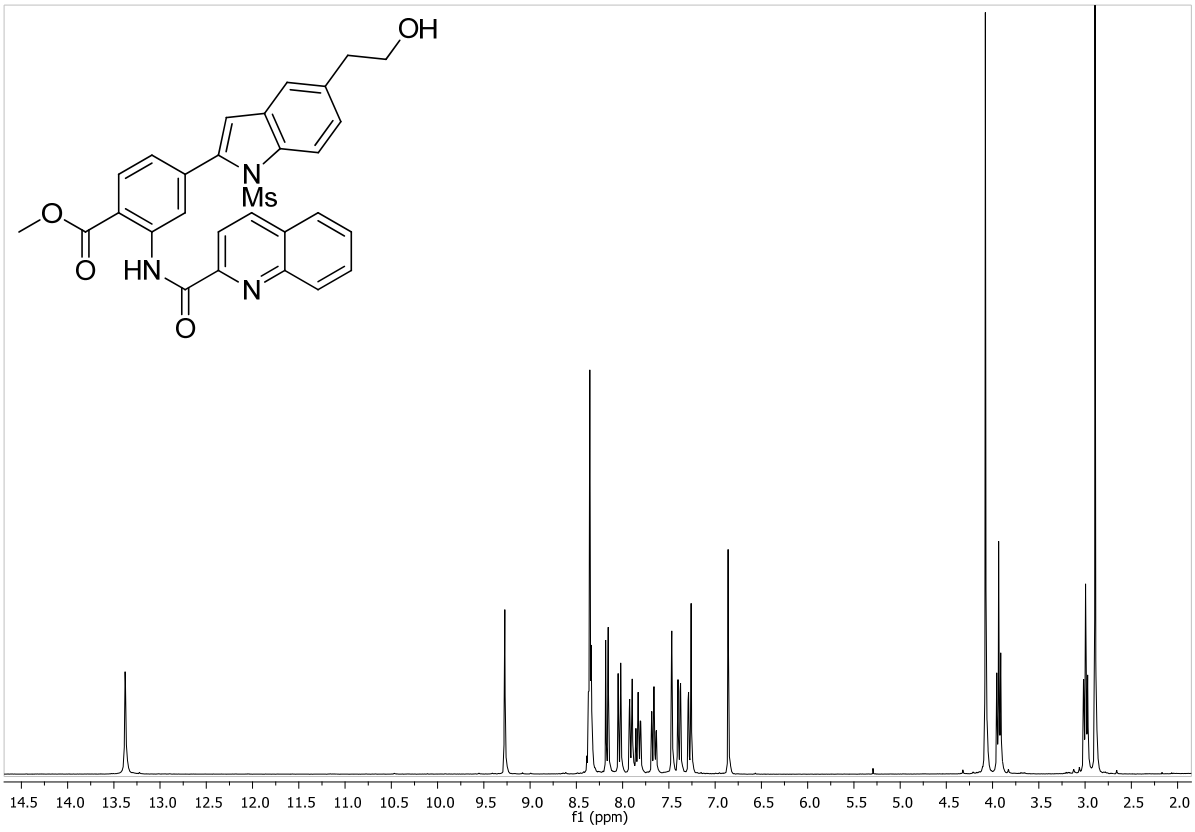


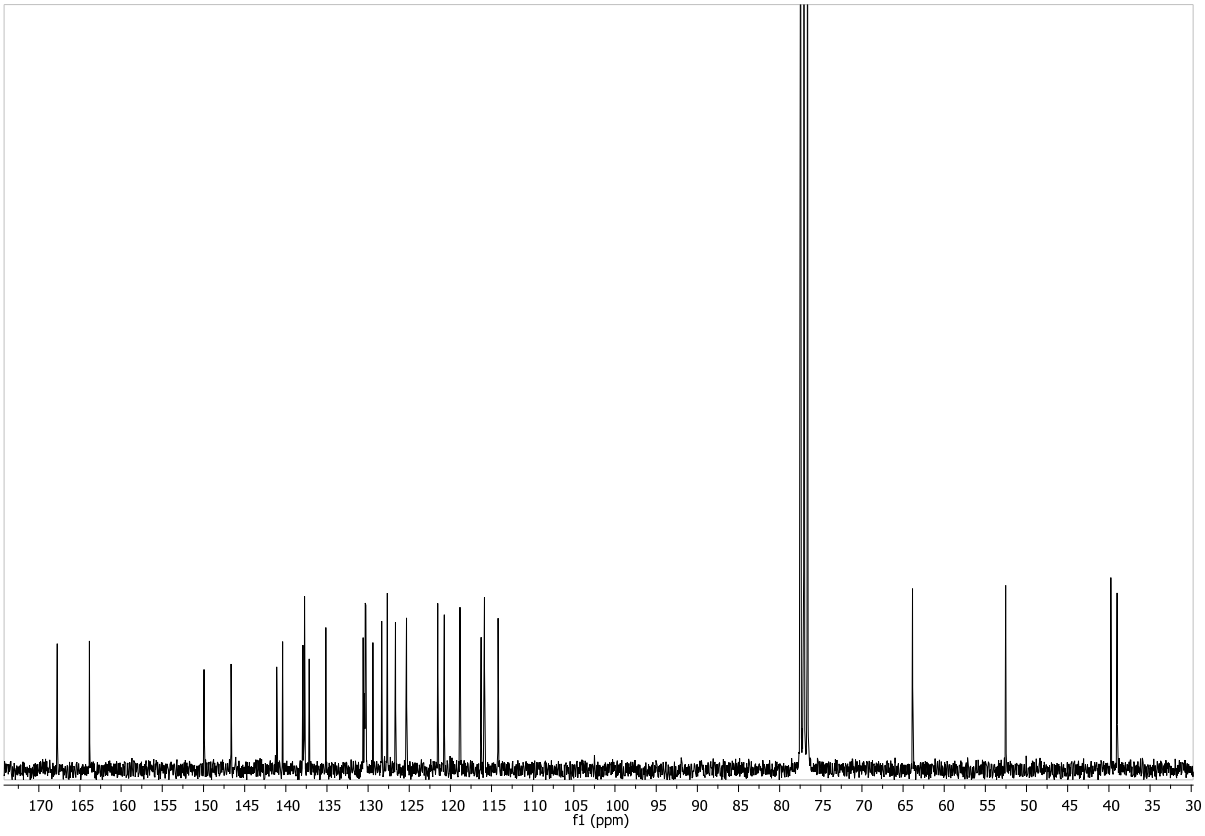
Methyl 4-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 14





Methyl 4-(5-(2-hydroxyethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)-benzoate 17





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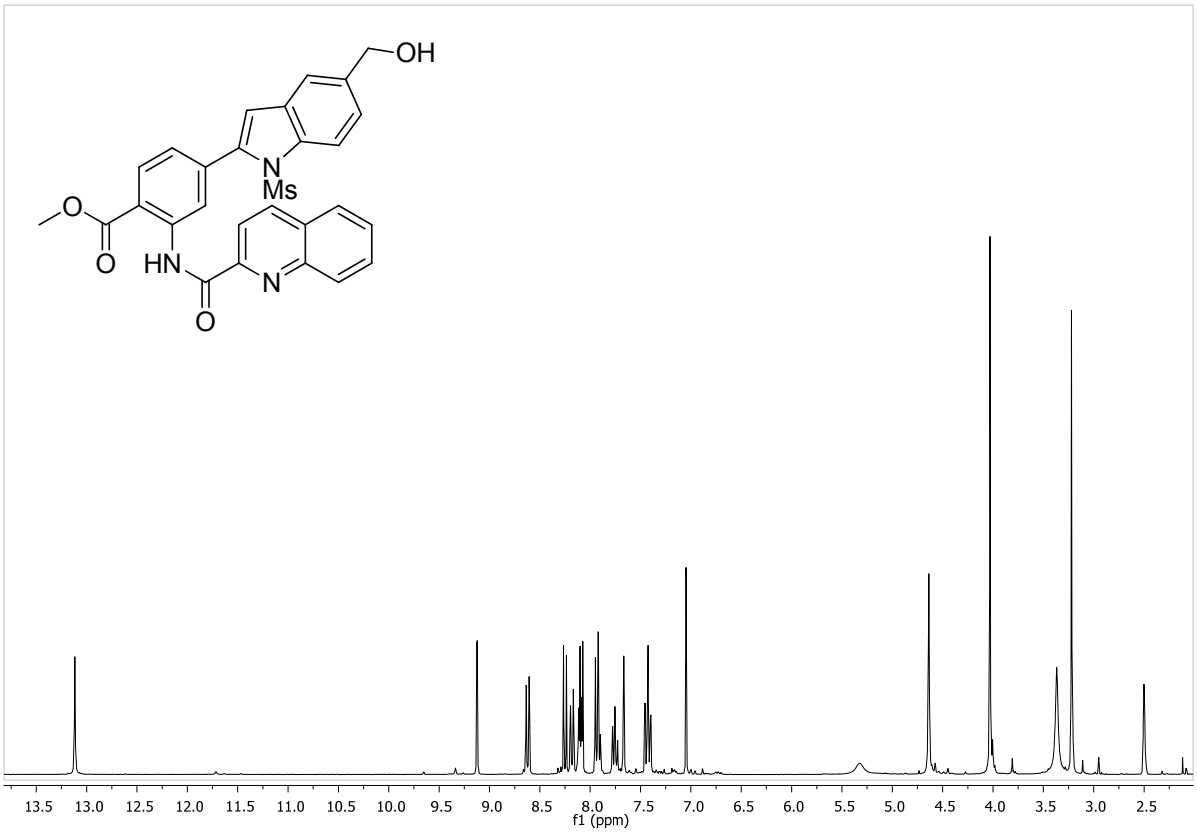

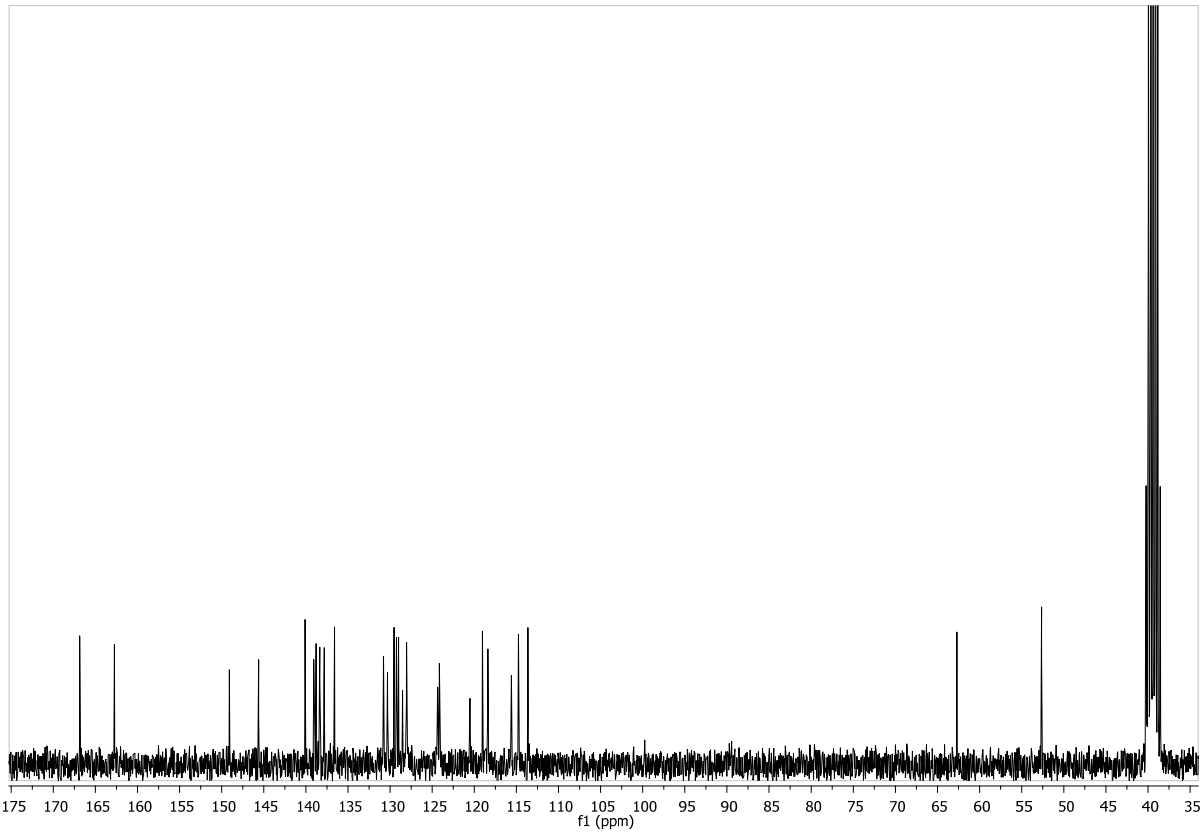

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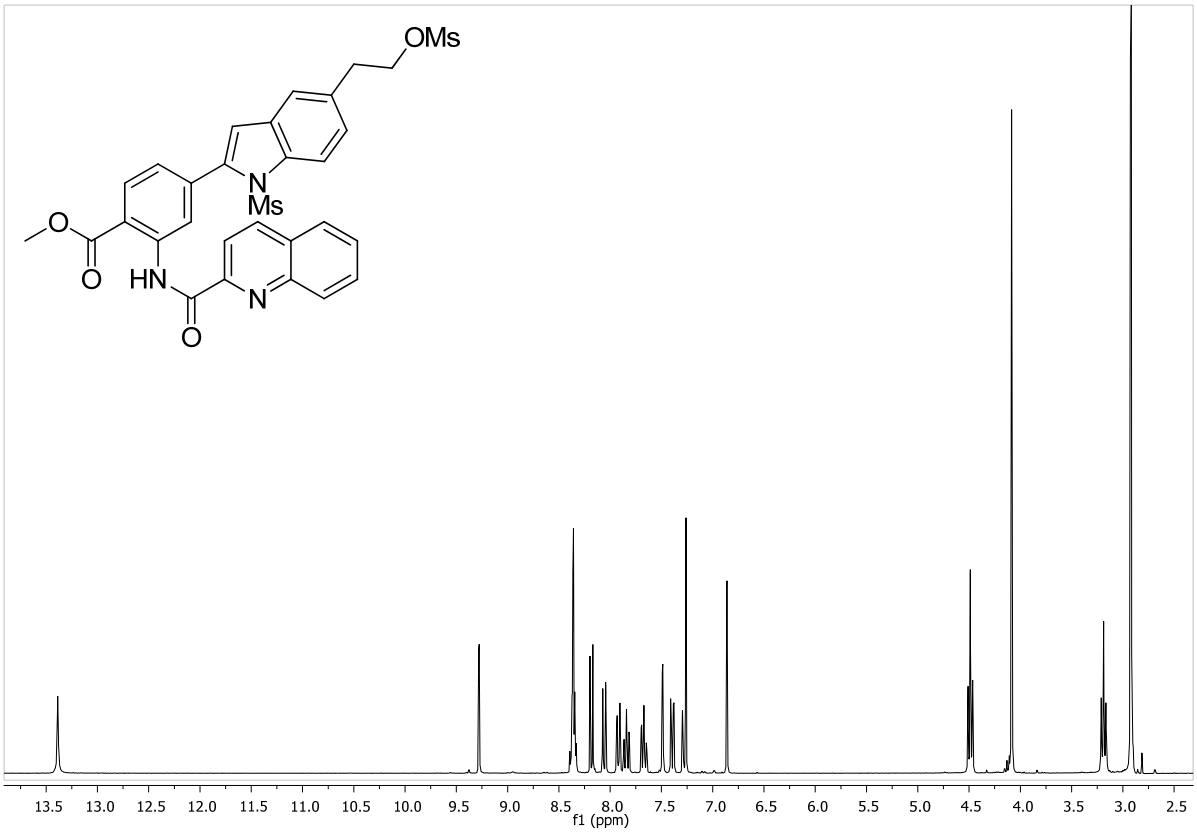
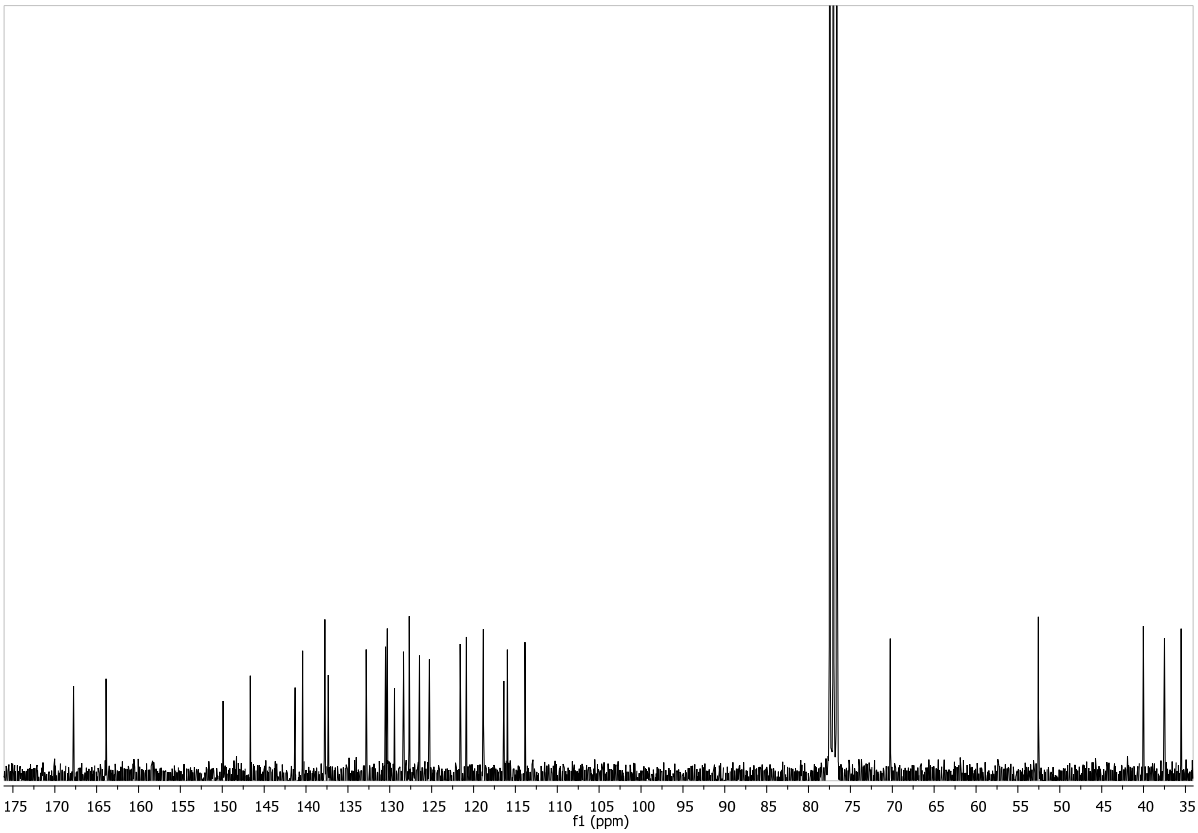
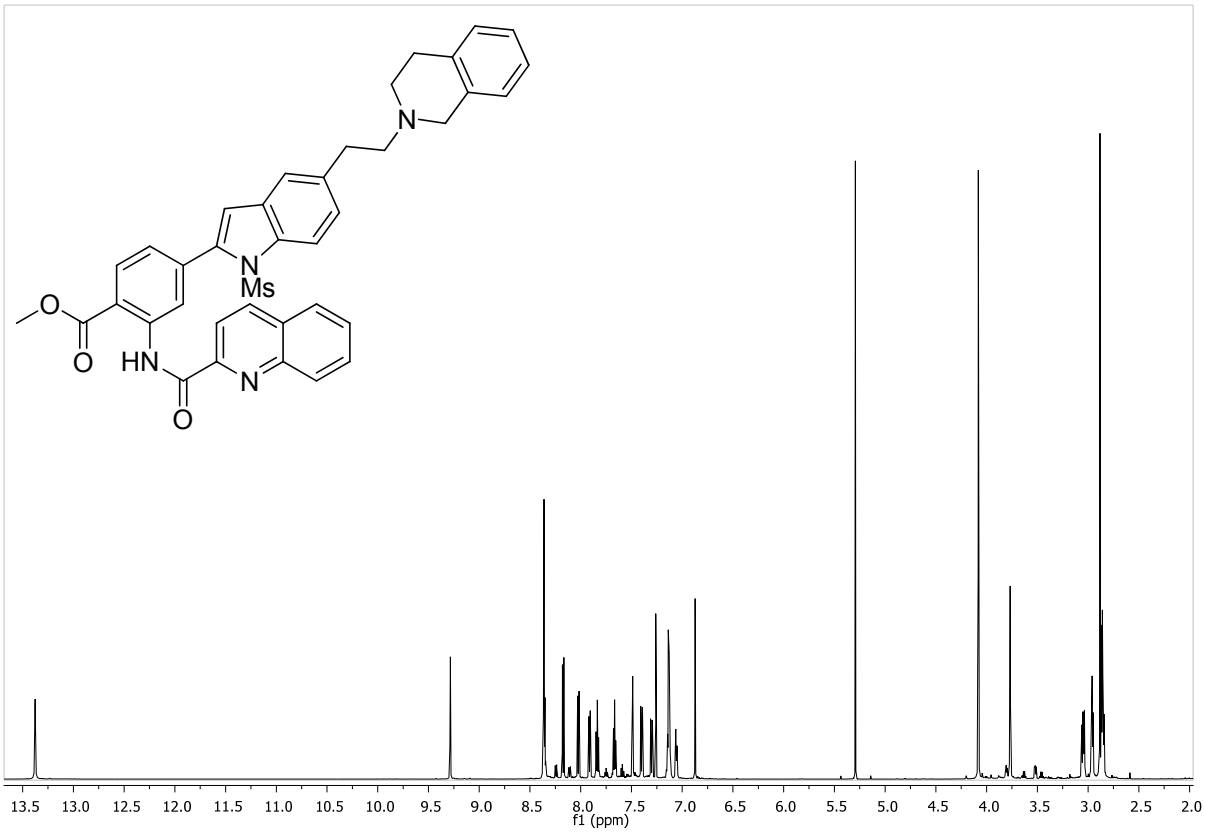
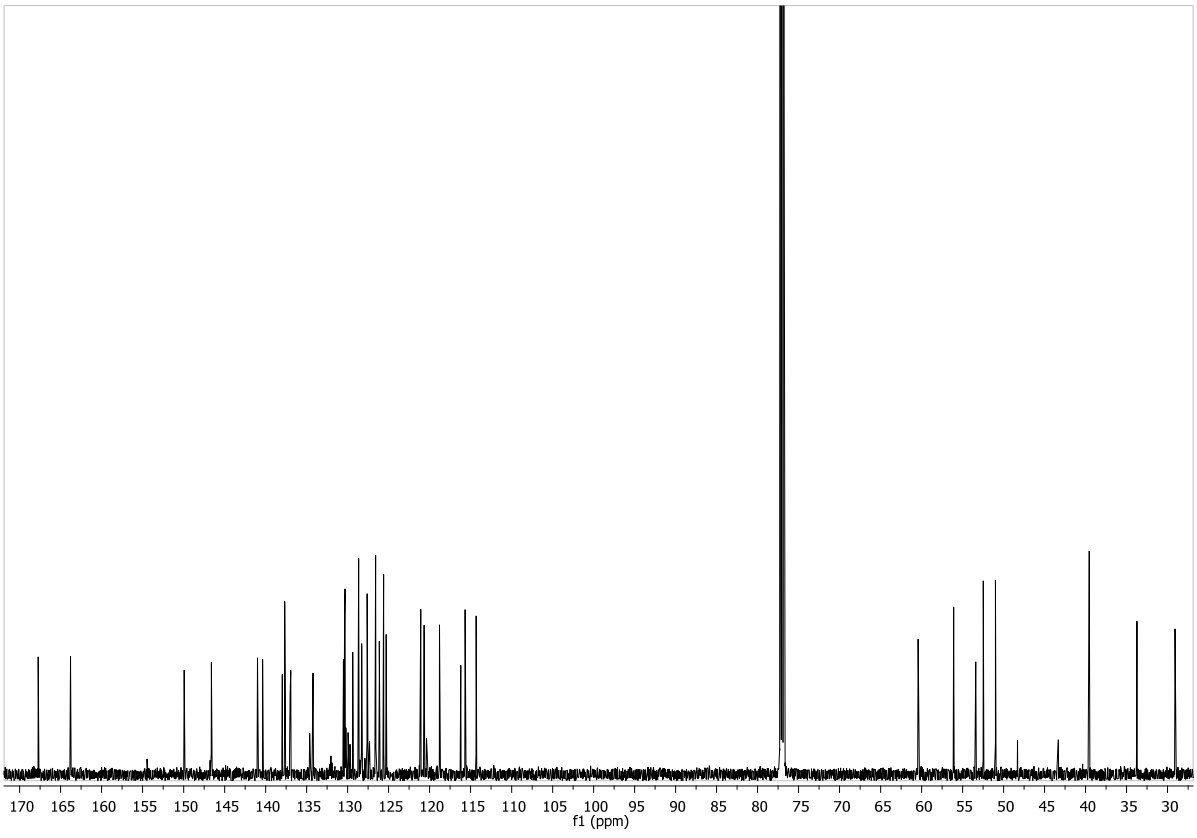


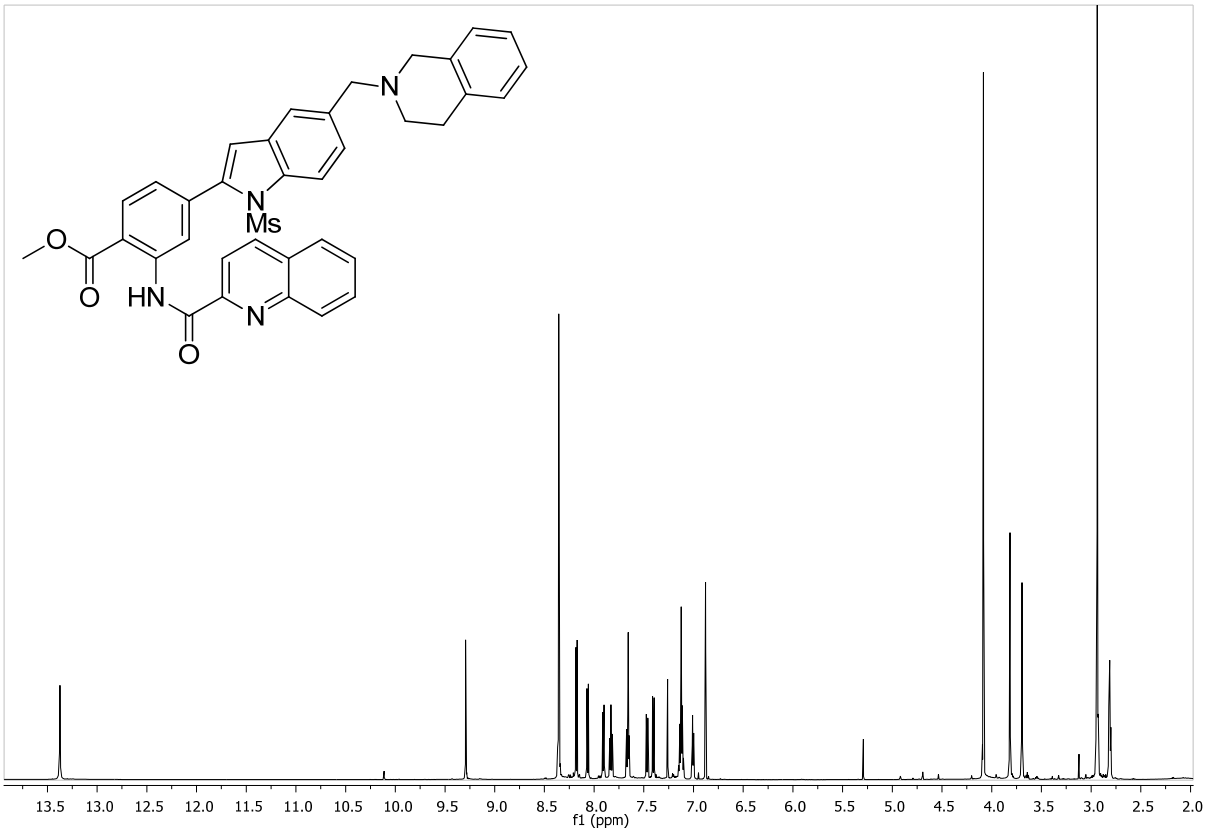


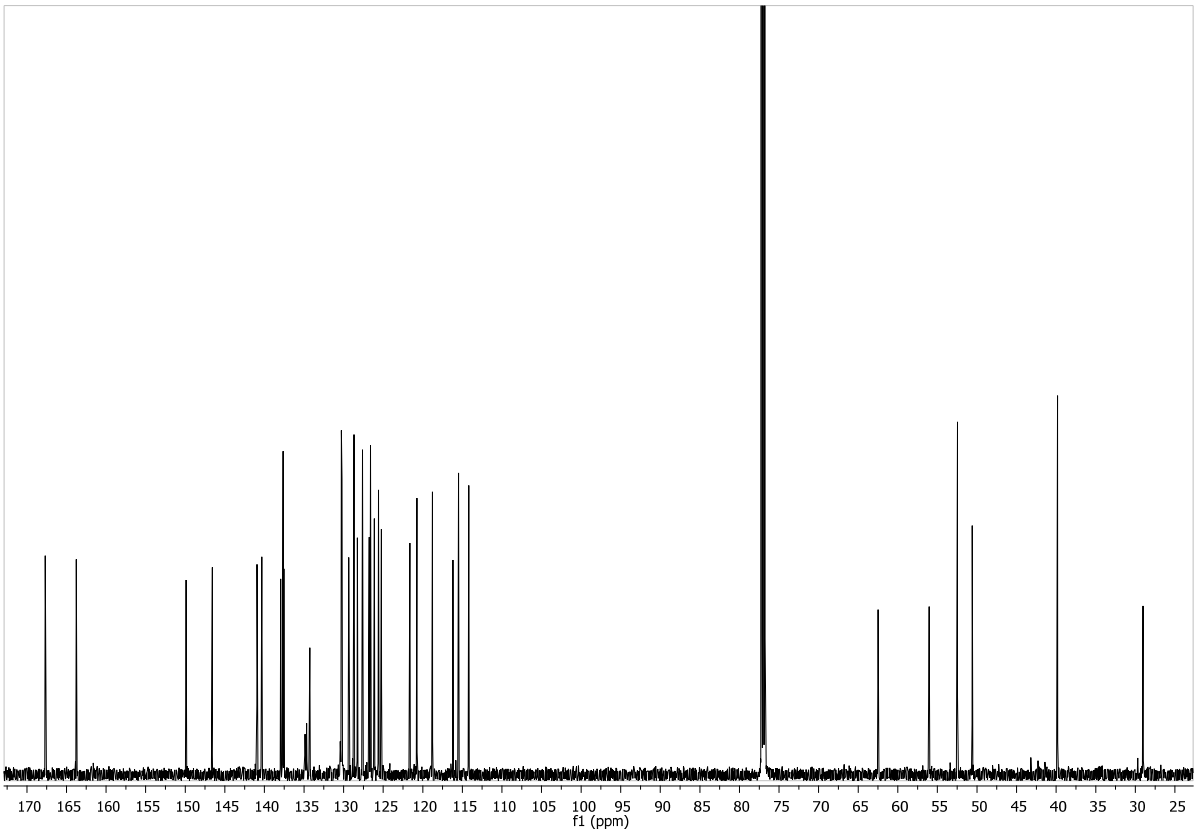
Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24e



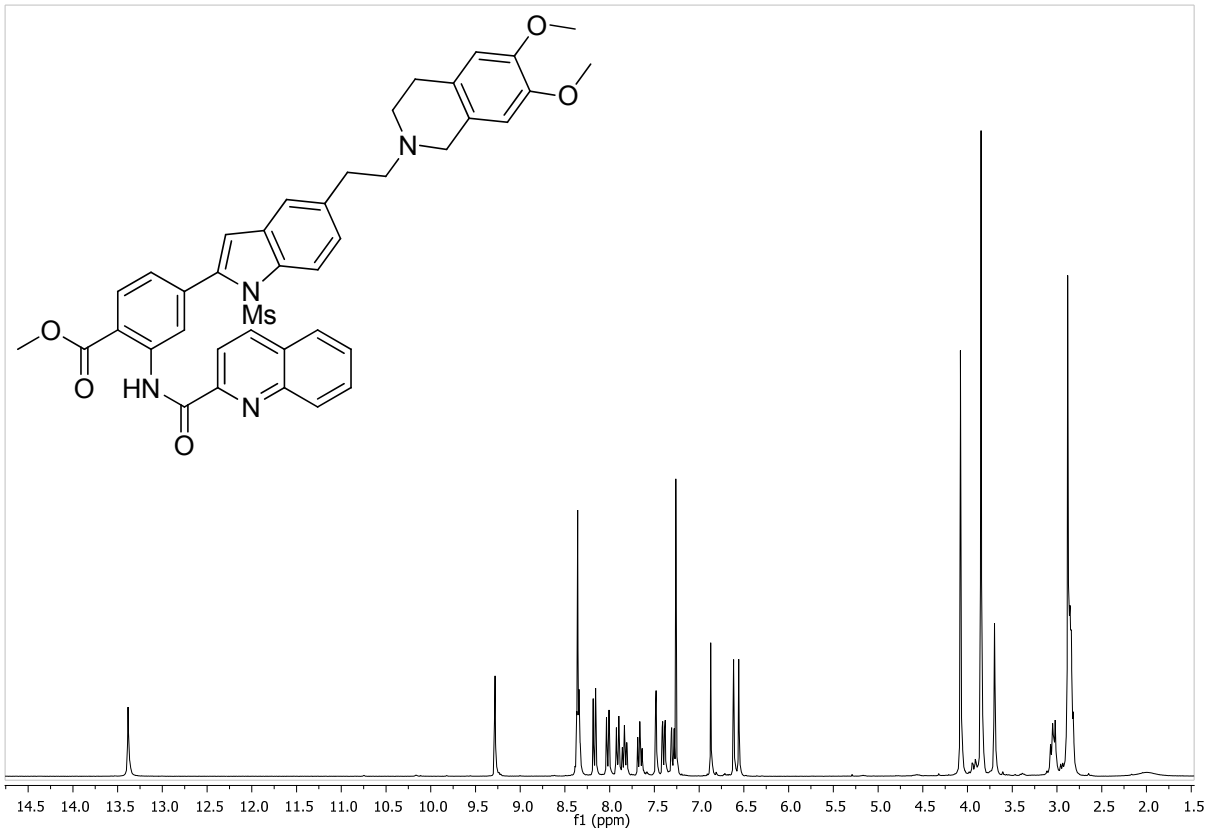


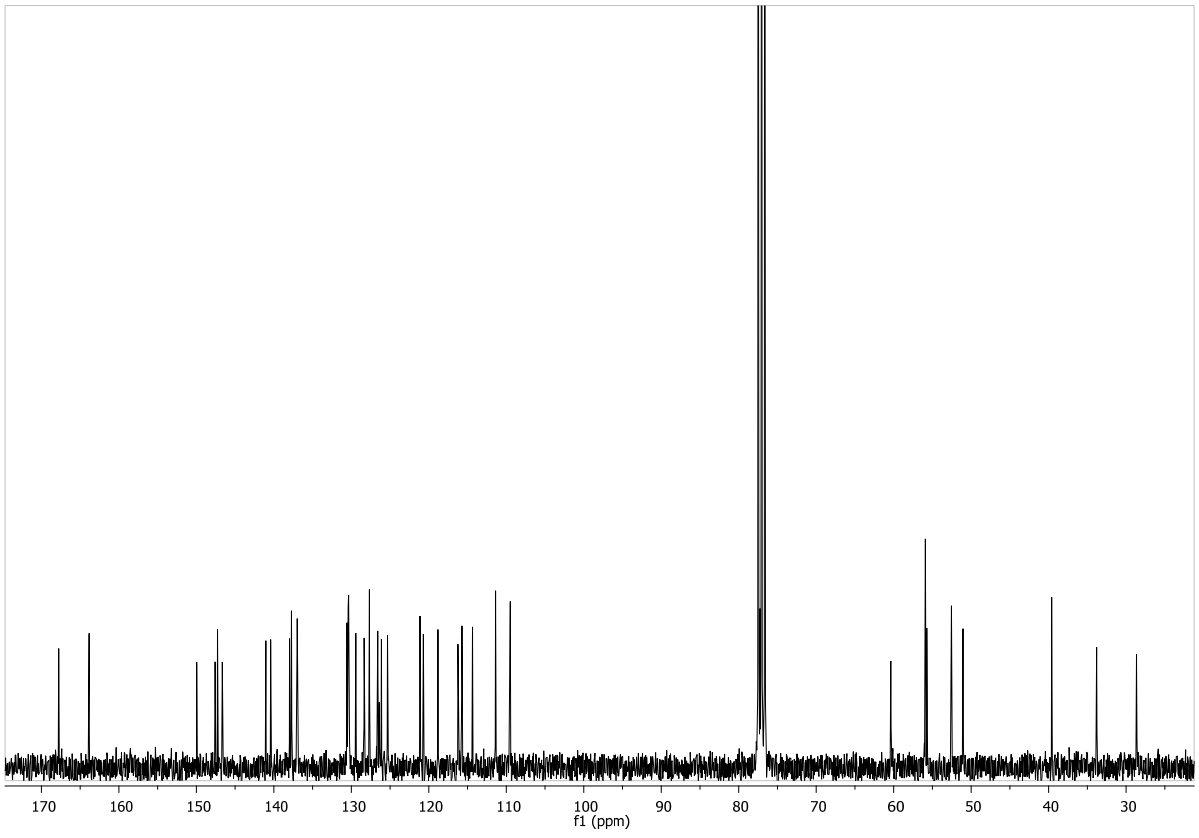
Methyl 4-(5-((3,4-dihydroisoquinolin-2(*1H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24a



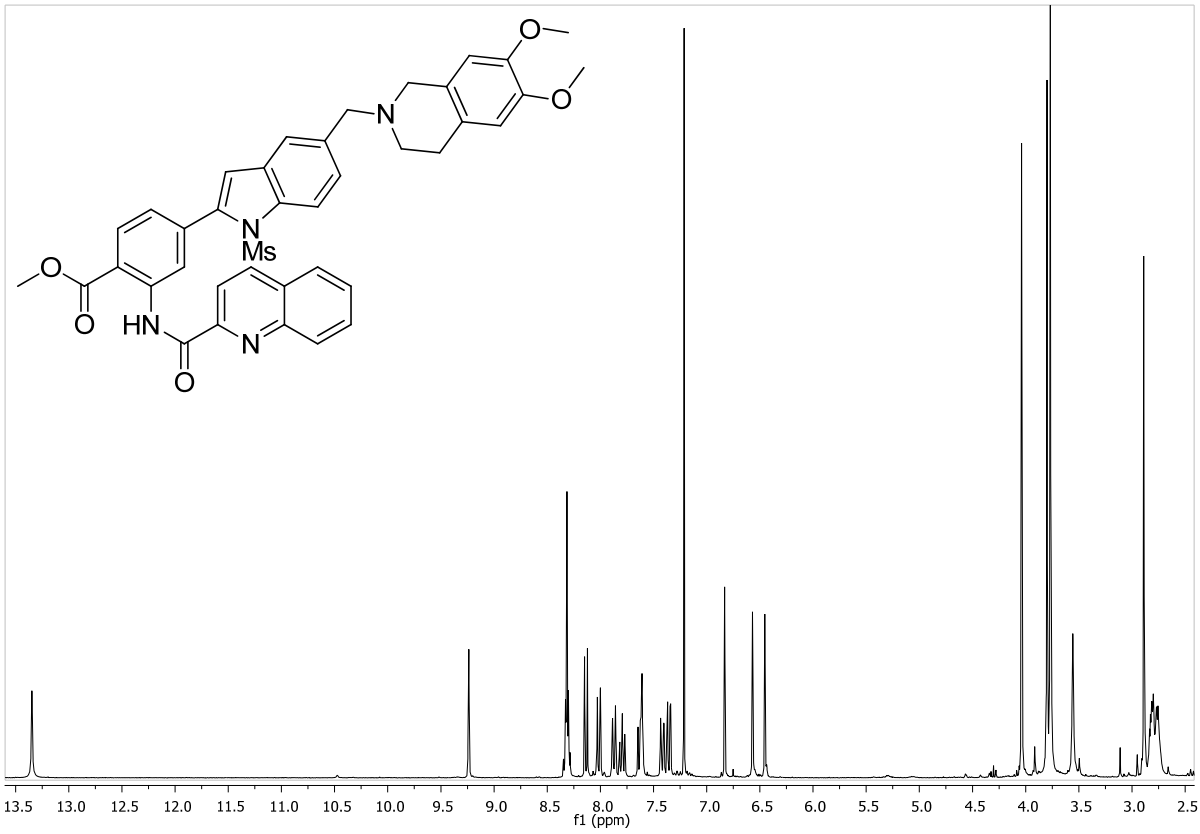


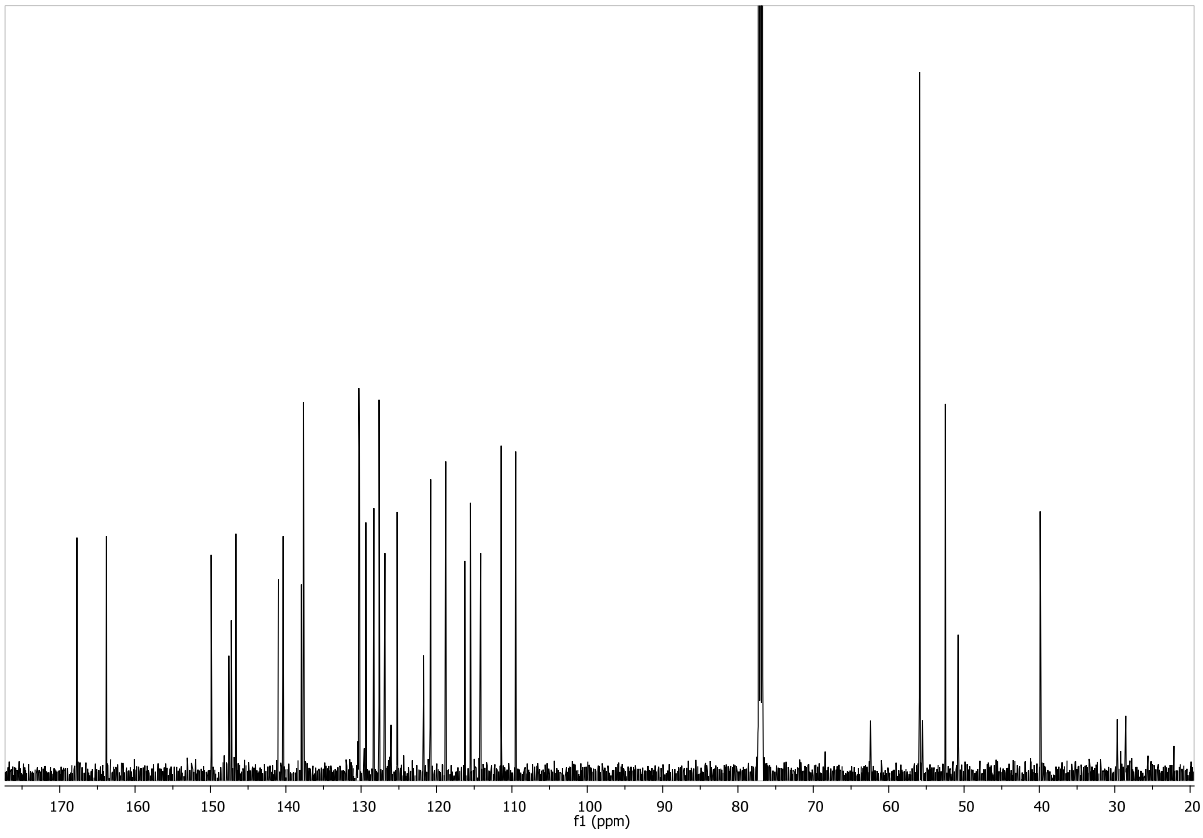
Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24f



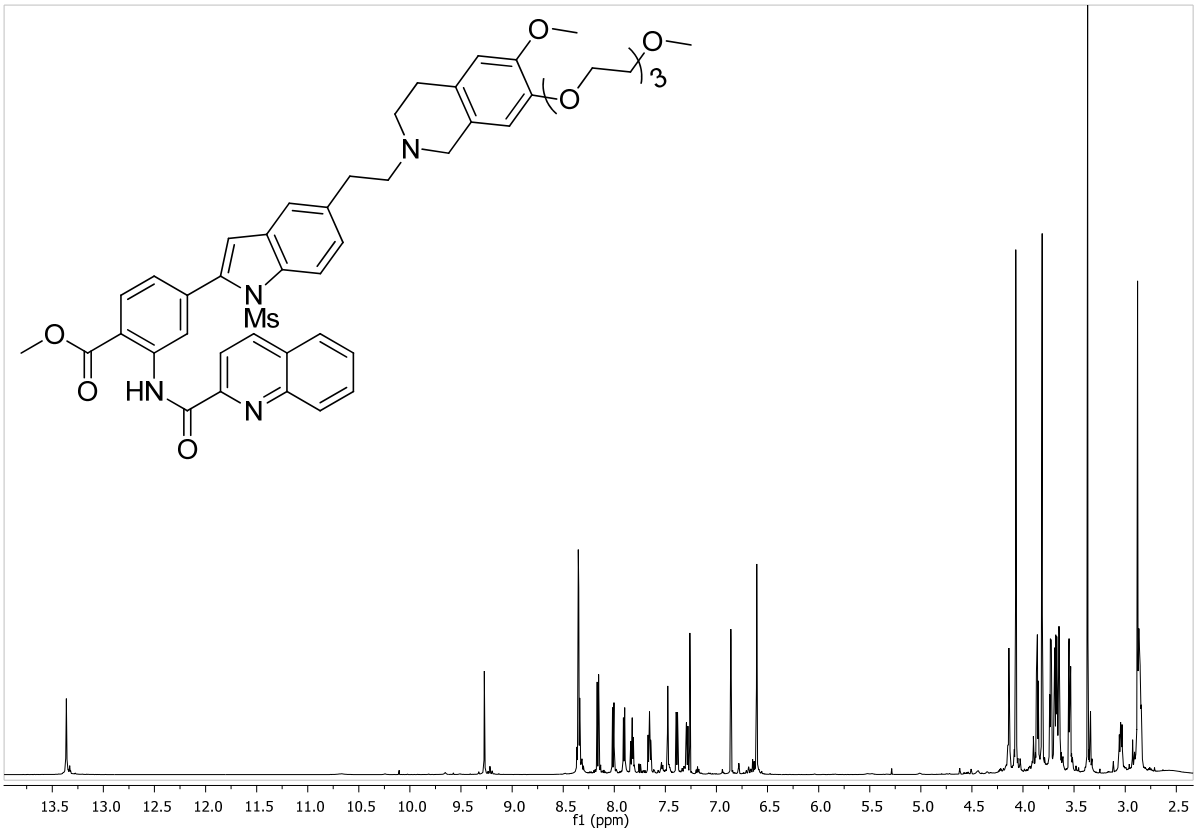


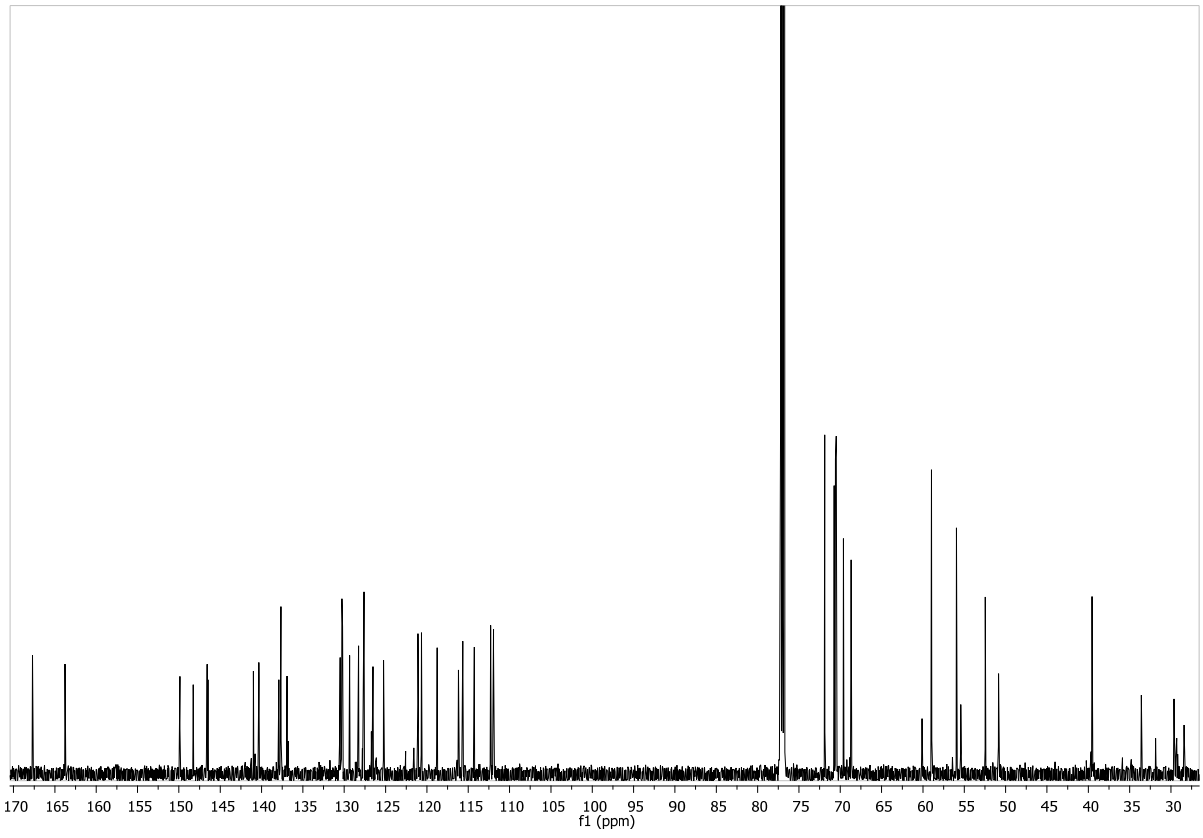
Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24b



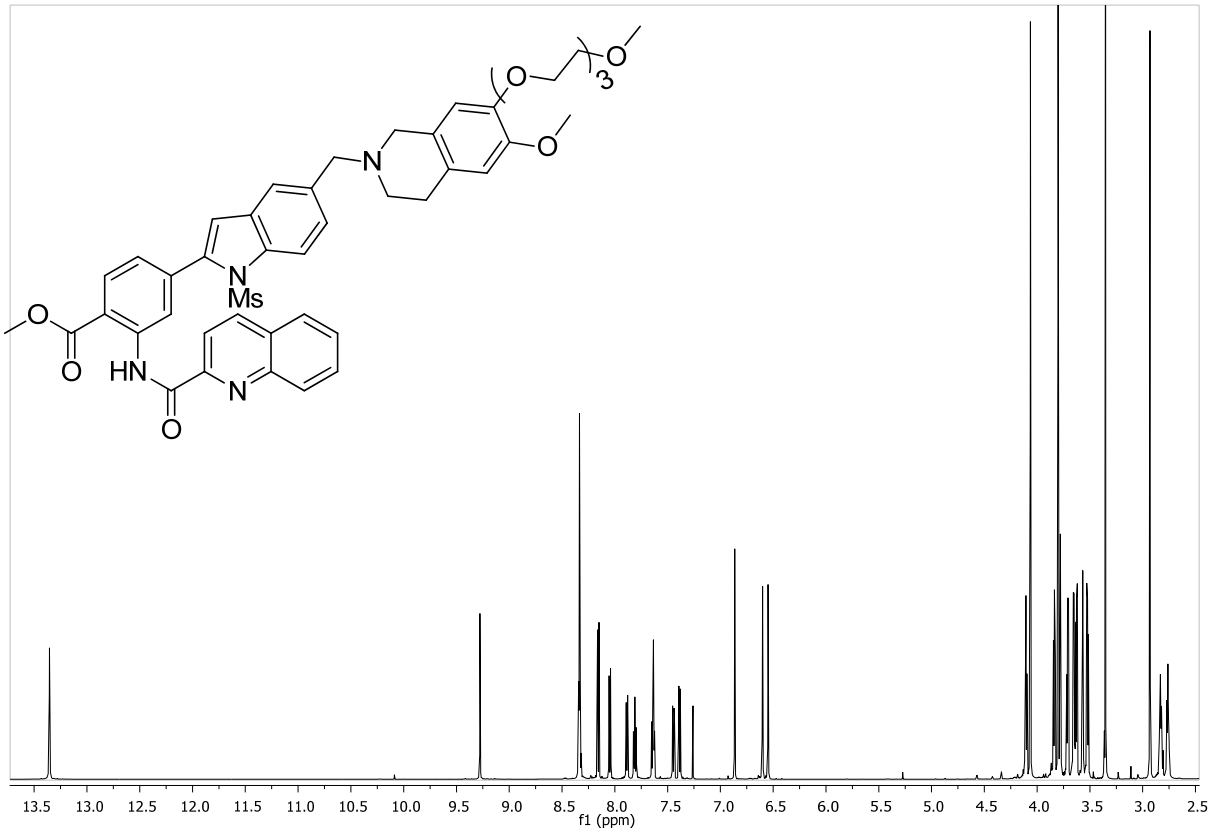


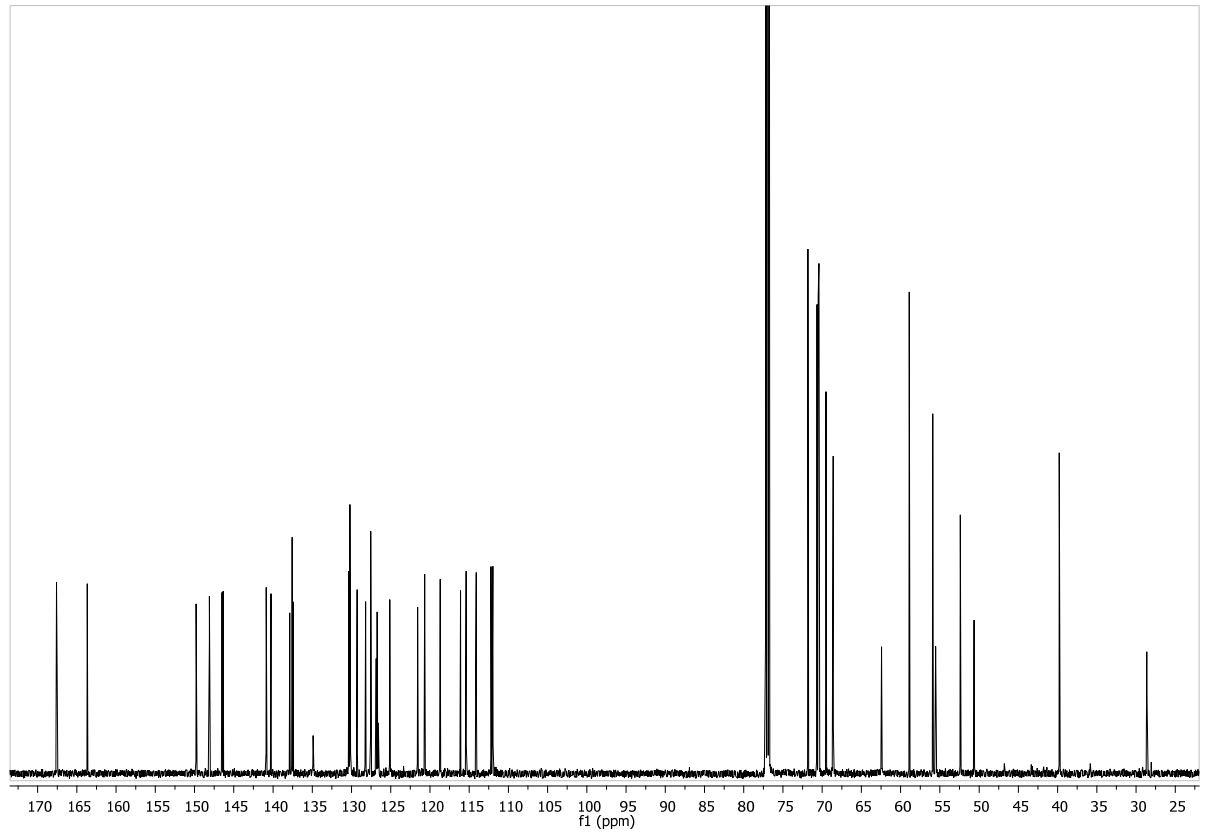
Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24g



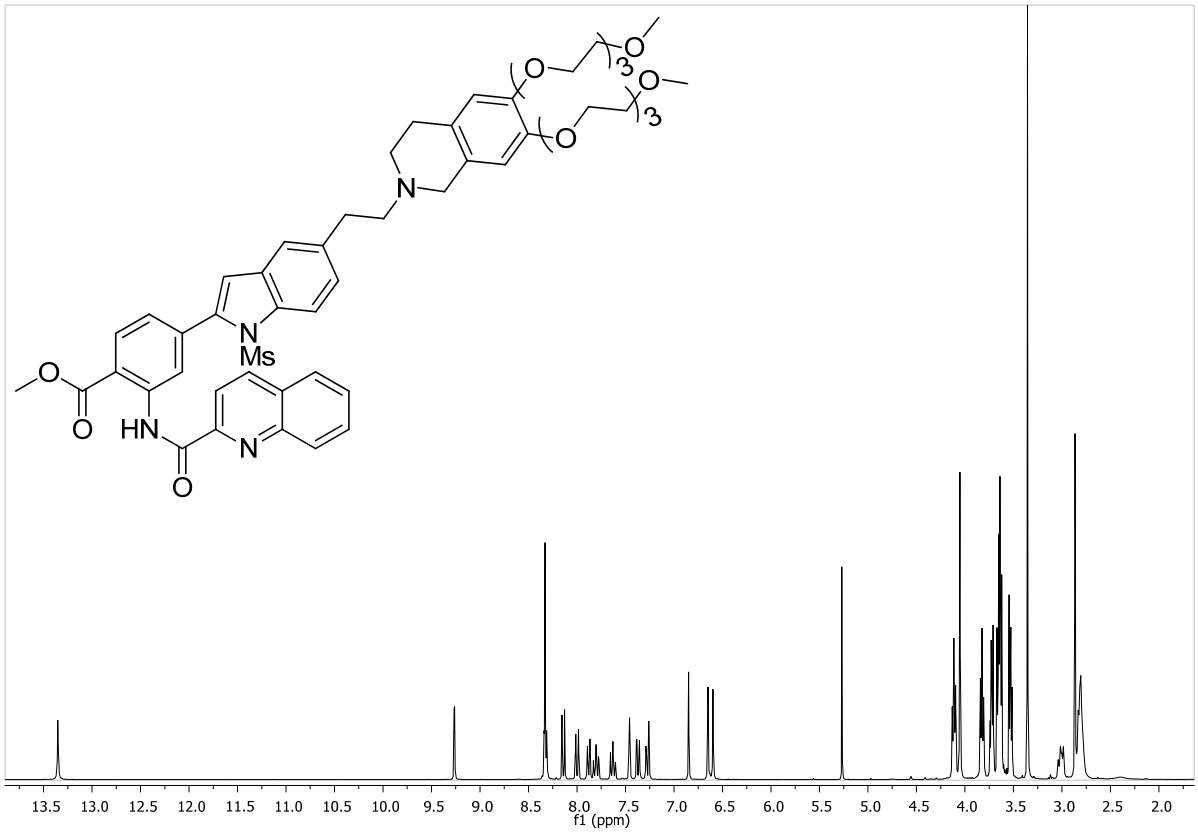


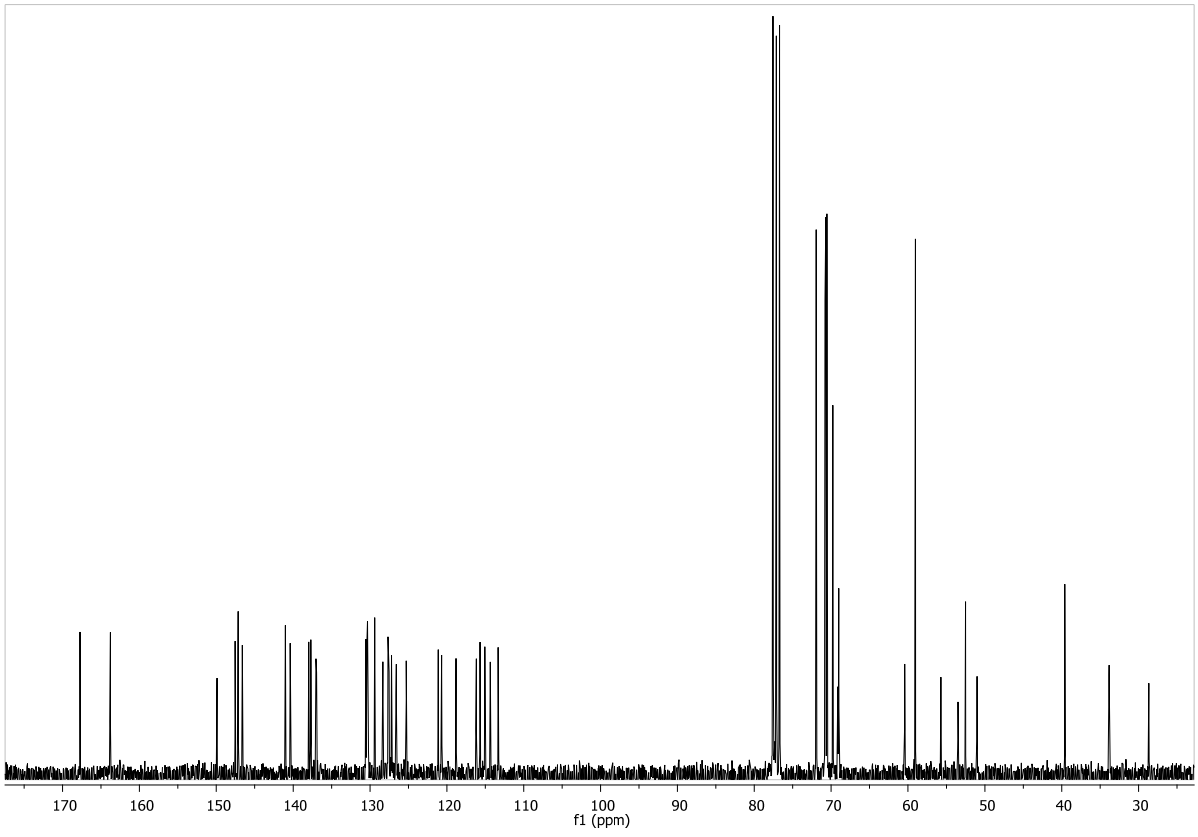
Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24c



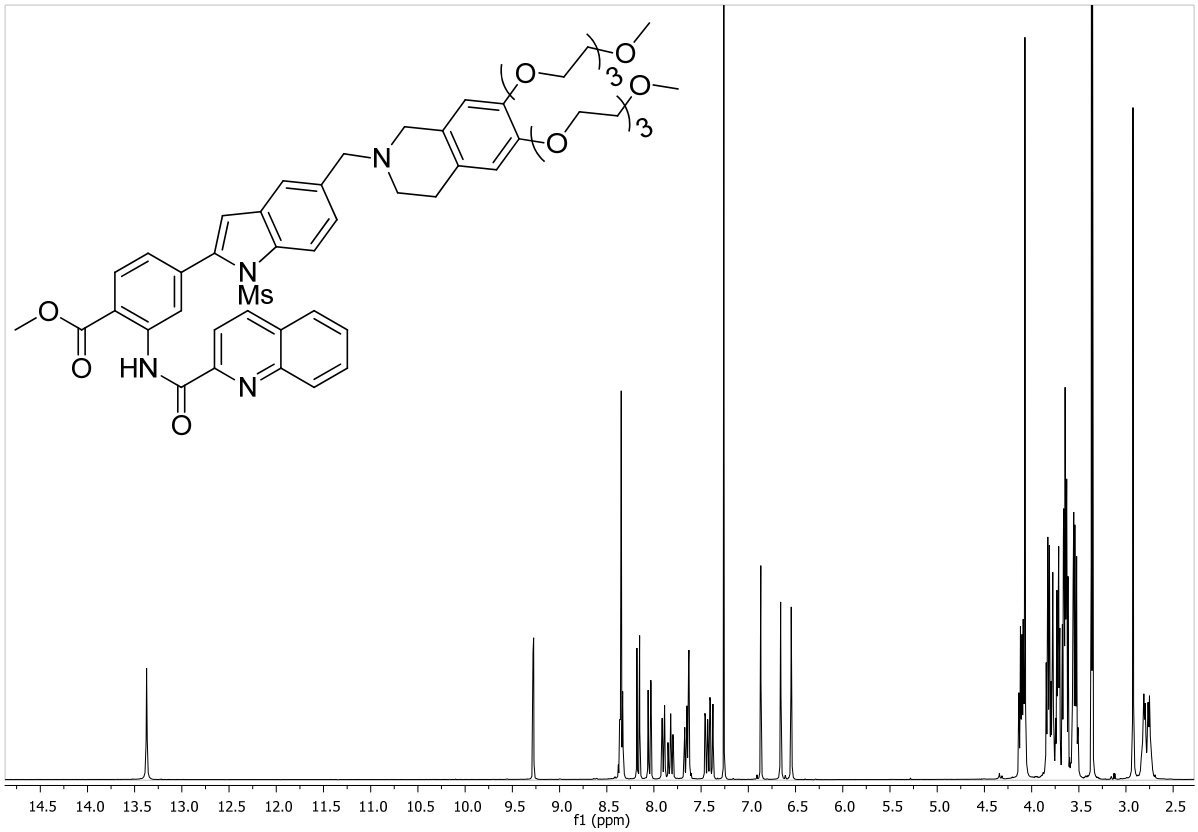


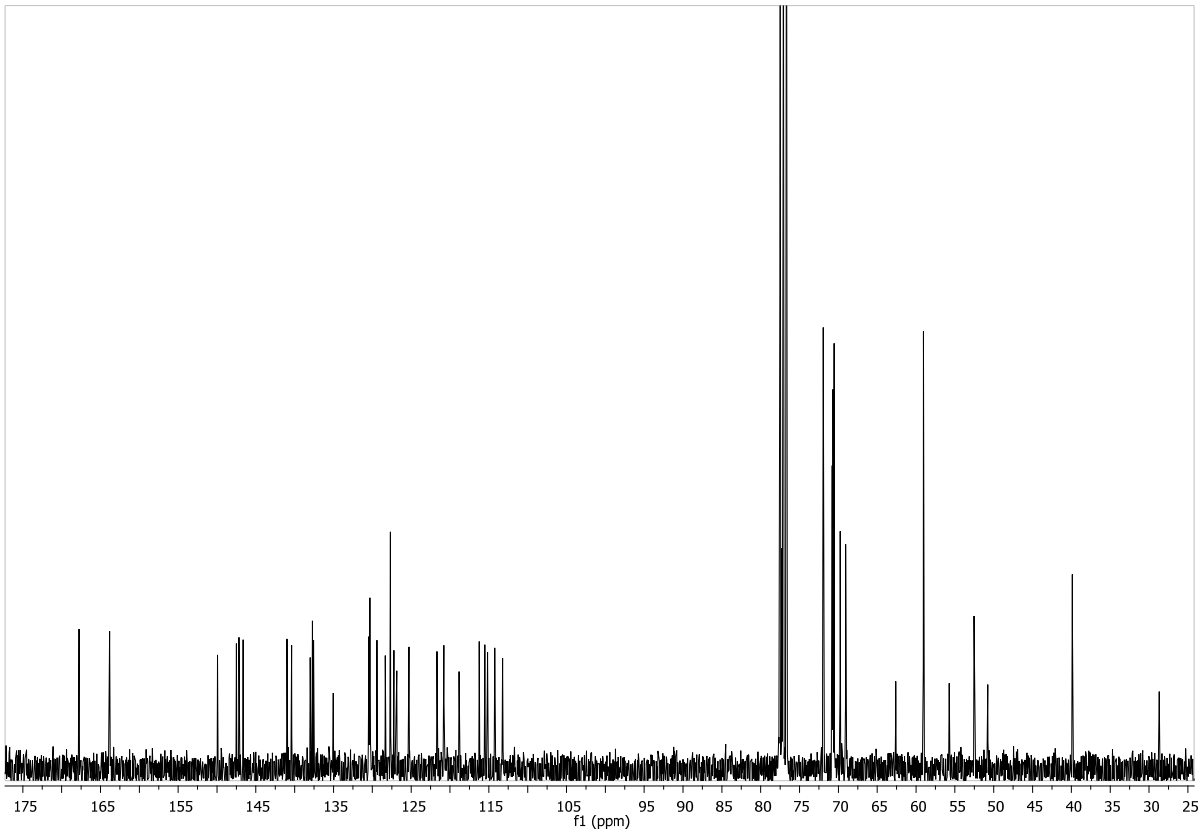
Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24h



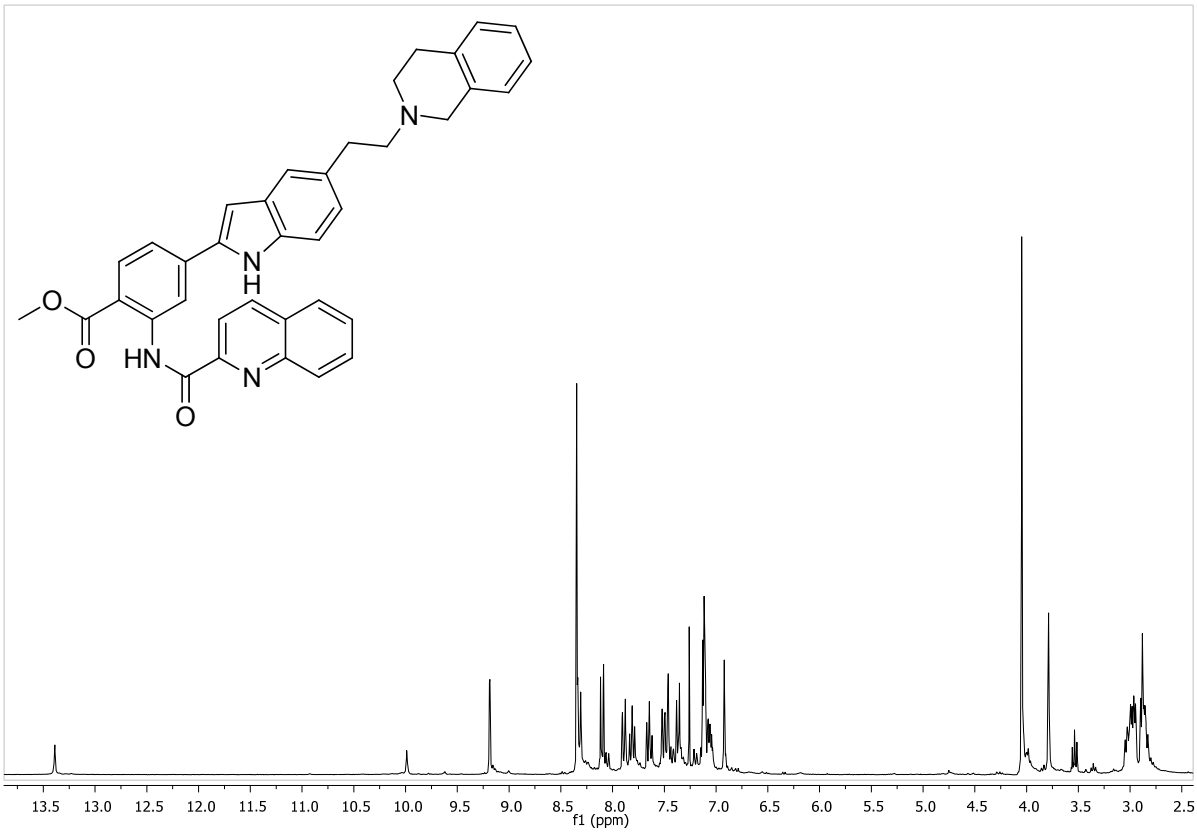


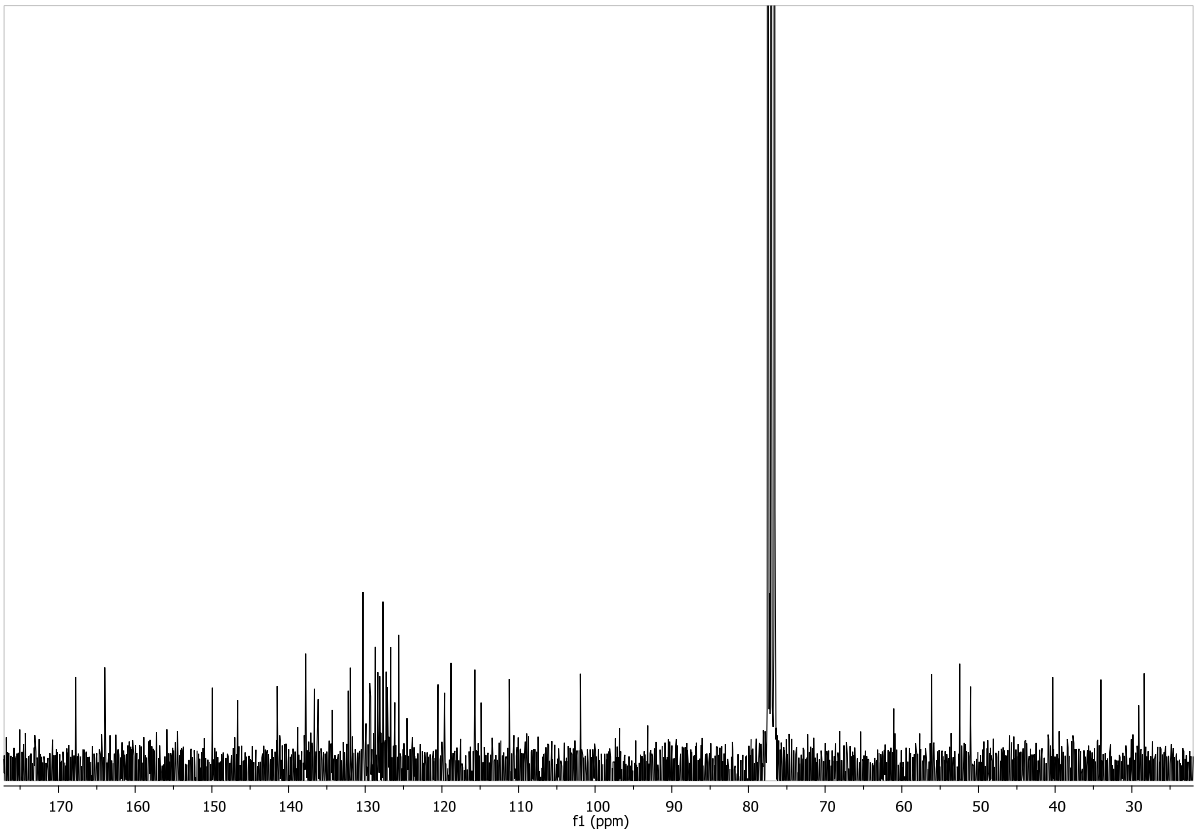
Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1-(methylsulfonyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 24d



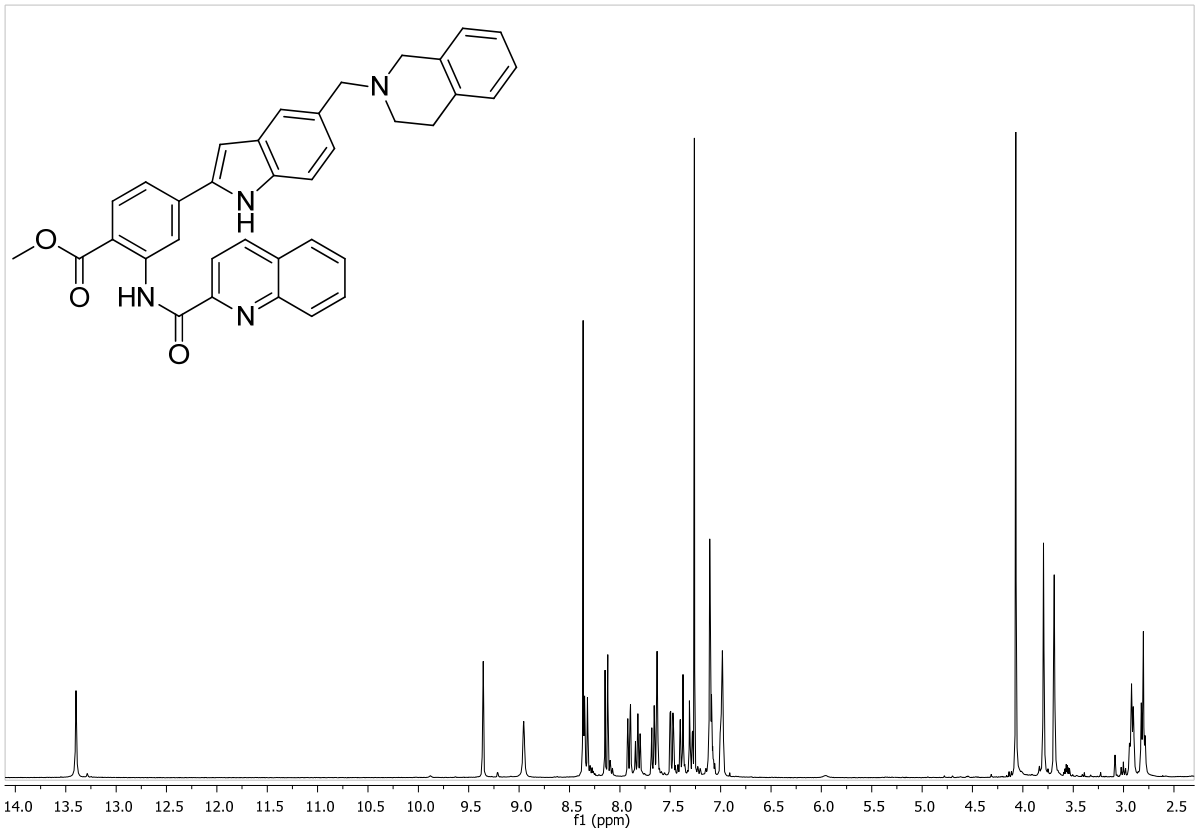


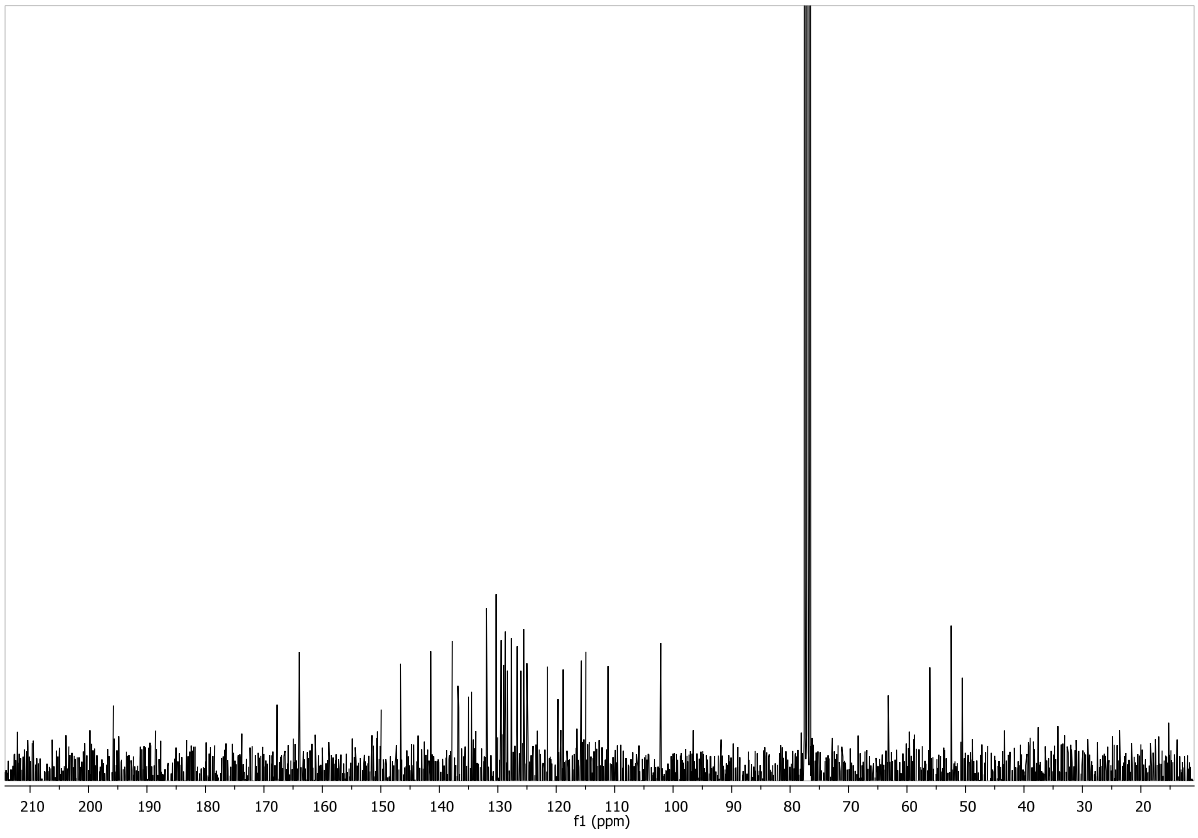
Methyl 4-(5-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonyl-amino)benzoate 25e



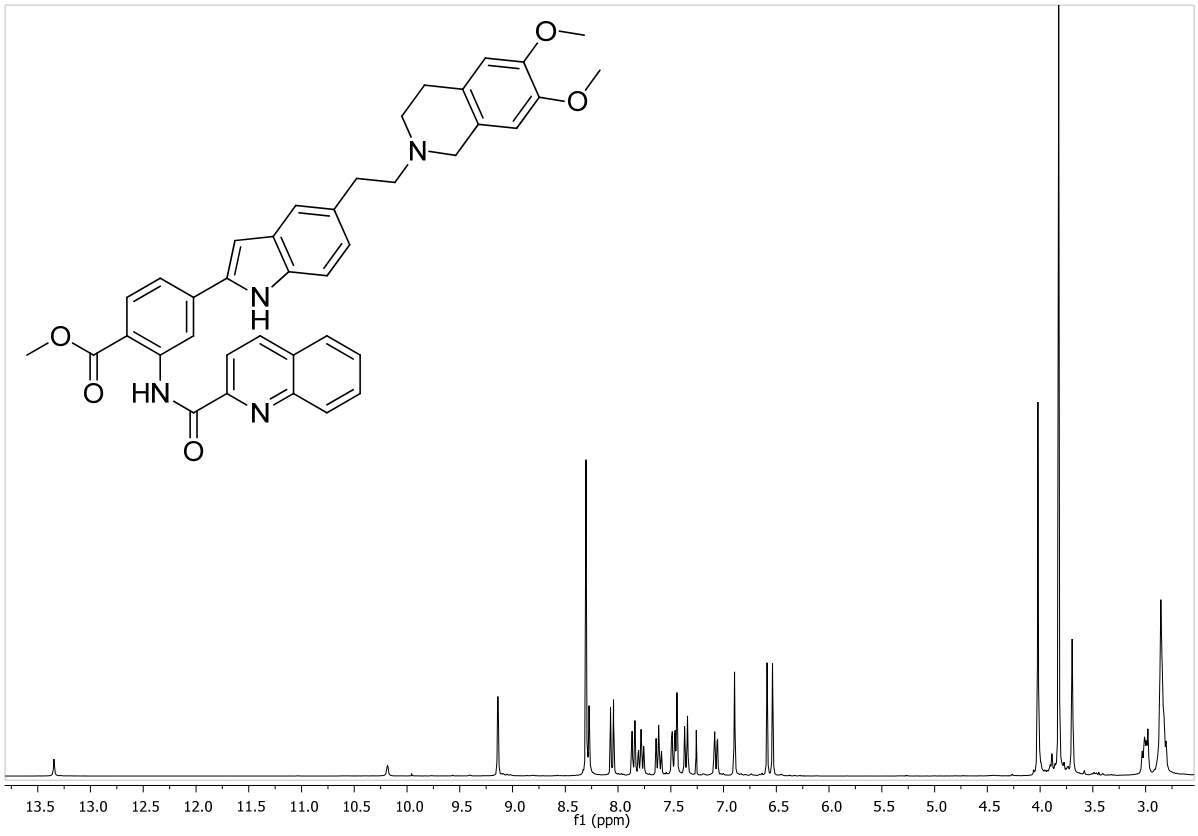


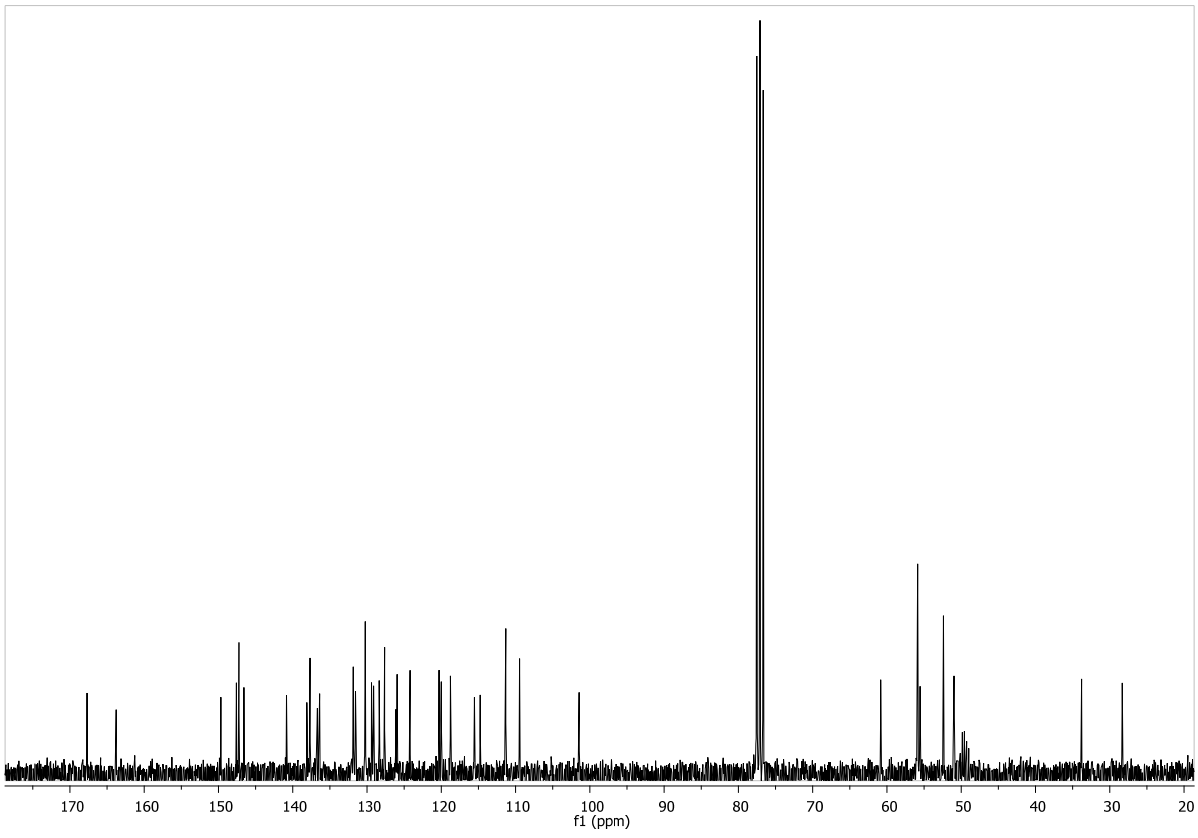
Methyl 4-(5-((3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonyl-amino)benzoate 25a



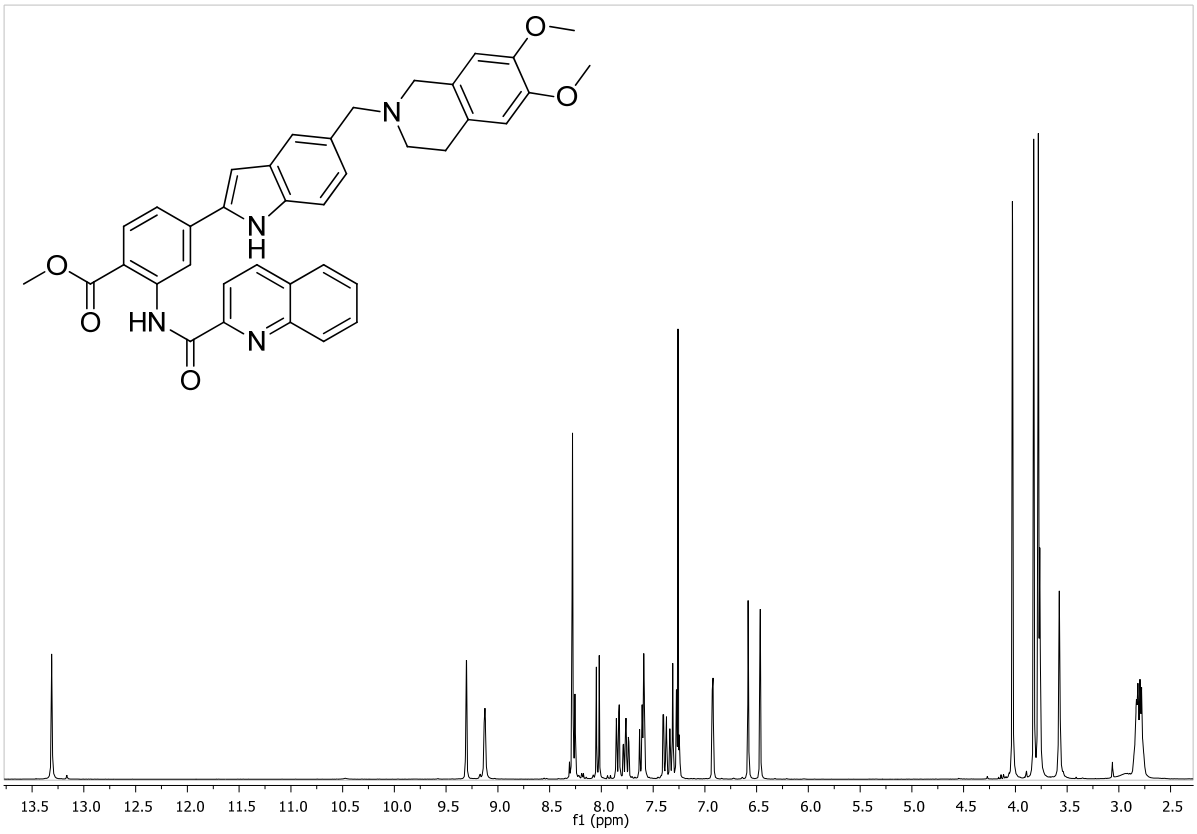


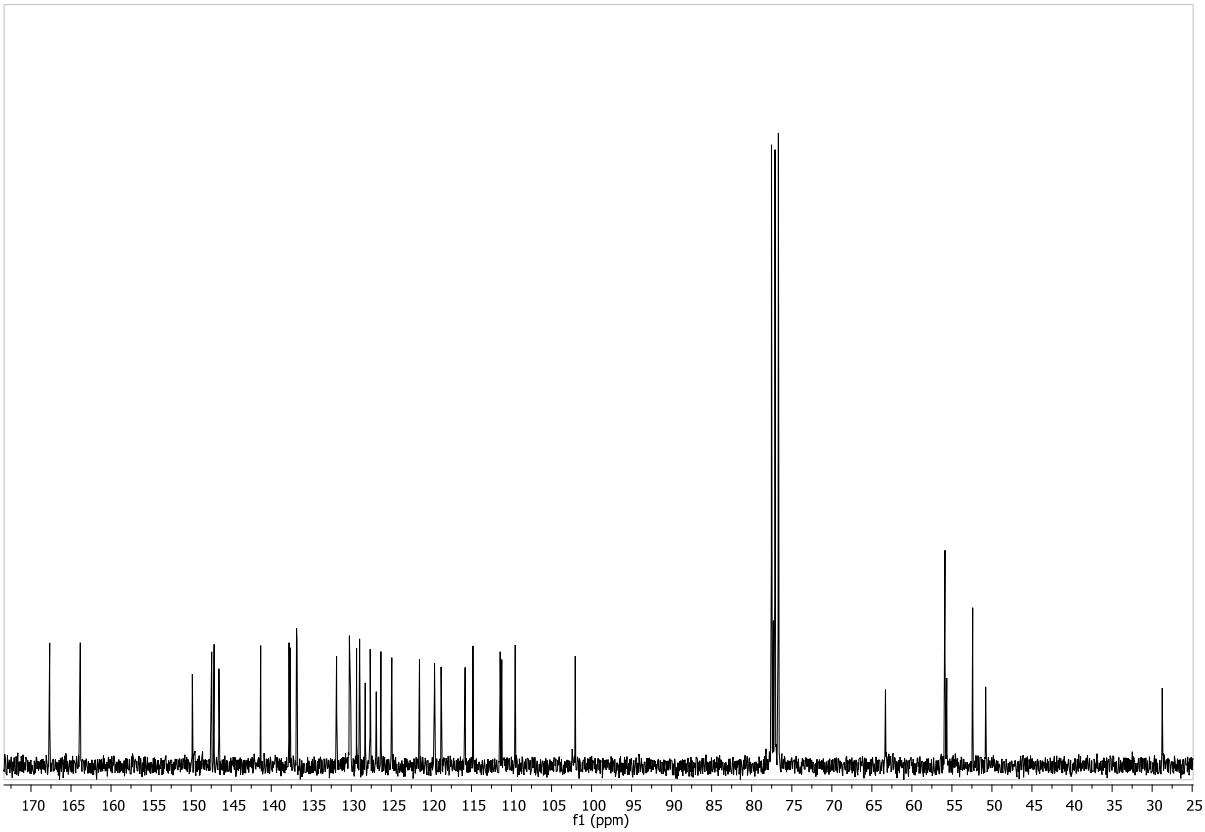
Methyl 4-(5-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25f



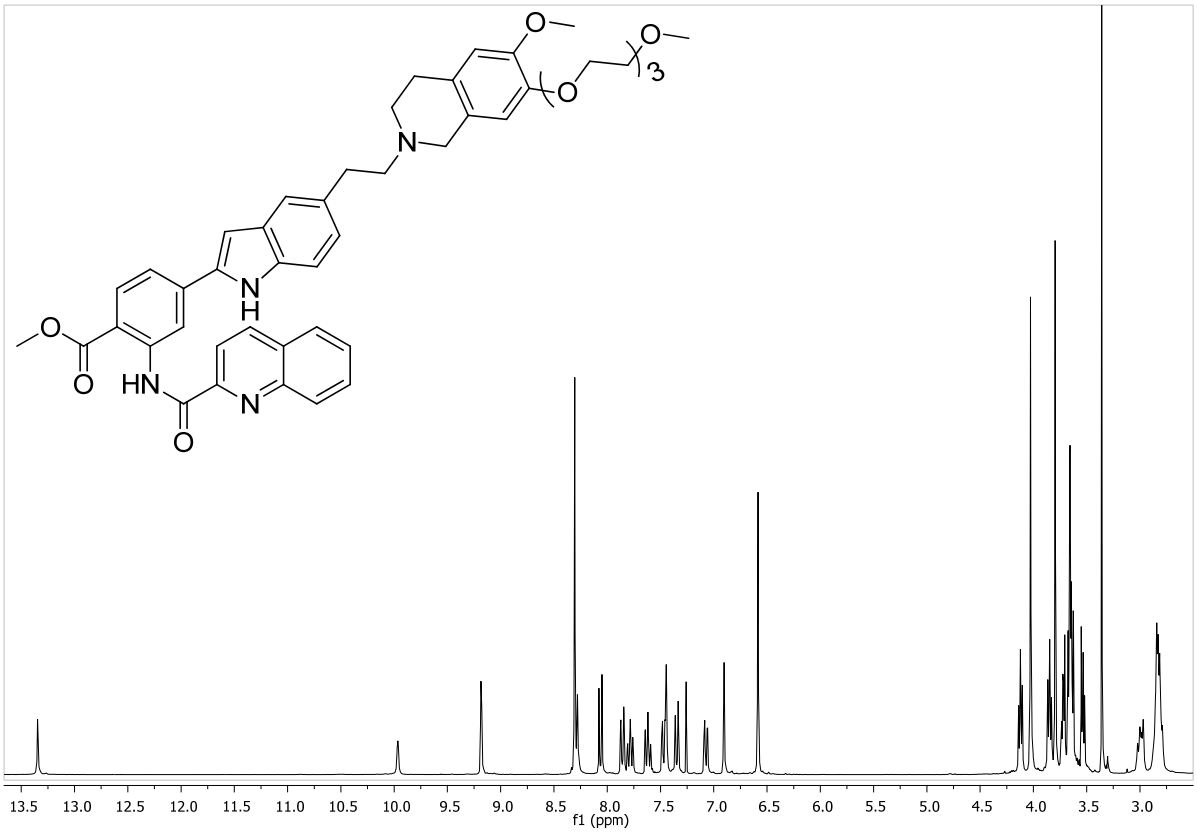


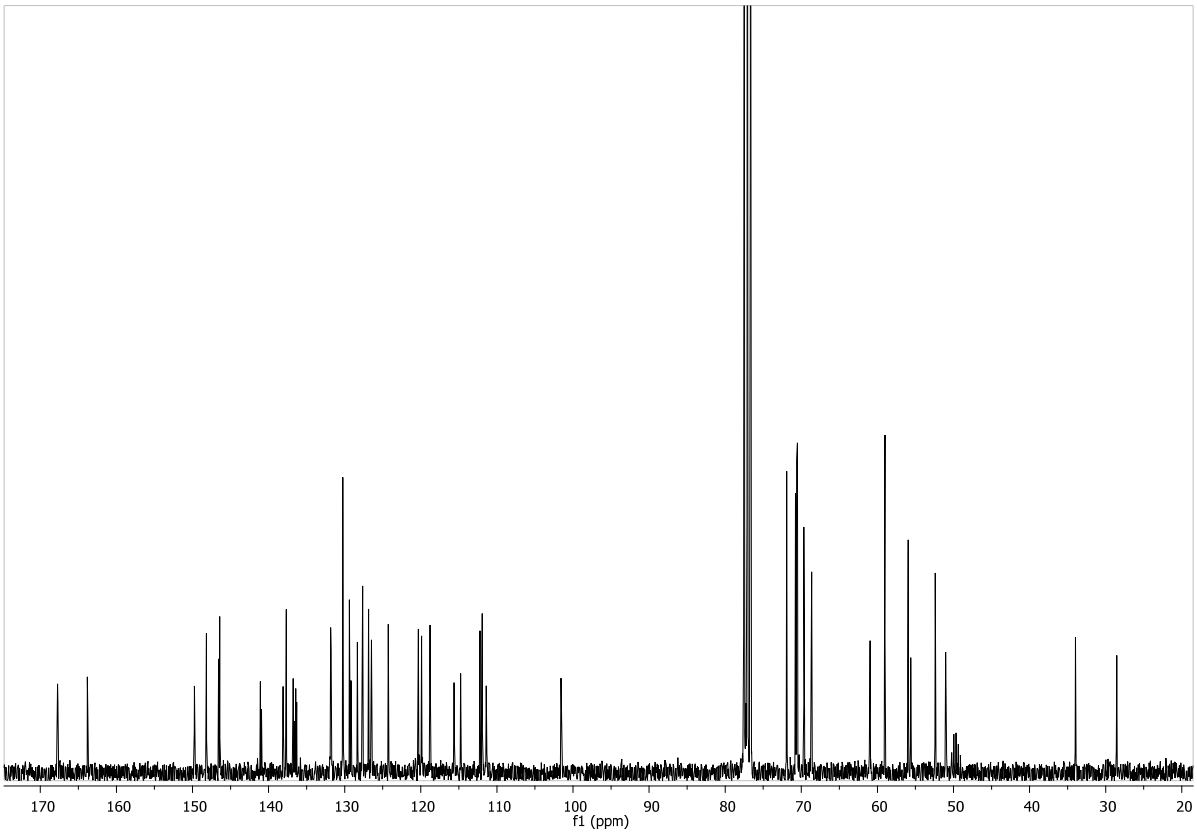
Methyl 4-(5-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25b



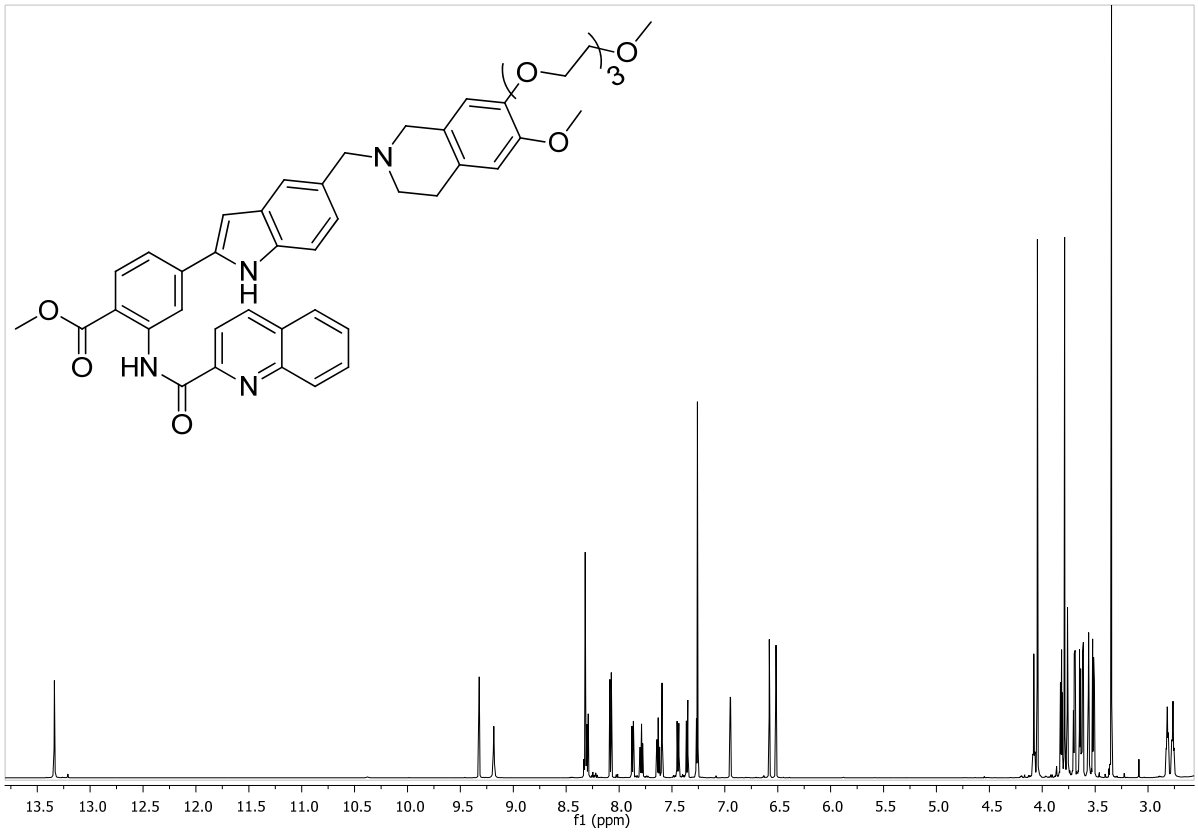


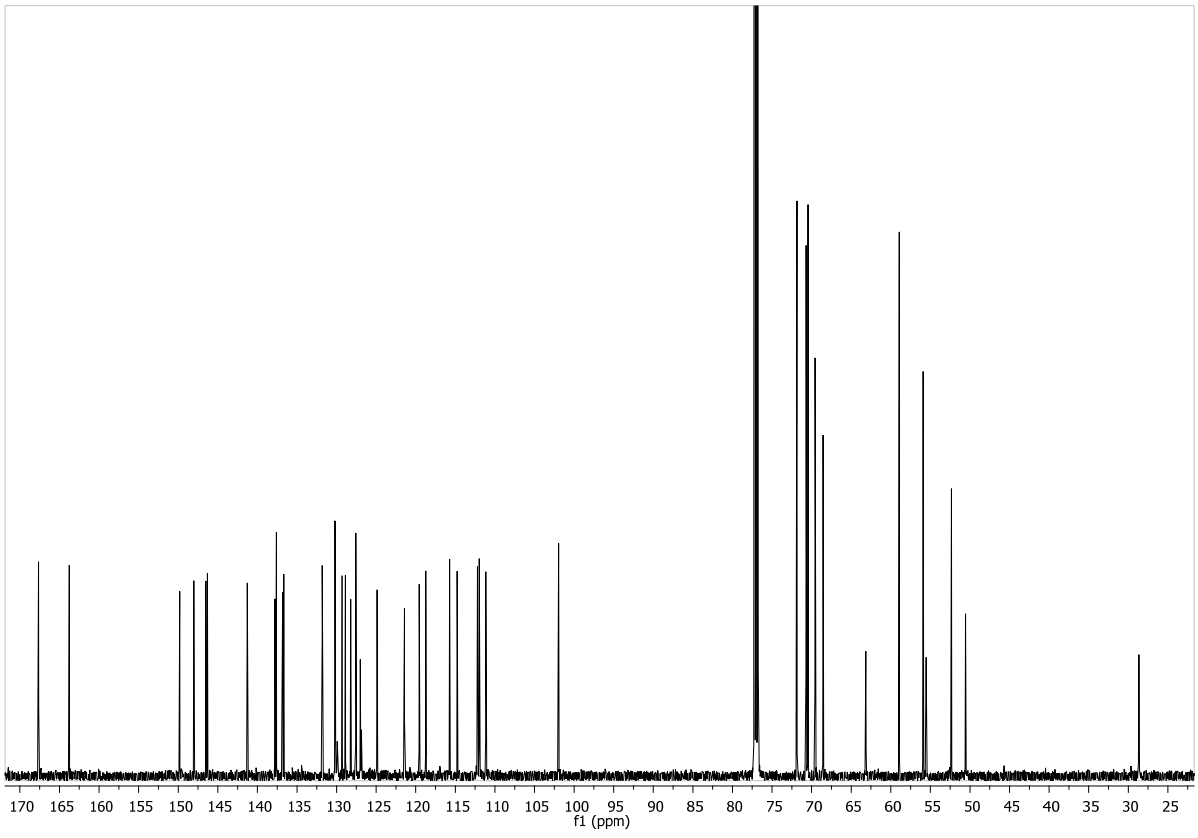
Methyl 4-(5-(2-(6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25g



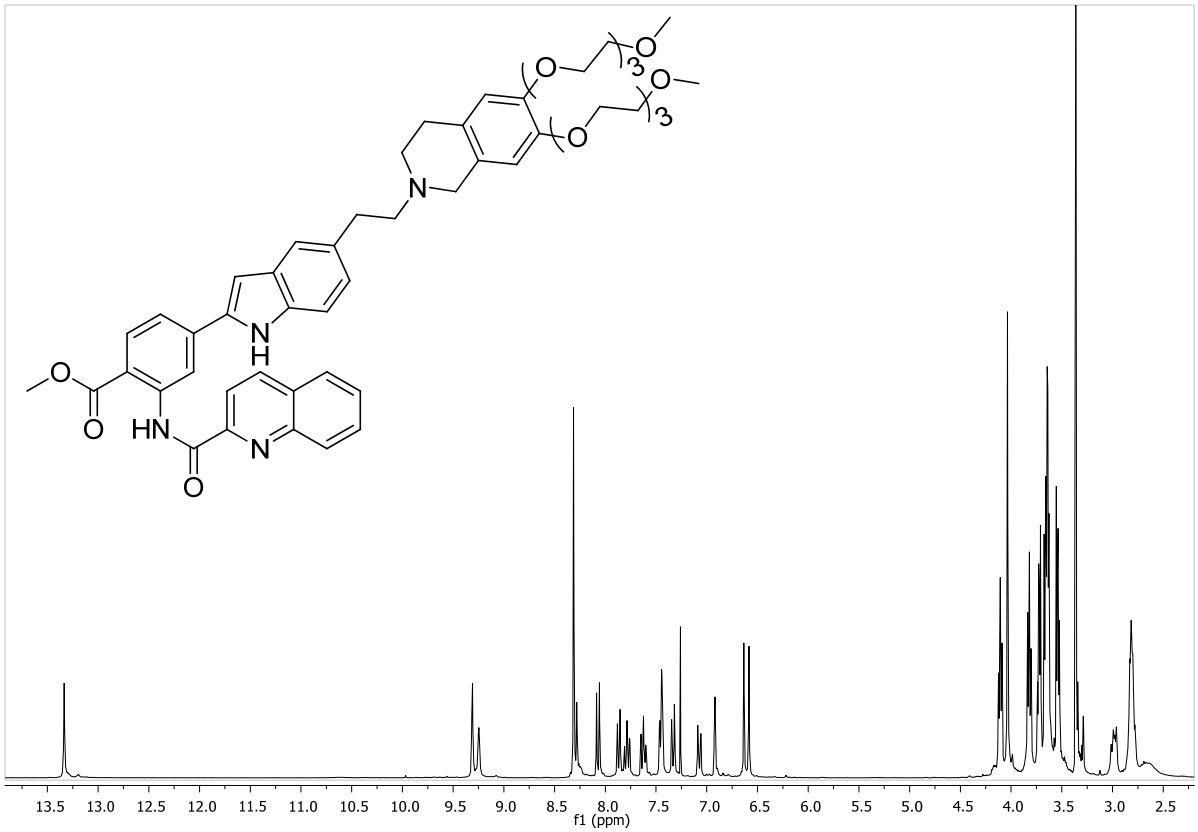


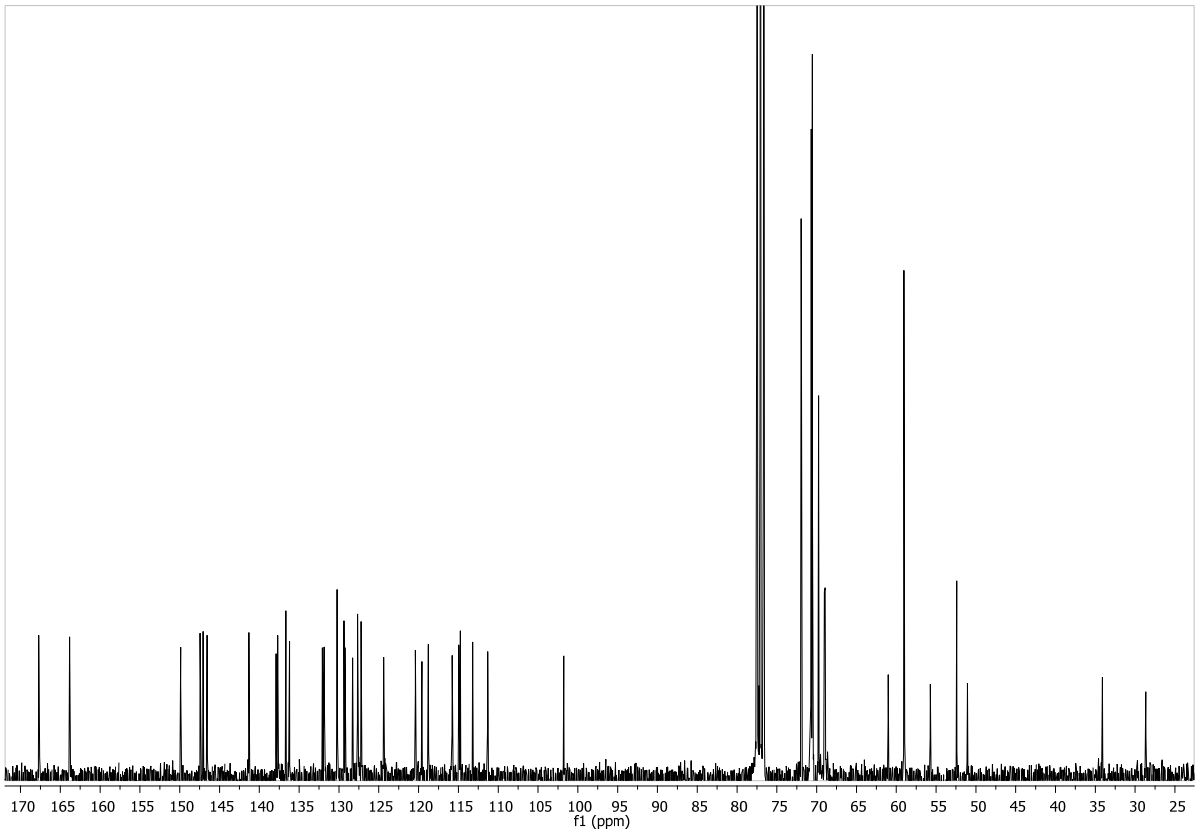
Methyl 4-(5-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25c



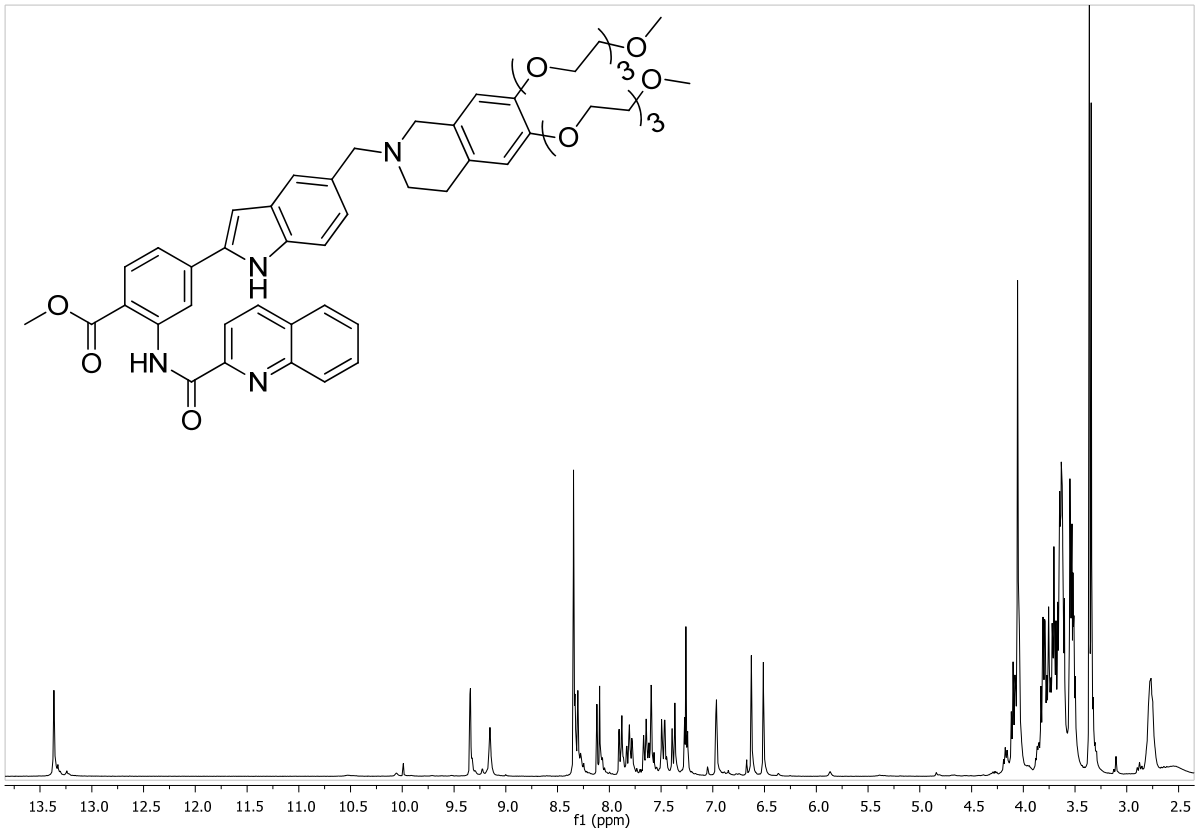


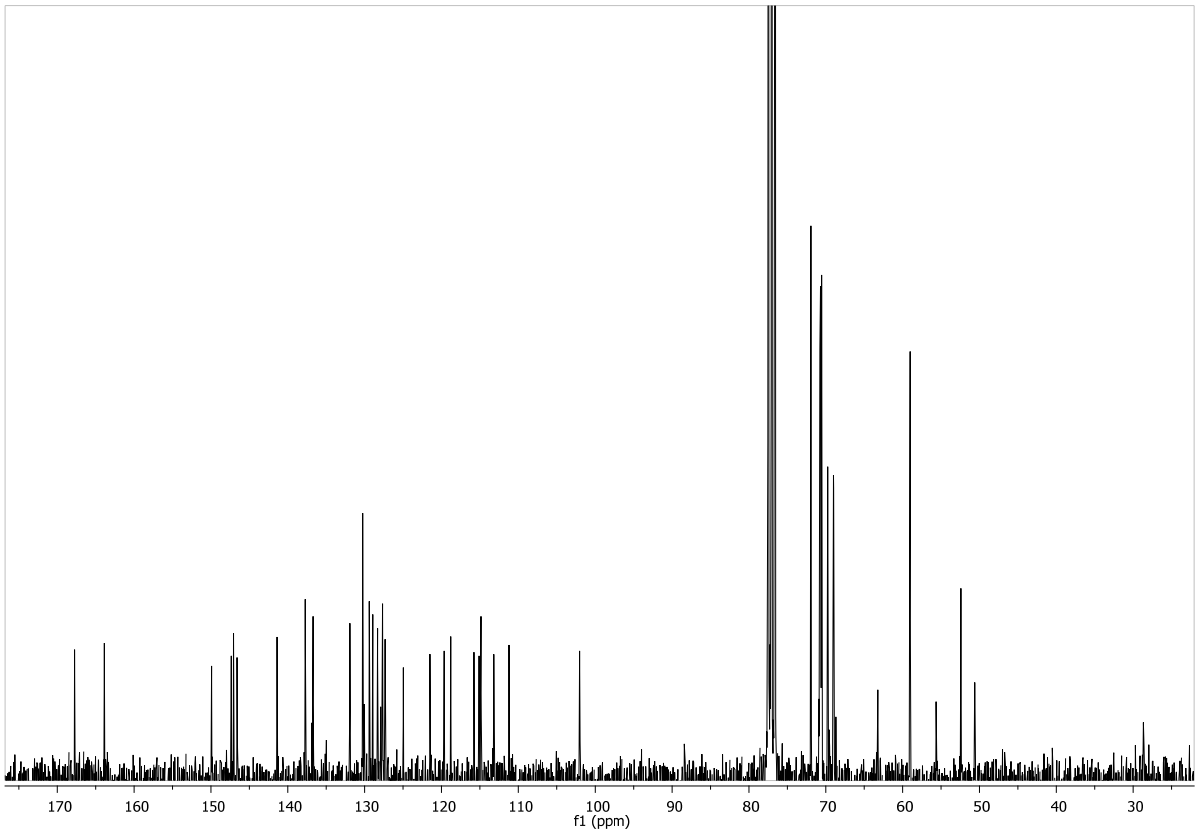
Methyl 4-(5-(2-(6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)-1*H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25h





Methyl 4-(5-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-*1H*-indol-2-yl)-2-(quinoline-2-carbonylamino)benzoate 25d



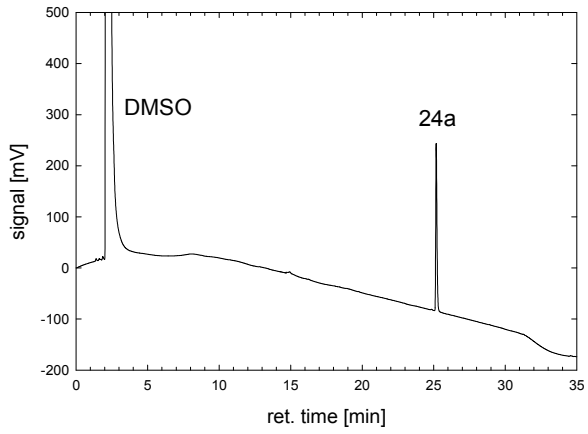


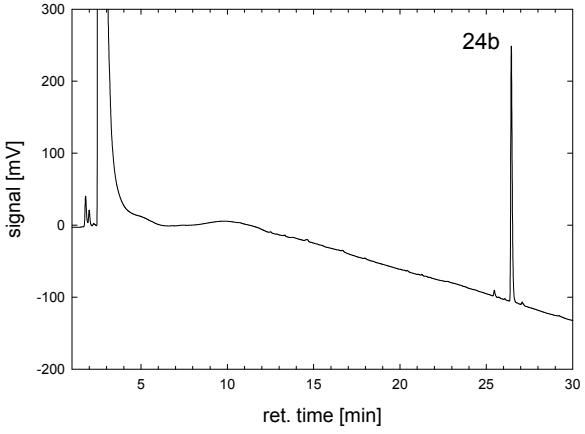
2.3 HPLC analysis of compounds 24a-g and 25a-h

The compounds (dissolved in DMSO) were analyzed by RP-HPLC performed with a Waters (Eschborn, Germany) system composed of a 600S controller and pump, a degasser, a temperature control module, a 717 plus autosampler and a 2487 UV-detector. A Luna RP-18 (Phenomenex, Aschaffenburg, Germany) analytical column (3 µm, 150 mm x 4.6 mm) thermostatted at 30 °C with a flow rate of 1.0 mL/min was used. The following gradient was applied: MeCN/0.05% TFA (aq.): 0 min: 15/85, 25 min: 85/15, 26 min: 95/5, 36 min: 95/5, 37 min: 15/85, 45 min: 15/85. UV-detection was performed at 210 nm.

Table 1. Purities of key compounds

compound	purity [%]	capacity factor k'
24a	99	13.8
24b	96	14.6
24c	99	13.6
24d	99	13.2
24e	99	14.1
24f	99	13.6
24g	97	13.7
25a	98	14.3
25b	97	13.8
25c	99	13.7
25d	98	13.7
25e	97	14.7
25f	97	14.7
25g	96	14.4
25h	96	14.0





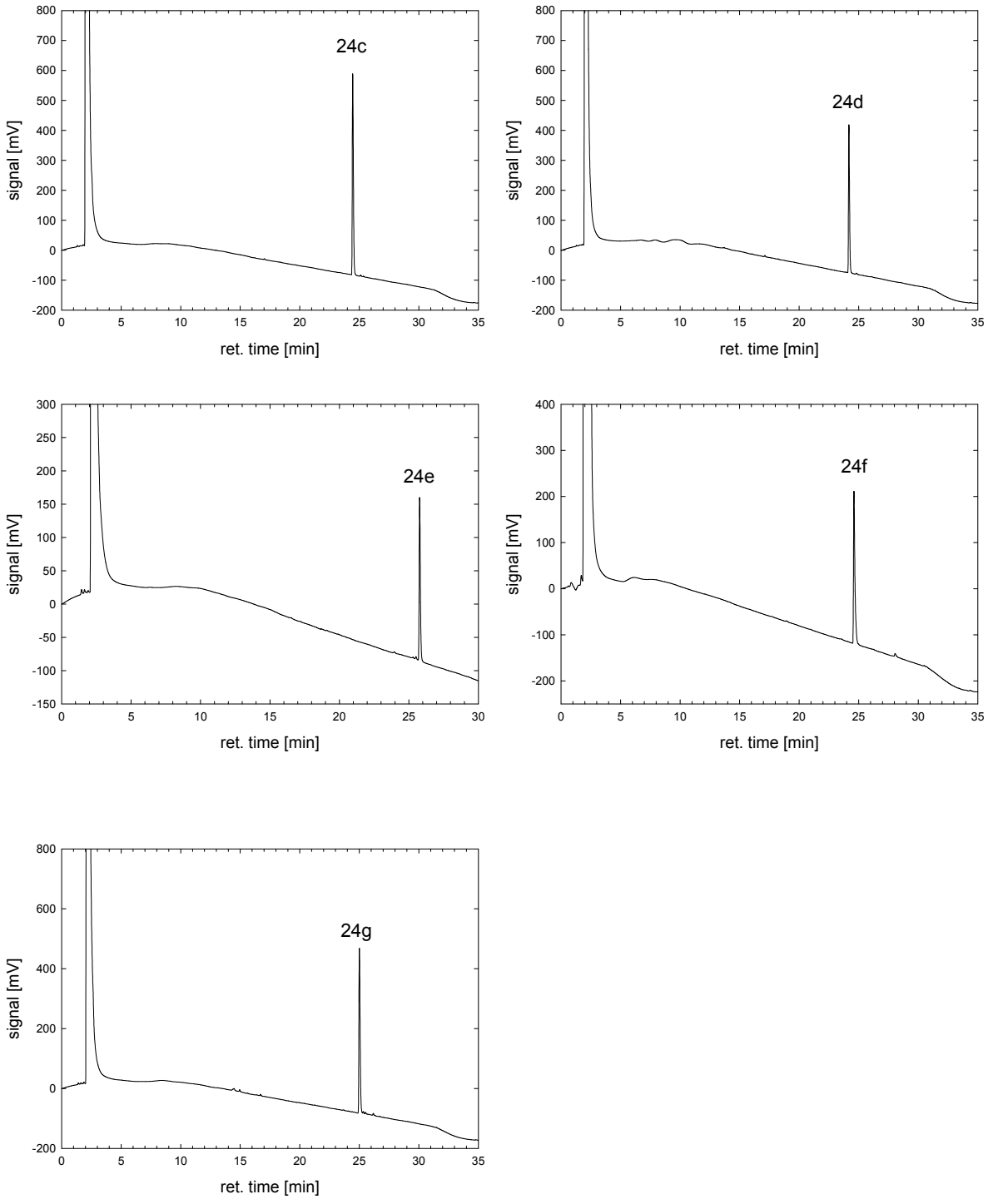
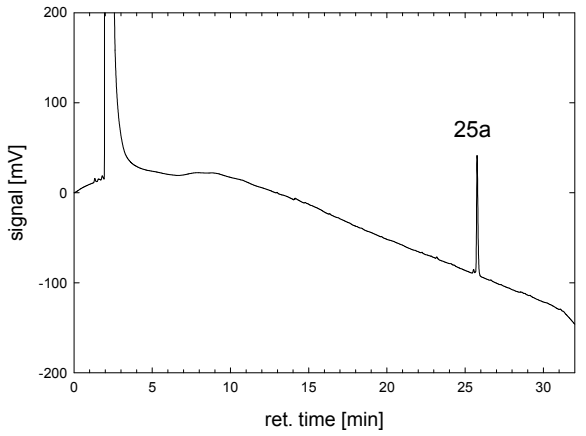
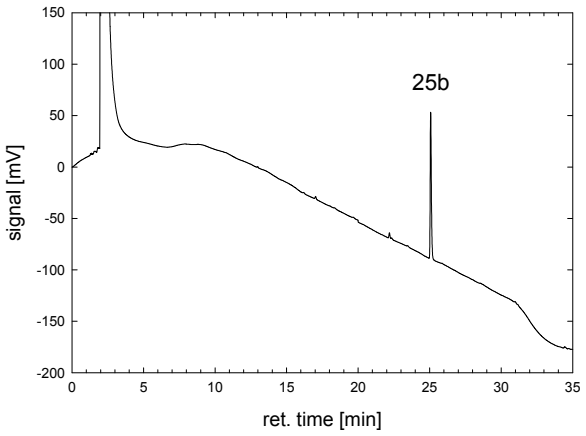
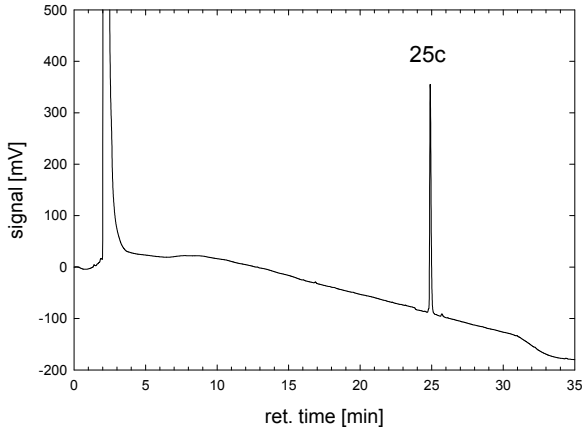
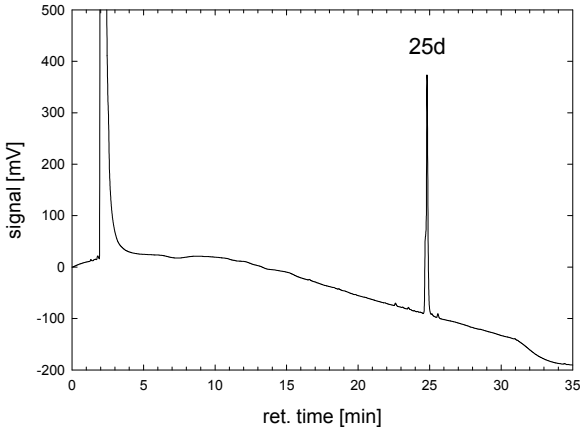


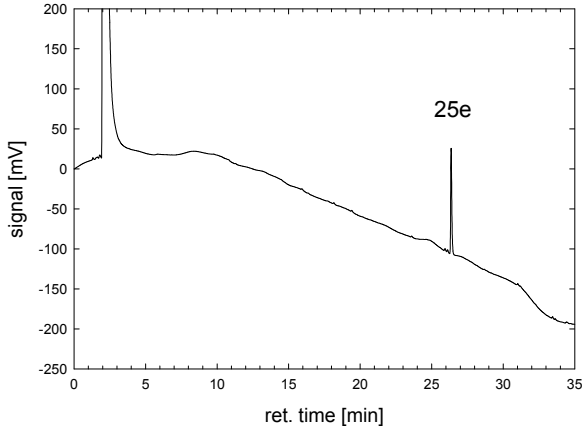
Figure 1. HPLC analysis of compounds **24a-g** (UV-detection at 210 nm).

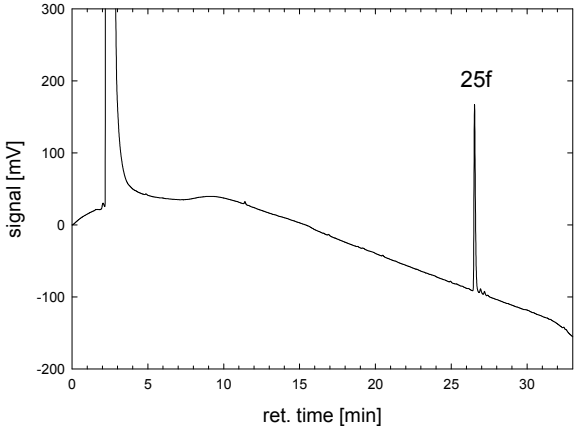

25a
signal [mV]
ret. time [min]


25b
signal [mV]
ret. time [min]


25c
signal [mV]
ret. time [min]


25d
signal [mV]
ret. time [min]


25e
signal [mV]
ret. time [min]


25f
signal [mV]
ret. time [min]

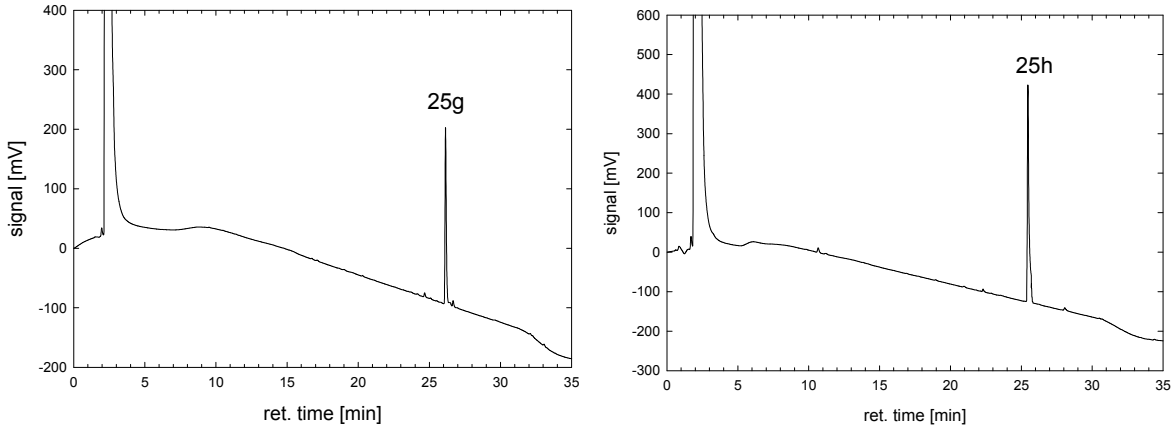
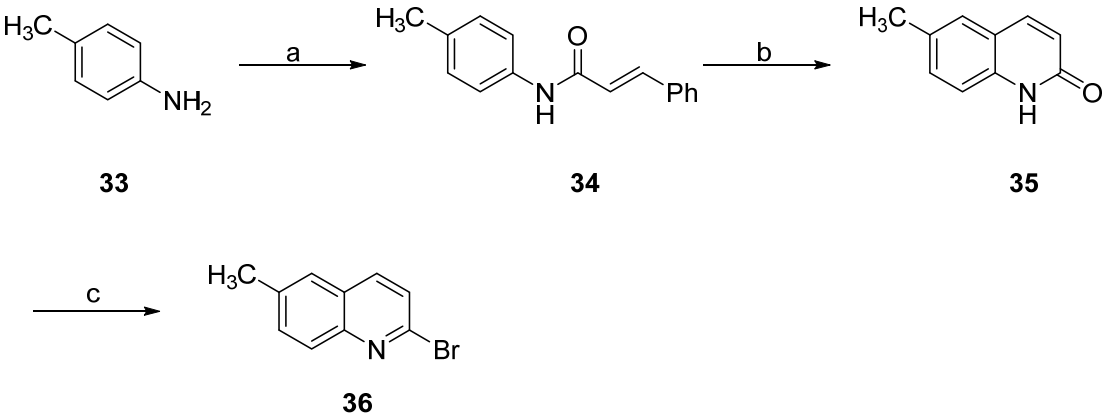


Figure 2. HPLC analysis of compounds **25a-h** (UV-detection at 210 nm).

3 Synthesis of compounds 26-28 and further analogs

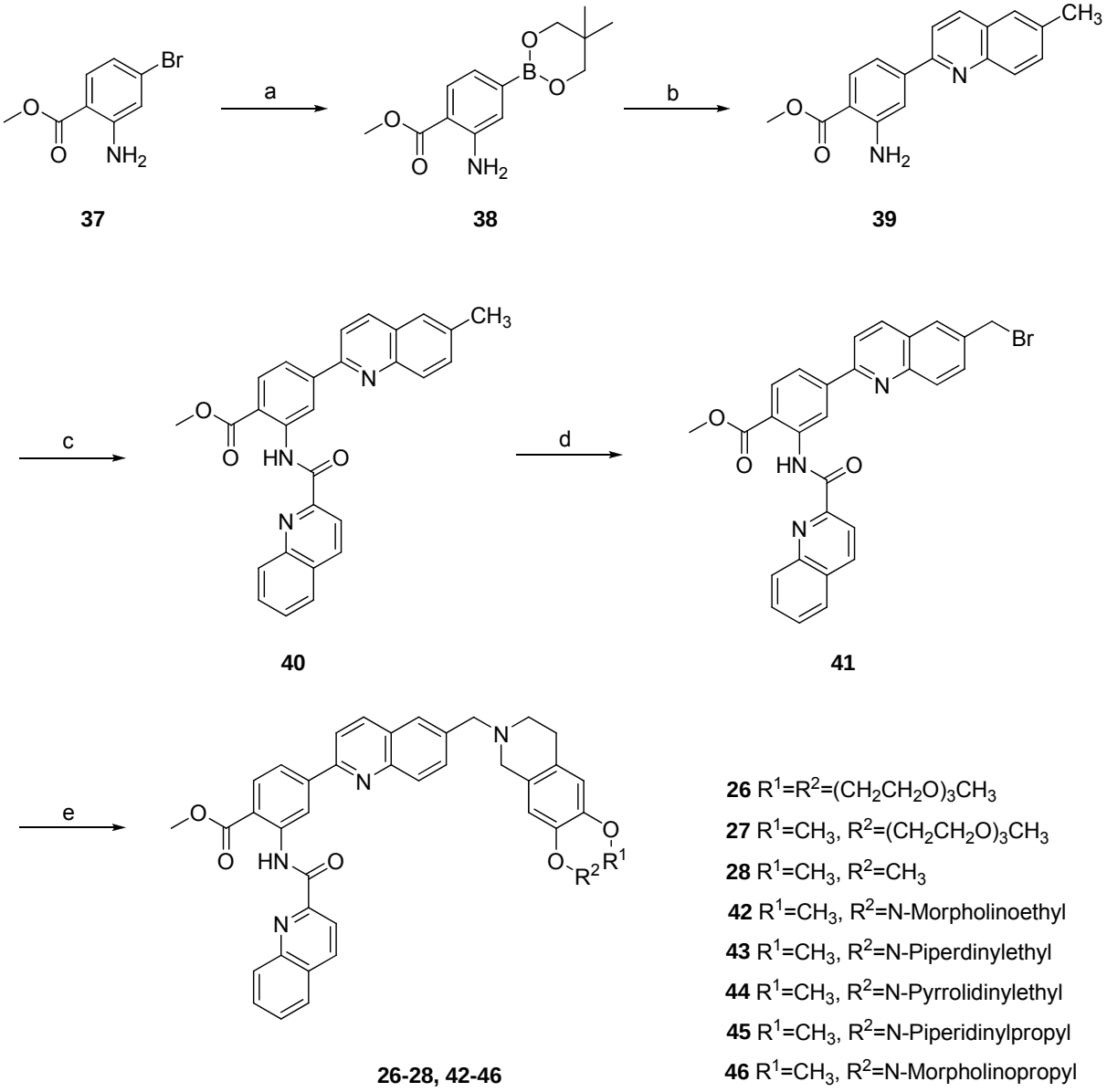
3.1 Experimental details and analytical data



33 **34** **35**

36

Scheme 2: Synthesis of **36**. *Reagents and conditions*: (a) *E*-PhCHCHCOCl, K_2CO_3, water, acetone, 0 °C, 2h; (b) $AlCl_3$, PhCl, 125 °C 24h; (c) $POBr_3$, 140 °C 3h.



Scheme 3: *Reagents and conditions*: (a) $PdCl_2$(dppf), KOAc, DMSO, 80 °C overnight; (b) 2-bromo-6-methylquinoline, $Pd(PPh_3)_4$, K_3PO_4, THF, 80 °C overnight ; (c) quinoline-2-carbonyl chloride, TEA, DCM, 40 °C, overnight; (d) NBS, dibenzoyl peroxide, CCl_4, 80 °C 9h; (e) substituted tetrahydro-isoquinolines, DIPEA, CH_3CN, 80 °C, overnight.

N-(5-Methylphenyl)cinnamamide 34[6]
E-3-Phenylpropenoyl chloride (1.00g, 9.30 mmol) was stirred vigorously with p-toluidine (1.55 g, 9.30mmol) and K_2CO_3 (1.99 g, 14.4 mmol) in water (4.6 mL) and acetone (4.6 mL) at 0 °C for 2 h. The mixture was then poured into ice-water (10 mL). The precipitate gave **34.** Yield: 100%, white powder. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.75 (d, J=15.6Hz, 1H, COCH), 7.50-7.54 (m, 4H, ArH), 7.37-7.39 (m, 3H, ArH), 7.16 (d, J=8.4Hz, 2H, ArH), 6.54(d, J=15.6Hz, 1H, ArCH), 2.33(s, 3H, CH_3).

6-Methylquinolin-2(1H)-one 35[7]
Compound **34** (1.00 g, 4.21 mmol) and $AlCl_3$ (2.660 g, 19.95 mmol) were heated to 125 °C in chlorobenzene (10mL) for 24 h. The mixture was cooled to 50 °C and poured onto ice. The mixture was extracted with EtOAc. Evaporation and recrystallisation (EtOH) gave **35**. Yield: 37%, pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.18 (s, 1H, NH), 7.78 (d, *J* = 9.5 Hz, 1H, COCH), 7.36 (d, *J* = 4.6 Hz, 3H, ArH), 6.72 (d, *J* = 9.5 Hz, 1H, ArCH), 2.42 (s, 3H, CH_3).

2-Bromo-6-methylquinoline 36
$POBr_3$ (0.72 g, 3.7 mmol) was heated with 7 (0.20mg, 1.26 mmol) at 140 °C for 3 h. The cooled mixture was poured into ice-water. The precipitate was collected and dried. Chromatography on silica gel (petroleum ether-EtOAc; 25:1) gave **36**. Yield: 50%, pale yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.90-7.95(m, 2H, ArH), 7.55-7.57(m, 2H, ArH), 7.48(d, J=8.7Hz, 1H, ArH), 2.53(s, 3H, CH_3).

Methyl 2-amino-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate 38[8]
A mixture of $PdCl_2$(dppf) (0.270 g, 0.331 mmol), KOAc (1.95 g, 19.870 mmol)), bis(neopentyl glycolato)diboron (1.80 g, 7.968 mmol), and methyl 2-amino-4-bromobenzoate **37** (1.50 g, 6.551 mmol) was added to a flask under anhydrous conditions. After addition of anhydrous DMSO, the mixture was stirred at 80 ºC for several hours and the reaction progress was checked by TLC. The reaction solution was cooled to room temperature and poured into ice-water. The mixture was extracted with ethyl acetate and the combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the corresponding aryl boronate. Yield: 90%, white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.04 (d, *J* = 8.0 Hz, 1H, ArH), 5.46 (s, br, 2H, NH_2), 3.86 (s, 3H, OCH_3), 3.76 (s, 4H, CH_2, CH_2), 1.02 (s, 6H, CH_3, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 148.5, 129.0(2C), 121.5, 120.2, 111.3, 71.3(2C), 50.5, 30.8, 20.8, 20.8. HRMS (EI-MS) calcd for $C_{13}H_{18}BNO_4$ [$M^{\bullet+}$] 262.1365; found 262.1361

Methyl 2-amino-4-(6-methylquinolin-2-yl)benzoate 39[9]
2-Bromo-6-methylquinoline **36** (1.38 g, 6.21 mmol), methyl 2-amino-4-(5, 5-dimethyl-1, 3, 2-dioxaborinan-2-yl) benzoate **38** (1.50 g, 5.70 mmol) and [$Pd(PPh_3)_4$] (0.72 g, 0.63 mmol) were placed into a *Schlenk flask* under a stream of nitrogen at room temperature. The mixture of solids was stirred and degassed three times before it was dissolved in anhydrousand degassed THF (10 mL), aqueous K_3PO_4(2 mol/L) was added and the reaction mixture was heated to 80 ^{o}C overnight. The resulting dark-brown reaction mixture was cooled to room temperature and diluted with water (10 mL). After extracted with CH_2Cl_2 , washed with brine and concentrated *in vacuo*, the residue was purified by flash column chromatography over silica gel (petroleum ether-EtOAc; 1:1) to give methyl 2-amino-4-(6-methylnaphthalen-2-yl)benzoate **39**. Yield: 60%, white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H, ArH), 8.10 (d, *J* = 8.4 Hz, 1H, ArH), 7.99 (d, *J* = 8.4 Hz, 1H, ArH), 7.82 (d, *J* = 8.6 Hz, 1H, ArH), 7.60 (s, 1H, ArH), 7.57 (d, *J=1.9* Hz, 1H, ArH), 7.55(d, J=1.6Hz, 1H, ArH), 7.35 (dd, *J1* = 8.4Hz, *J2*=1.7 Hz, 1H, ArH), 5.87 (s, br, 2H, NH_2), 3.91 (s, 3H, OCH_3), 2.56 (s, 3H, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 154.4, 149.7, 145.6, 143.7, 135.6, 135.2, 131.1, 130.8, 128.3, 126.5, 125.3, 118.1, 114.5, 114.3, 110.1, 50.6, 20.6. HRMS (EMS) calcd for $C_{18}H1_6N_2O_2$ [MH^+] 293.1285; found 293.1290

Methyl 4-(6-methylquinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 40
Quinoline-2-carboxylic acid was suspended in $SOCl_2$ (10-15 mL) and heated to reflux for 2 h. Excess $SOCl_2$ was removed under reduced pressure and the resulting quinoline-2-carbonyl chloride was obtained as yellow solid.
Methyl 2-amino- 4-(6-methylnaphthalen-2-yl)benzoate **39** and NEt_3 were dissolved in CH_2Cl_2 and the freshly prepared quinoline-2-carbonyl chloride derived was added in small portions and stirred at room temperature for 30 min. Then, the solution was refluxed at 40℃ overnight, washed with 1N HCl and saturated aqueous solution of Na_2CO_3 (3×), dried over anhydrous Na_2SO4 and concentrated to give the crude product which was purified by flash chromatography (petroleum ether-EtOAc; 4:1) on silica

gel. Yield: 90%, white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.38 (s, 1H, NH), 9.79 (d, *J* = 1.6 Hz, 1H, ArH), 8.43 (d, *J* = 8.4 Hz, 1H, ArH), 8.40 (s, 1H, ArH), 8.38 (d, *J* = 3.9 Hz, 1H, ArH), 8.36 (s, 1H, ArH), 8.30 (d, *J* = 8.3 Hz, 1H, ArH), 8.23 (d, *J* = 8.5 Hz, 1H, ArH), 8.14 (d, *J* = 7.5 Hz, 1H, ArH), 8.05 (d, *J* = 8.6 Hz, 1H, ArH), 7.93 (d, *J* = 8.1 Hz, 1H, ArH), 7.86 – 7.82 (m, 1H, ArH), 7.69 – 7.65 (m, 1H, ArH), 7.64 (s, 1H, ArH), 7.62 – 7.59 (m, 1H, ArH), 4.11 (s, 3H, OCH_3), 2.57 (s, 3H, $ArCH_3$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 163.8, 154.9, 150.1, 146.7, 141.2, 137.7, 137.1(2C), 136.9(2C), 132.5(2C), 131.9, 130.3, 130.2, 129.4, 128.3, 127.7, 126.4, 122.2(2C), 119.5, 119.5, 118.9, 116.9, 52.5, 21.7. HRMS (ESI) calcd. for $C_{28}H_{21}N_3O_3$ [MH^+]:448.1656; found 448.1658.

Methyl 4-(6-(bromomethyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 41[10]

A solution of methyl 4-(6-methylnaphthalen-2-yl)-2-(quinoline-2-carboxamido)benzoate (**40**) (1g, 2.23 mmol), 0.48 g (0.268 mmol) of NBS, and 0.03 g (0.12 mmol) of dibenzoyl peroxide in 50 mL of carbon tetrachloride was refluxed for 6 h. After the reaction mixture was filtered, it was washed with aqueous $NaHCO_3$ and brine. The solvent was evaporated to obtain compound 41 which was sufficiently pure to be used without further purification

Yield: 52%, white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.36 (s, 1H, -CONH), 9.79 (d, *J* = 1.5 Hz, 1H, ArH), 8.41 (d, *J* = 8.4 Hz, 1H, ArH), 8.38 – 8.36 (m, 1H, ArH), 8.35 (d, *J* = 8.5 Hz, 1H, ArH), 8.27 (d, *J* = 8.3 Hz, 1H, ArH), 8.23 (d, *J* = 3.4 Hz, 1H, ArH), 8.22 (d, *J* = 3.5 Hz, 1H, ArH), 8.11 – 8.08 (m, 1H, ArH), 8.07 (d, *J* = 8.6 Hz, 1H, ArH), 7.91 (d, *J* = 7.8 Hz, 1H, ArH), 7.85 – 7.81 (m, 2H, ArH), 7.77 (dd, *J* = 8.7, 1.9 Hz, 1H, ArH), 7.66 (t, *J* = 7.3 Hz, 1H, ArH), 4.68 (s, 2H, CH_2Br), 4.10 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 163.8, 156.4, 150.0, 147.7, 146.6, 144.5, 141.2, 137.7, 137.1, 136.2, 131.8, 130.9, 130.6, 130.3, 130.2, 129.4, 128.3, 127.7, 127.4, 127.3, 126.6, 122.1, 119.9, 119.5, 118.9, 117.0, 52.5. HRMS (EI-MS) calcd for $C_{28}H_{20}BrN_3O_3$ [MH^+] 526.0761; found 526.0764.

General procedure for the preparation of compounds 26-28 and 42-46.

Tetrahydroisoquinoline derivatives (1 equiv.), methyl 4-(6-(bromomethyl) naphthalen-2-yl)-2-(quinoline-2-carboxamido) benzoate **41** (1 equiv.) and diisopropylethylamine (2 equiv.) were dissolved in CH_3CN and the mixture was refluxed overnight. Flash column chromatography ($CHCl_3$:CH_3OH; 20:1) gave the corresponding products.

Methyl 4-(6-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)-methyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 26

Compound according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH=20:1) to obtain **26** as pale yellow solid. Mp.108℃（decomposition）,^{1}H NMR (300 MHz, $CDCl_3$) *δ* = 13.59 (s, 1H, -CONH), 9.81 (d, *J* = 1.7 Hz, 1H, ArH), 8.44-8.41(d, *J* = 8.5Hz, 1H, ArH), 8.39-8.36 (d, *J* = 8.4 Hz, 1H, ArH), 8.37-8.34 (d, *J* = 8.4Hz, 1H, ArH), 8.29-8.23 (dd, J_1 = 8.6 Hz, J_2=9.4 Hz, 2H, ArH), 8.20-8.17 (d, *J* = 8.6, 1H, ArH), 8.12-8.08 (dd, J_1 = 8.4, J_2=1.8 Hz, 1H, ArH), 8.08-8.05 (d, *J* = 8.6Hz, 1H, ArH), 7.95-7.90 (d, *J* = 8.1, 1H, ArH), 7.86-7.83 (dd, J_1 = 6.8Hz, J_2=1.4 Hz, 1H, ArH) , 7.85-7.80 (dd,J_1= 8.6, J_2=1.7Hz, 2H, ArH), 7.69-7.61(m, 1H, ArH), 6.67(s, 1H, ArH), 6.54 (s, 1H, ArH), 4.14-4.05 (m, 7H, ArOCH3, ArOCH2), 3.88 (s, 2H, -NCH2), 3.85-3.80 (dd, J_1 = 8.7Hz, J2=5.3Hz, 2H, -NCH_2Ar), 3.82-3.79(d, *J* = 8.7 Hz, 2H, PEG), 3.75-3.60(m, 14H, PEG), 3.66-3.50 (m, 4H, PEG), 3.37 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.85(s, br, 4H, -NCH2CH2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 162.8, 154.7, 149.1, 146.8, 146.5, 146.2, 145.6, 144.1, 140.2, 136.7, 135.8, 130.8, 130.3, 129.3, 129.2, 129.0, 128.4, 127.3, 126.7, 126.4, 126.0(2C), 121.0, 118.5, 118.4, 117.9, 115.7, 114.1, 112.2, 70.9, 70.9, 69.8, 69.8, 69.7, 69.7, 69.5, 69.5, 68.7, 68.7, 68.0, 61.4, 58.0, 58.0, 54.6, 51.6, 49.8, 28.7, 28.5. HRMS (EI-MS) calcd for $C_{51}H_{58}N_4O_{11}$ [MH^+] 903.4175; found 903.4173.

Methyl 4-(6-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 27

Compound **27** was prepared according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH=20:1) to obtain **27** as pale yellow solid. Mp.102℃ (decomposition), ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H, -CONH), 9.81 (d, *J* = 1.7 Hz, 1H, ArH), 8.43 (d, *J* = 8.5 Hz, 1H, ArH), 8.38 (d, *J* = 8.1 Hz, 1H, ArH), 8.36 (d, *J* = 7.8 Hz, 1H, ArH), 8.28 (d, *J* = 8.4 Hz, 1H, ArH), 8.25 (d, *J* = 8.6 Hz, 1H, ArH), 8.19 (d, *J* = 8.6 Hz, 1H, ArH), 8.11 (dd, *J* = 8.4, 1.8 Hz, 1H, ArH), 8.07 (d, *J* = 8.6 Hz, 1H, ArH), 7.92 (dd, J_1 = 8.2, J_2=0.9 Hz, 1H, ArH), 7.84 (m, 3H, ArH), 7.67 (m, 1H, ArH), 6.62 (s, 1H, ArH), 6.55 (s, 1H, ArH), 4.12-4.09(m, 5H, $ArOCH_3$, $ArOCH_2$), 3.89(s, 2H, -NCH_2Ar), 3.85-3.82(m, 5H, PEG), 3.72-3.69(m, 2H, -NCH_2Ar), 3.66-3.61(m, 5H, PEG), 3.53-3.50(m, 2H, PEG), 3.35(s, 3H, OCH_3), 2.87-2.83(m, 4H, -NCH_2CH_2). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 167.9, 163.8, 155.7, 150.1, 148.3, 147.9, 146.6, 146.6, 145.1, 141.2, 137.7, 136.8, 131.8, 131.3, 130.5, 130.3, 130.2, 130.0, 129.4, 128.3, 127.7, 127.2, 127.1, 126.8, 122.0, 119.5(2C), 118.9, 116.8 , 112.4, 112.1, 71.9, 70.8, 70.6, 70.5, 69.6, 68.7, 62.4, 59.0, 56.0, 55.6, 53.4, 52.5, 50.8, 28.6. HRMS (EI-MS) calcd for $C_{45}H_{46}N_4O_8$ [MH^+] 771.3394; found 771.3388.

Methyl 4-(6-((6,7-dimethoxy-3, 4-dihydroisoquinolin-2(1H)-yl)methyl) quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 28

Compound **28** according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH; 20:1) to obtain **28** as pale yellow solid. Mp. 158 °C (decomposition), ^{1}H NMR (600 MHz, $CDCl_3$) δ = 13.4(s, 1H, -CONH), 9.82(d, *J* = 1.7 Hz, 1H, ArH), 8.44(d, *J* = 8.4Hz, 1H, ArH), 8. 39(d, *J* = 8.5Hz, 1H, ArH), 8.37(d, *J* = 8.5Hz,1H, ArH), 8.29 (d, *J* = 8.3 Hz, 1H, ArH), 8.27 (d, *J* = 8.6 Hz, 1H, ArH), 8.20 (d, *J* = 8.6 Hz, 1H, ArH), 8.11 (dd, J_1 = 8.3, J_2=1.8 Hz, 1H, ArH), 8.08 (d, *J* = 8.6 Hz, 1H, ArH), 7.93 (d, *J* = 8.0 Hz, 1H, ArH), 7.84 (ddd, J_1= 8.3, J_2=6.9, J_3=1.3 Hz, 2H, ArH), 7.78 (d, *J* = 8.6Hz, 1H, ArH), 7.68 (ddd, J_1= 8.0, J_2=6.9, J_3=1.1 Hz, 1H, ArH), 6.63(s,1H, ArH), 6.49(s, 1H, ArH), 4.11 (s,3H, OCH_3), 3.86-3.85(m, 2H, -NCH_2Ar), 3.9 (s, 3H, ArOCH_3), 3.8 (s, 3H, ArOCH_3), 3.70 (s, br, 2H, ArCH_2N-), 2.89-2.86 (m,4H, -NCH_2CH_2Ar). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 163.8, 160.1, 154.7, 150.1, 147.9, 147.4, 146.7, 145.1, 141.2, 137.7(2C), 136.8, 131.8, 131.3, 130.3, 130.2, 129.4, 128.3, 127.7 (2C), 127.4, 126.4, 122.0, 119.6 , 119.5 (2C), 118.9 (2C), 116.8, 111.4, 109.5, 55.9, 55.9, 53.4, 52.5 (2C), 48.5, 28.2. HRMS (EI-MS) calcd for $C_{46}H_{47}N_5O_5$ [MH^+] 639.2602; found 639.2604.

Methyl 4-(6-((6-methoxy-7-(2-morpholinoethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl) quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 42

Compound **42** was prepared according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH; 20:1) to obtain **42** as pale yellow solid. Mp. 158 °C (decomposition), ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.38 (s, 1H, -CONH), 9.81 (d, *J* = 1.7 Hz, 1H, ArH), 8.43 (d, *J* = 8.4 Hz, 1H, ArH), 8.39 (d, *J* = 8.5 Hz, 1H, ArH), 8.37 (d, *J* = 8.6 Hz, 1H, ArH), 8.29 (d, *J* = 8.3 Hz, 1H, ArH), 8.25 (d, *J* = 8.5 Hz, 1H, ArH), 8.20 (d, *J* = 8.6 Hz, 1H, ArH), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H, ArH), 8.07 (d, *J* = 8.6 Hz, 1H, ArH), 7.92 (d, *J* = 8.0 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.84 (ddd, J_1=8.8Hz, J_2=5.8Hz, J_3=4.6Hz, 2H, ArH), 7.68-7.67 (m, 1H, ArH), 6.63 (s, 1H, ArH), 6.52 (s, 1H, ArH). 4.11 (s, 3H, OCH_3), 4.09 (t, *J* = 6.0 Hz, 2H, OCH_2), 3.91 (s, 2H, -NCH_2Ar), 3.82 (s, 3H, ArOCH_3), 3.75 – 3.71 (m, 4H, OCH_2, OCH_2), 3.63 (s, 2H, -NCH_2Ar), 2.88 (d, *J* = 5.0 Hz, 2H, CH_2Ar), 2.87 – 2.80 (m, 4H, -NCH_2, -NCH_2), 2.60 (s, br, 4H, -NCH_2, -NCH_2). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 163.8, 155.8, 150.1, 148.3, 147.9, 146.6, 146.4, 145.1, 141.2, 137.7, 136.8, 131.8, 131.3, 130.3 , 130.2, 130.1, 129.4, 128.3, 127.7, 127.4, 127.2, 126.8, 126.3, 122.0, 119.5, 119.5, 118.9, 116.8, 112.1, 112.0, 66.7, 62.3, 57.4, 56.0, 55.5, 53.9, 52.5, 50.8, 29.7, 28.8, 28.5, 19.6, 19.2. HRMS (EMS) calcd for $C_{44}H_{43}N_5O_6$ [MH^+] 738.3286; found 738.3293.

Methyl 4-(6-((6-methoxy-7-(2-(piperidin-1-yl)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 43

Compound **43** was prepared according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH; 20:1) to obtain **43** as pale yellow solid. Mp. 163 °C (decomposition), ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.39 (s, 1H, -CONH), 9.81 (d, *J* = 1.7 Hz, 1H, ArH), 8.43 (d, *J* = 8.4 Hz, 1H, ArH), 8.39 (d, *J* = 8.5 Hz, 1H, ArH), 8.37 (d, *J* = 8.4 Hz, 1H, ArH), 8.29 (d, *J* = 8.3 Hz, 1H, ArH), 8.26 (d, *J* = 8.5 Hz, 1H, ArH), 8.19 (d, *J* = 8.6 Hz, 1H, ArH), 8.12 (dd, J_1 = 8.3, J_2=1.7 Hz, 1H, ArH), 8.08 (d, *J* = 8.6 Hz, 1H, ArH), 7.93 (d, *J* = 7.9 Hz, 1H, ArH), 7.84 (dtd, J_1 = 8.3, J_2=6.8, J_3=1.6 Hz, 3H, ArH), 7.69-7.66 (m, 1H, ArH), 6.62 (s, 1H, ArH), 6.54 (s, 1H, ArH). 4.11 (s, 3H, OCH_3), 3.87 (s, 2H, -NCH_2Ar), 3.82 (s, 3H, ArOCH_3), 3.61 (s, 2H, -NCH_2Ar), 2.86 (t, *J* =5.5Hz, 2H, -NCH_2), 2.80 (t, *J* = 5.6 Hz, 2H, -NCH_2), 2.59 (s, br, 4H, -NCH_2, -NCH_2), 1.66-1.46(m, 6H, $CH_2CH_2CH_2$). ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 163.8, 155.7, 150.2, 148.1, 147.8, 146.7, 145.2, 141.2, 137.7(2C), 137.4, 136.8, 131.8, 131.3, 130.3, 130.2, 130.0(2C), 129.4, 128.4, 127.7, 127.4, 126.9, 126.8(2C), 122.0 , 119.5, 119.5, 118.9, 116.8, 112.0, 62.6, 57.4, 56.0, 55.8, (2C), 54.7, 52.5(2C), 50.9, 29.7, 28.8(2C), 24.3. HRMS (EI-MS) calcd for $C_{45}H_{45}N_5O_5$ [MH^+] 736.3493; found 736.3498.

Methyl 4-(6-((6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 44

Compound **44** was prepared from **41** and **10** according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH=20:1) to obtain **44** as pale yellow solid. Mp. 158 °C (decomposition), ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.40 (s, 1H, -CONH), 9.81 (d, *J* = 1.7 Hz, 1H, ArH), 8.44 (d, *J* = 8.6 Hz, 1H, ArH),8.40 (d, *J* = 8.6Hz, 1H, ArH),8.38 (d, *J* = 8.6Hz, 1H, ArH), 8.30 (d, *J* = 6.4 Hz, 1H, ArH), 8.27 (d, *J* = 6.6 Hz, 1H, ArH), 8.20 (d, *J* = 8.6 Hz, 1H, ArH), 8.11 (dd, J_1 = 8.4, *J2*=1.7 Hz, 2H, ArH), 8.08 (d, *J* = 8.7 Hz, 1H, ArH), 7.93 (d, *J* = 8.1Hz, ArH), 7.85 (m, 3H, ArH), 6.63 (s, 1H, ArH), 6.57 (s, 1H, ArH), 4.43 (s, br, 2H, $ArOCH_2$), 4.12 (s, 3H, OCH_3), 3.90 (d, *J* = 2.1 Hz, 2H, -NCH_2Ar), 3.82 (s, 3H, OCH_3), 3.62 (s, 2H, -NCH_2Ar), 3.43 (s, 2H, -NCH_2), 2.87(s, 2H, CH_2Ar), 2.82 (s, 2H, -NCH_2), 2.15 (s, *br*, 4H, CH_2, CH_2), 1.34 – 1.20 (m, 4H, CH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 163.8, 155.7, 150.1, 148.1, 147.8, 146.6, 145.4, 145.1, 141.2, 137.8, 137.2, 136.9, 131.8, 131.3, 130.3, 130.2, 130.0, 129.4, 128.3, 127.8, 127.7, 127.4, 127.1, 126.8, 122.1, 119.5, 119.5, 118.9, 116.8, 112.6, 112.0, 65.9, 62.5, 55.9, 55.6, 54.3(2C), 54.2, 52.6, 50.8, 28.8, 23.3(2C). HRMS (EI-MS) calcd for $C_{44}H_{43}N_5O_5$ [MH^+] 738.3286; found 738.3293.

Methyl 4-(6-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 45

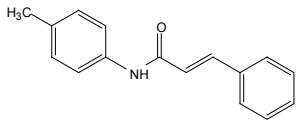
Compound **45** was prepared according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH; 20:1) to obtain **45** as pale yellow solid. Mp. 156 °C (decomposition), ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.36 (s, 1H, -CONH), 9.79 (d, *J* = 1.6 Hz, 1H, ArH), 8.41 (d, *J* = 8.4 Hz, 1H, ArH), 8.36 (dd, J_1 = 8.2Hz, J_2=7.8Hz, 2H, ArH), 8.26 (d, *J* = 8.3 Hz, 1H, ArH), 8.23 (d, *J* = 8.5 Hz, 1H, ArH), 8.19 (d, *J* = 8.3 Hz, 1H, ArH), 8.09 (dd, J_1 = 8.3, J_2=1.7 Hz, 1H, ArH), 8.05 (d, *J* = 8.6 Hz, 1H, ArH), 7.90 (d, *J* = 7.6 Hz, 1H, ArH), 7.83-7.82 (m, 2H, ArH), 7.81 (d, *J* = 2.1Hz, 1H, ArH), 7.66-7.63 (m, 1H, ArH), 6.61 (s, 1H, ArH), 6.51 (s, 1H, ArH). 4.09 (s, 3H, OCH_3), 3.97 (t, *J* = 6.7 Hz, 2H, CH_2), 3.85 (s, 2H), 3.81 (s, 3H, $ArOCH_3$), 3.59 (s, 2H, -NCH_2Ar), 2.85 (t, *J* = 6.0 Hz, 2H, -NCH_2), 2.80 (t, *J* = 5.4 Hz, 2H, CH_2Ar), 2.48 (t, *J* = 7.2Hz, 2H, -NCH_2), 2.41 (s, br, 4H, -NCH_2, -NCH_2), 2.02 – 1.97 (m, 2H, OCH_2), 1.59 – 1.54 (m, 4H, CH_2CH_2), 1.41 (s, br, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.9, 163.7, 155.6, 150.0, 148.0, 147.8, 146.6, 146.6, 145.0, 141.1, 137.7, 137.3, 136.7, 131.7, 131.2, 130.2, 130.2, 129.9, 129.3, 128.2, 127.6, 127.4, 126.9, 126.6, 126.4, 122.0, 119.4, 119.4, 118.8, 116.7, 112.0, 111.6, 67.7, 62.6, 56.0, 55.7, 55.7, 54.3(2C), 52.4, 51.0, 28.7, 26.4, 25.6(2C), 24.2. HRMS (EI-MS) calcd for $C_{46}H_{47}N_5O_5$ [MH^+] 750.3650; found 750.3659.

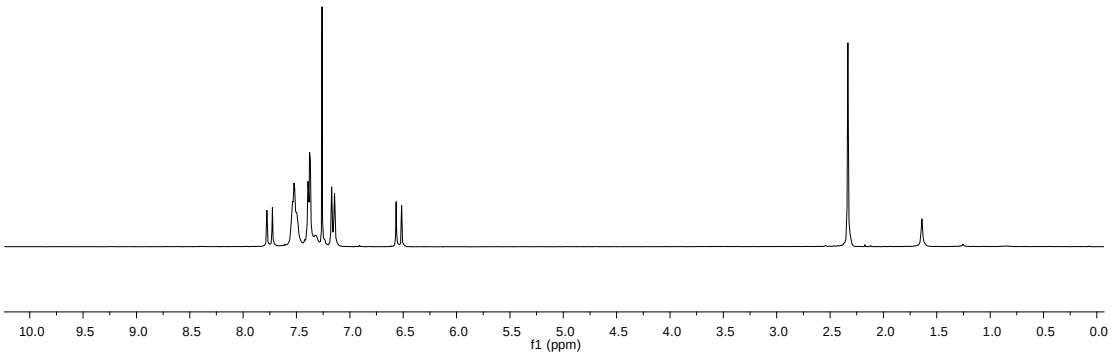
Methyl 4-(6-((6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 46

Compound **46** was prepared according to the general procedure. The crude product was purified with flash column chromatography (EtOAc→$CHCl_3$: MeOH; 20:1) to obtain **46** as pale yellow solid. Mp. 155 °C (decomposition), ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.38 (s, 1H, -CONH), 9.80 (s, 1H, ArH), 8.42 (d, *J* = 8.5 Hz, 1H, ArH), 8.37 (dd, J_1= 9.4, J_2=5.4 Hz, 2H, ArH), 8.27 (dd, J_1= 14.4, J_2=6.0 Hz, 2H, ArH), 8.19 (d, *J* = 8.8 Hz, 1H, ArH), 8.12 – 8.03 (m, 2H, ArH), 7.91 (d, *J* = 8.1 Hz, 1H, ArH), 7.82 (d, *J* = 8.2 Hz, 3H, ArH), 7.66 (t, *J* = 7.5 Hz, 1H, ArH), 6.65 (s, 1H, ArH), 6.61(s, 1H, ArH), 4.09 (s, 3H, OCH_3), 3.99 (t, *J* = 6.6 Hz, 2H, OCH_2), 3.85 (d, *J* = 5.6 Hz, 2H, -NCH_2Ar), 3.82 (s, 3H, $ArOCH_3$), 3.76 – 3.63 (m, 4H, -OCH_2,-OCH_2), 3.59 (s, 2H,-NCH_2Ar), 2.84 (dd, J_1 = 10.7, J_2=4.4 Hz, 4H, -NCH_2CH_2Ar), 2.51 – 2.44 (m, 6H, -NCH_2, -NCH_2, -NCH_2), 2.00-1.95 (m, 2H,CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 163.8, 155.7, 150.1, 148.0, 147.8, 147.0, 146.6, 146.6, 145.1, 141.2, 137.8, 137.3, 136.8, 131.8, 131.3, 130.3, 130.3, 130.0, 129.4, 128.3, 127.7, 127.5, 127.0, 126.6, 126.4, 122.0, 119.5, 118.9, 116.8, 112.0, 111.5, 67.4, 66.9, 62.6, 56.1, 55.8, 55.5, 53.7, 53.7, 52.5, 51.1, 28.7, 28.5, 26.3. HRMS (EI-MS) calcd for $C_{45}H_{45}N_5O_6$ [MH^+] 752.3443; found 752.3448.

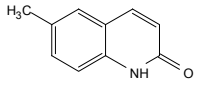
3.2 ^{1}H and ^{13}C NMR spectra

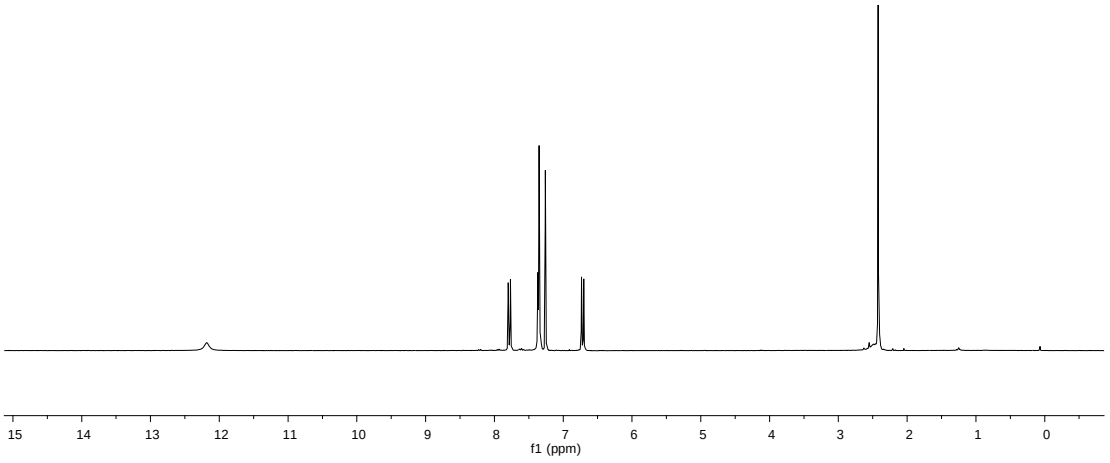
N-(4-Methylphenyl)cinnamamide 34



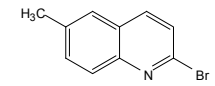


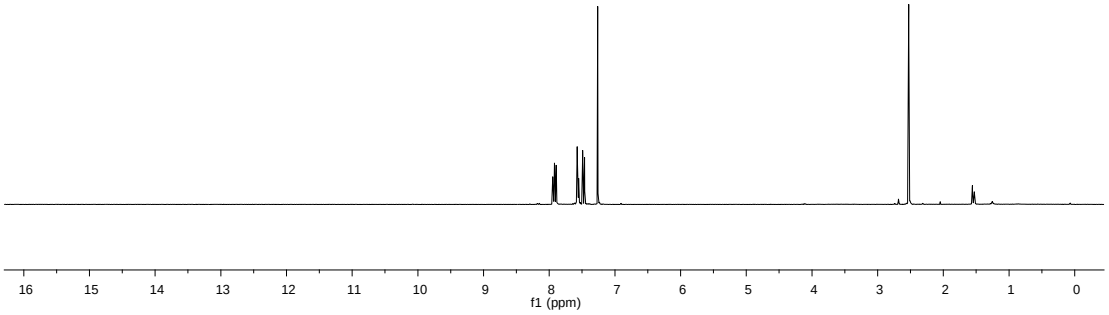
6-Methylquinolin-2(1H)-one 35



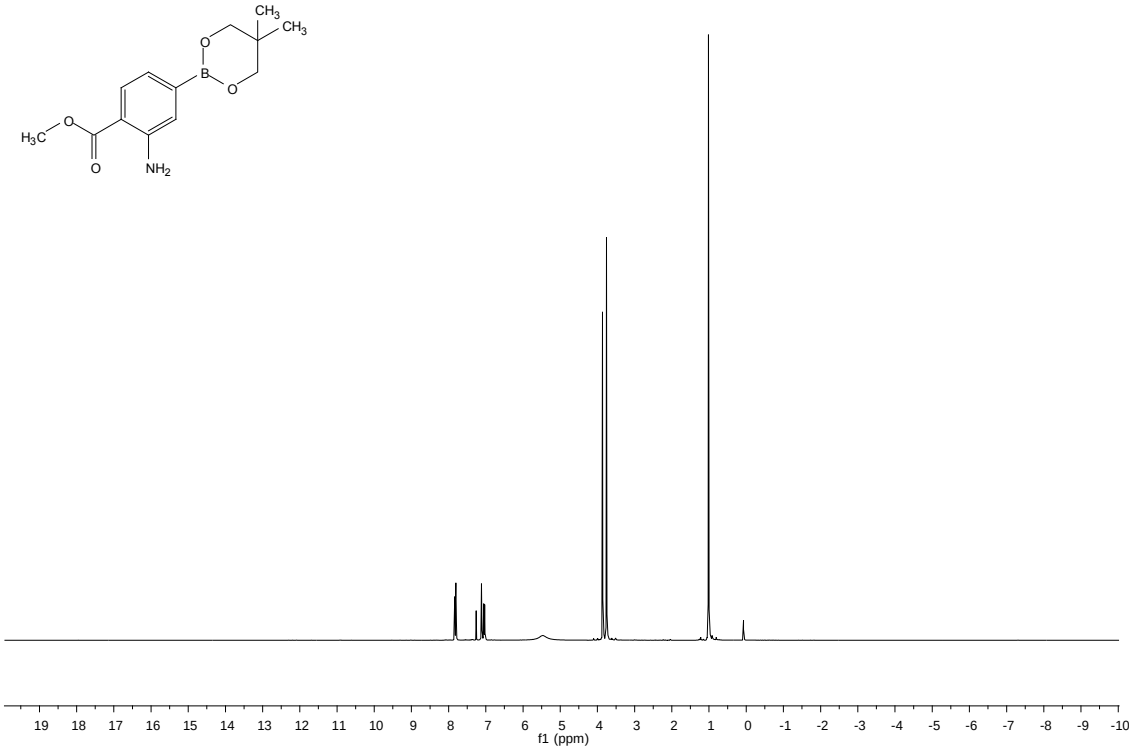


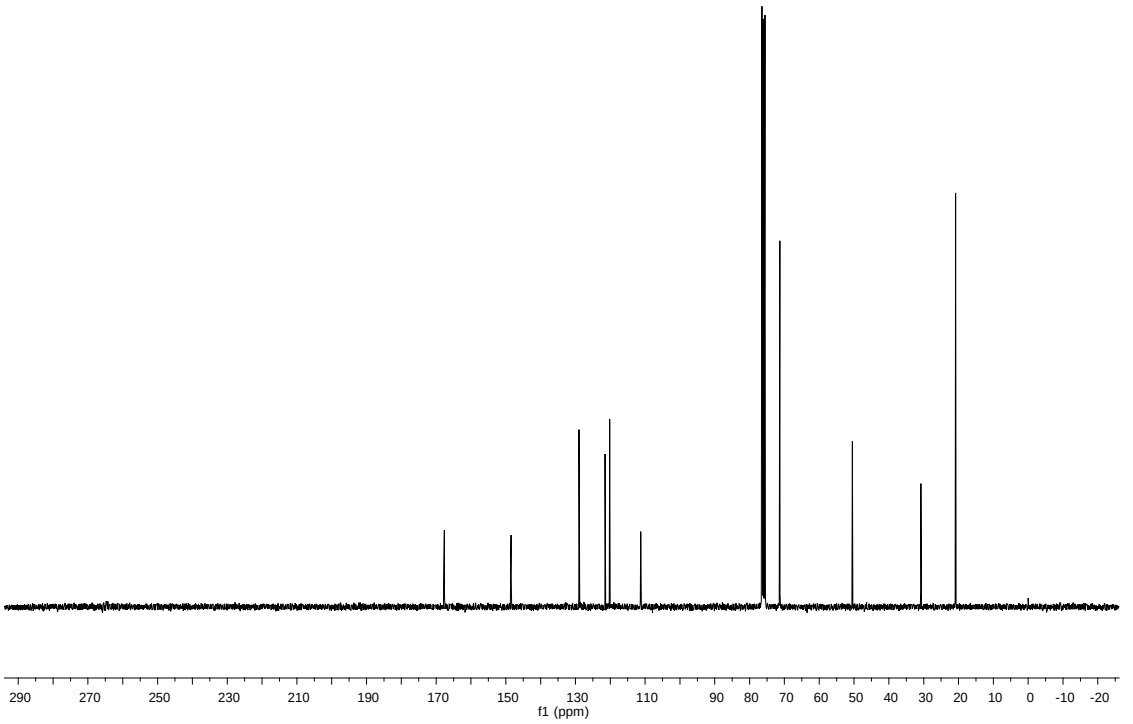
2-Bromo-6-methylquinoline 36



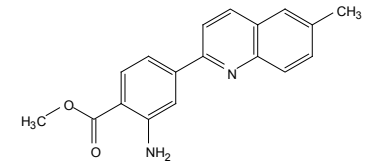


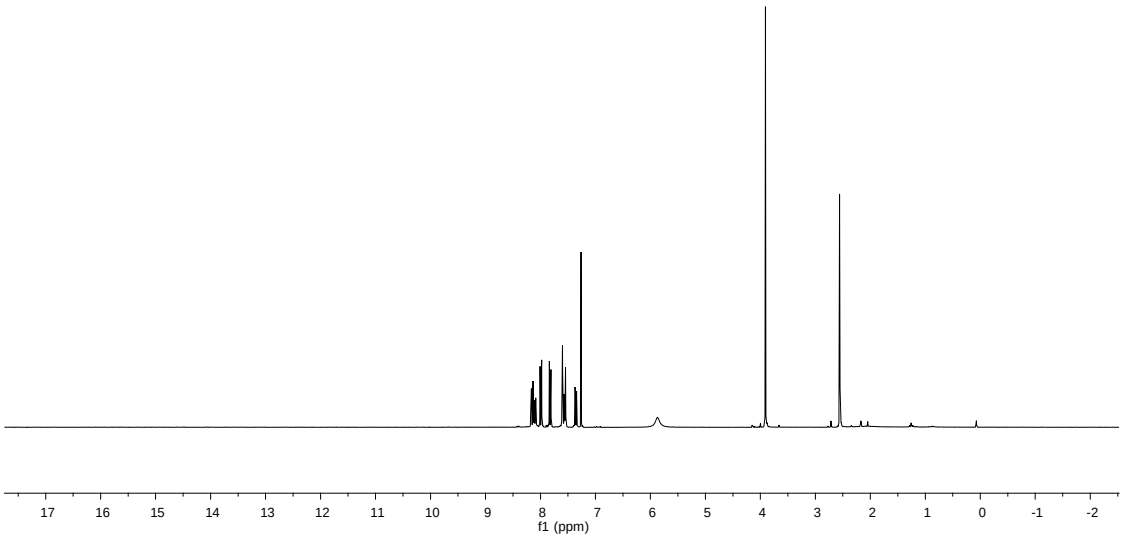
Methyl 2-amino-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate 38

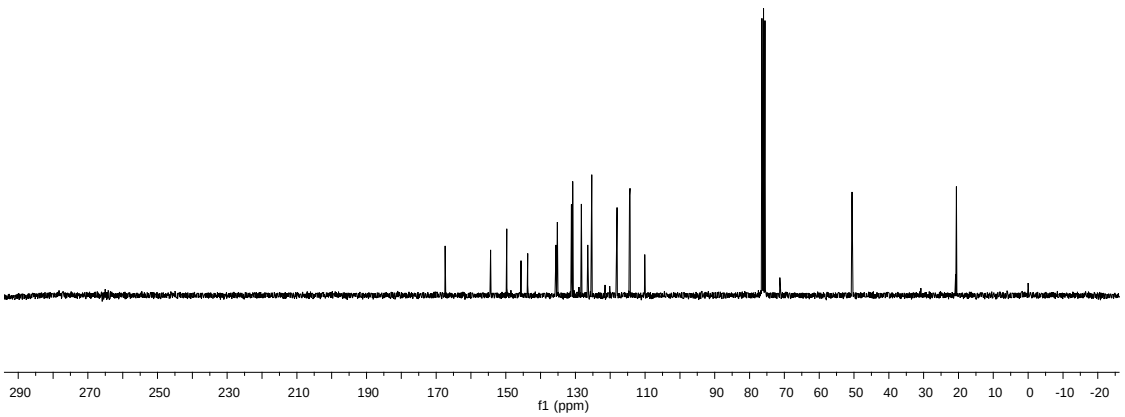




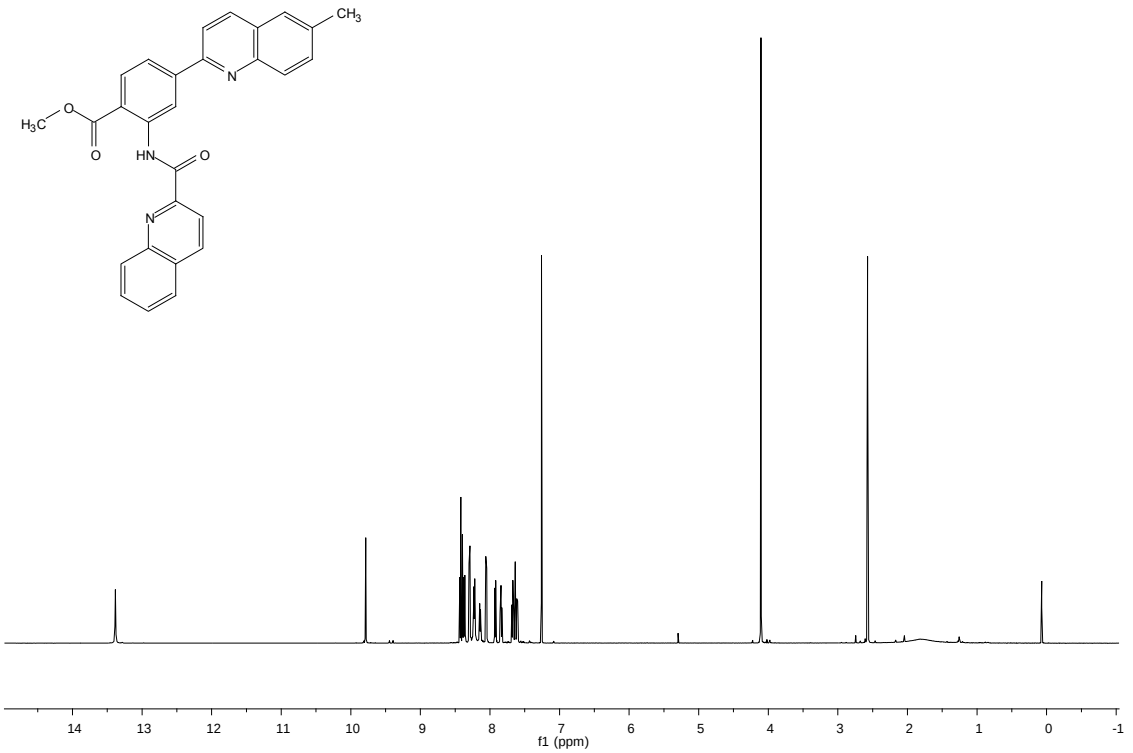
Methyl 2-amino-4-(6-methylquinolin-2-yl)benzoate 39

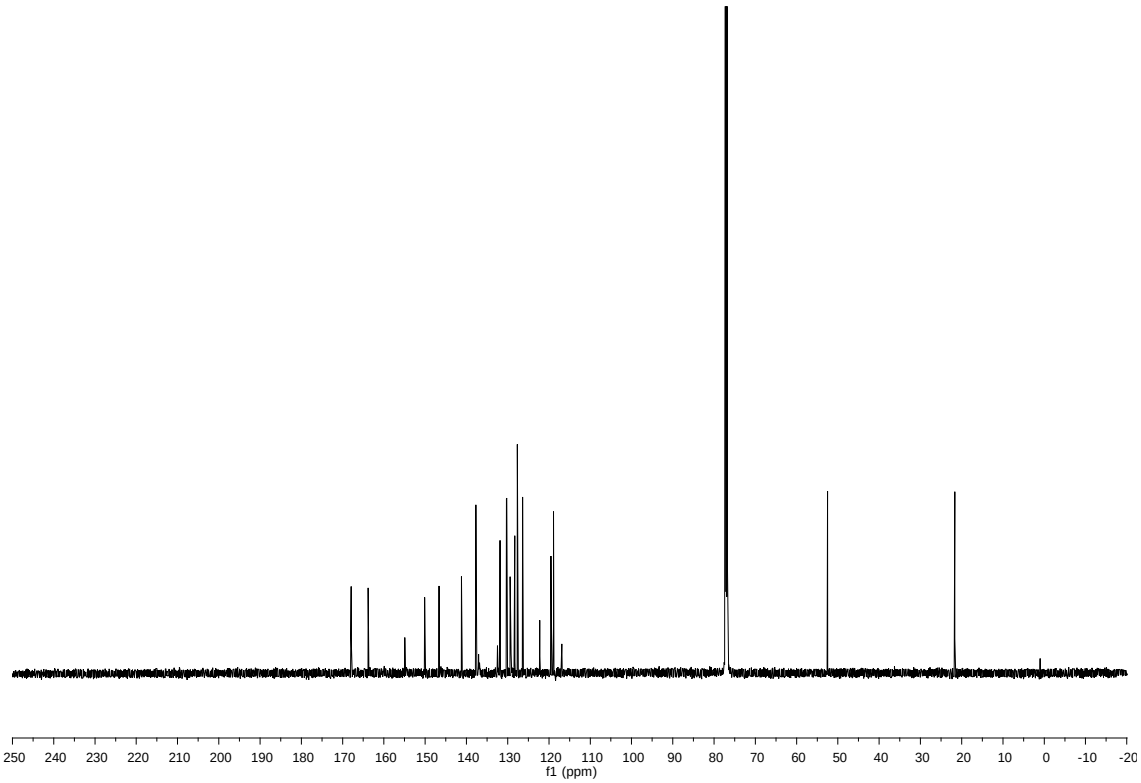




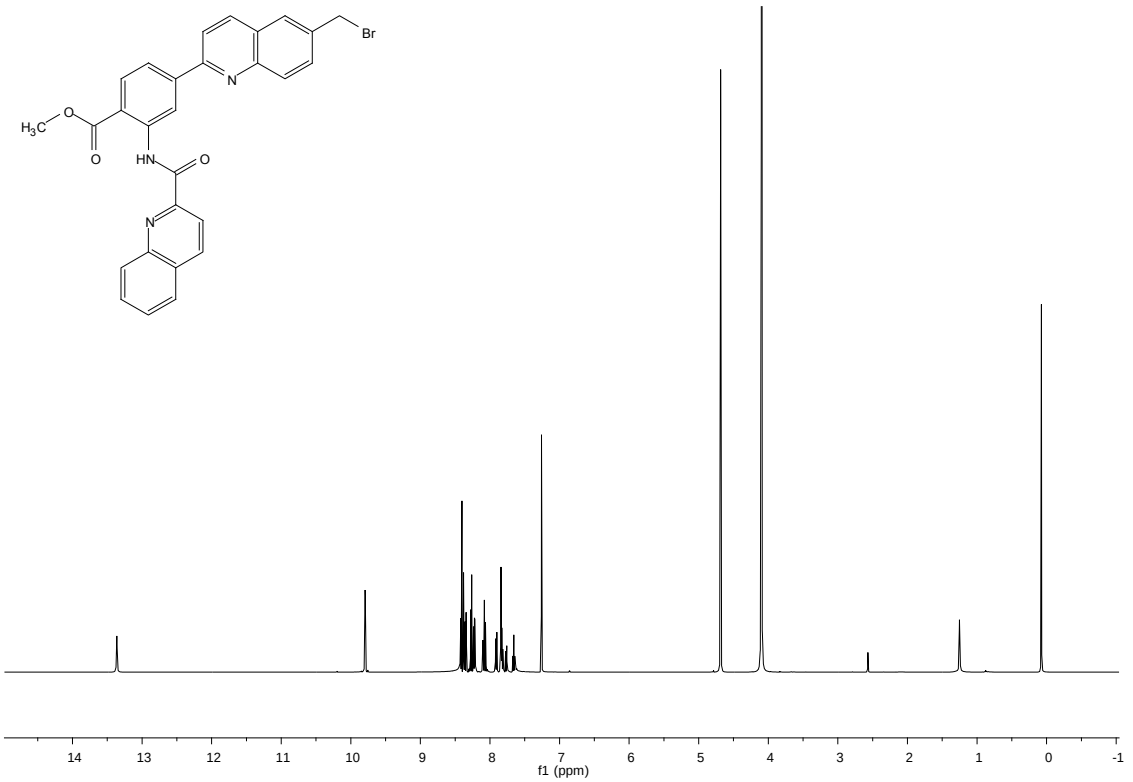


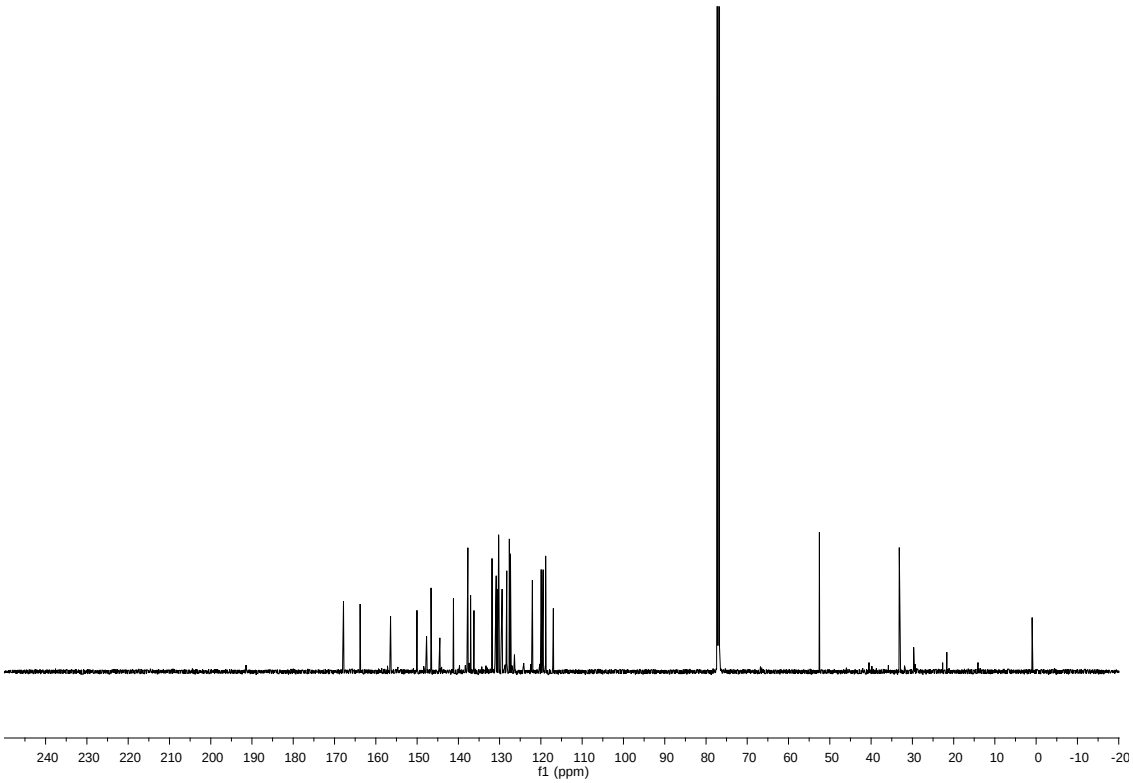
Methyl 4-(6-methylquinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 40



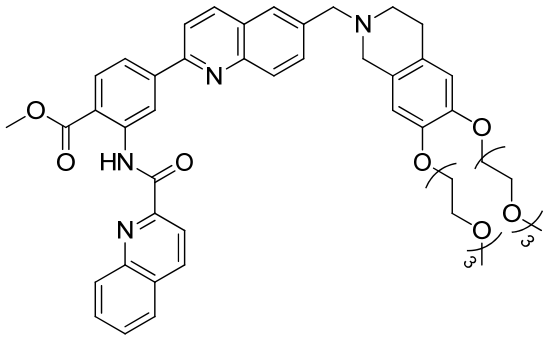


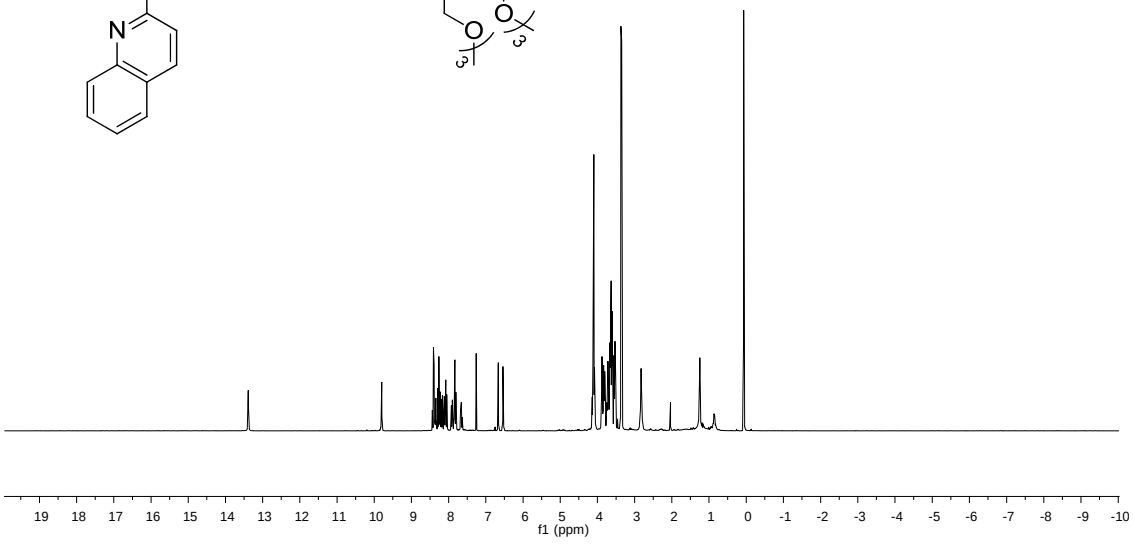
Methyl 4-(6-(bromomethyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 41

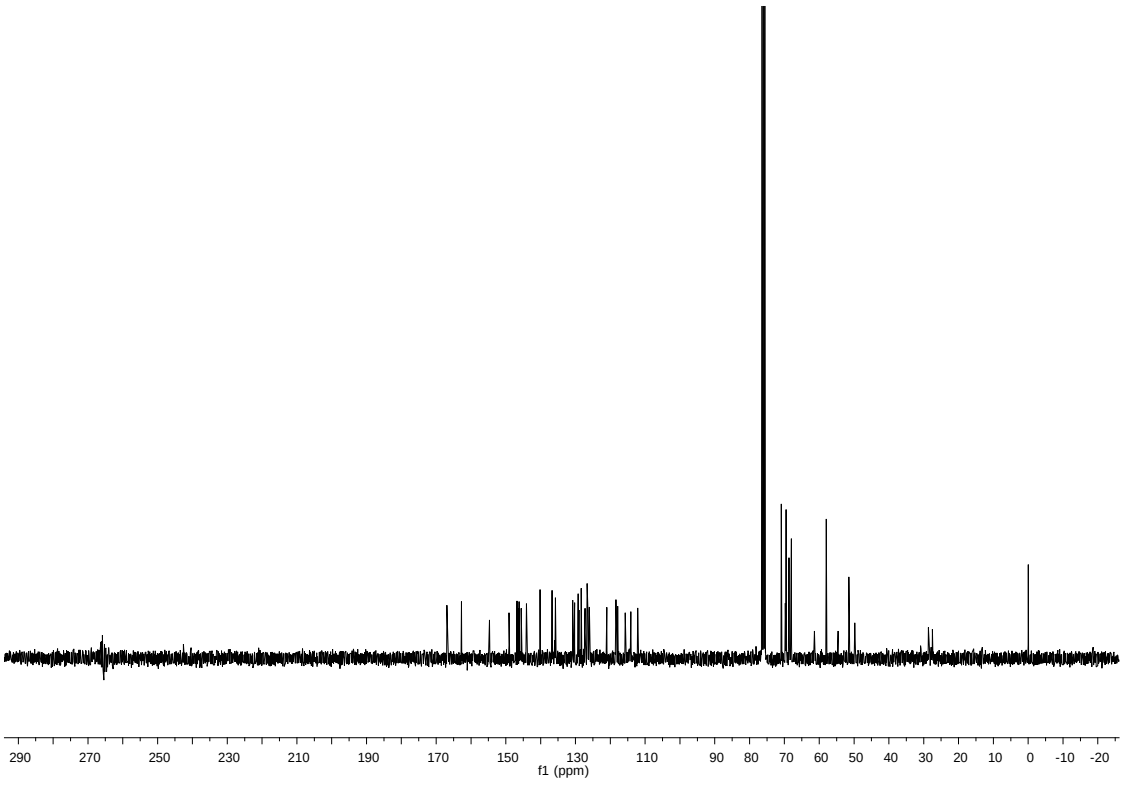




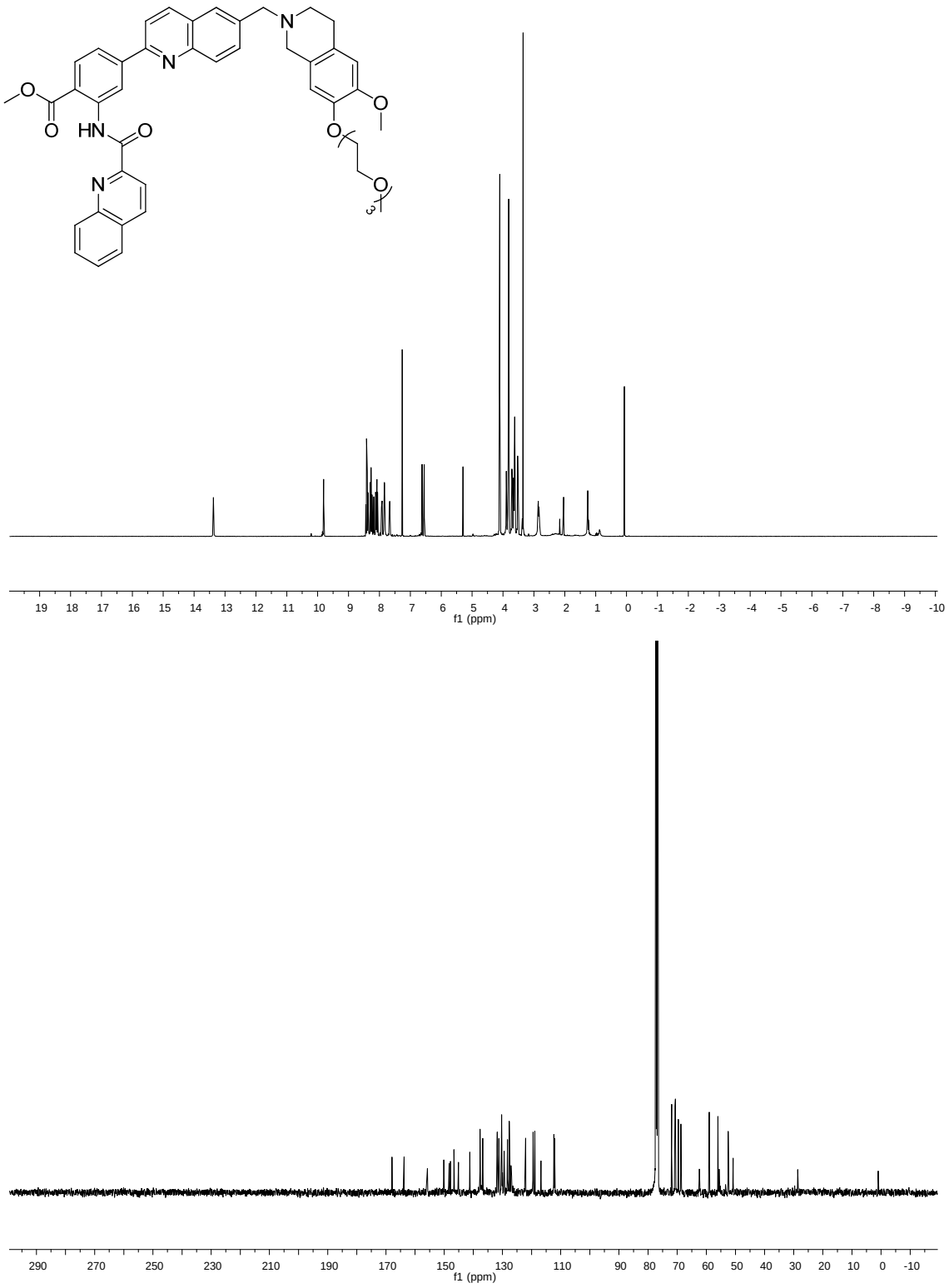
Methyl 4-(6-((6,7-bis(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)-methyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 26



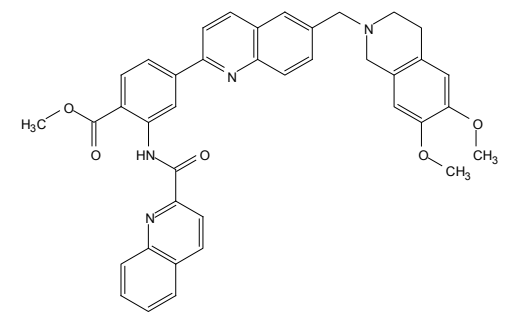


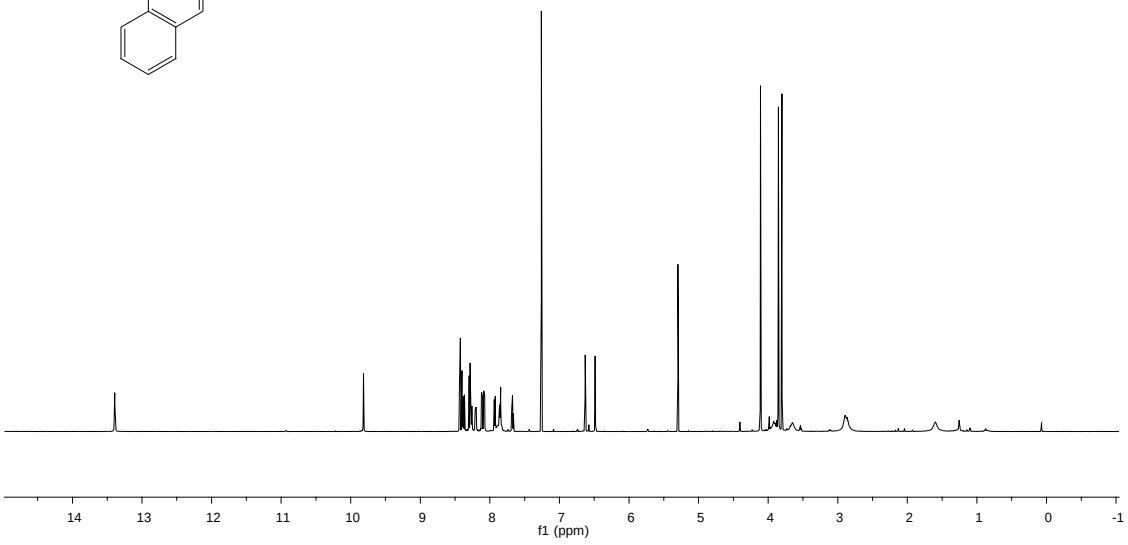


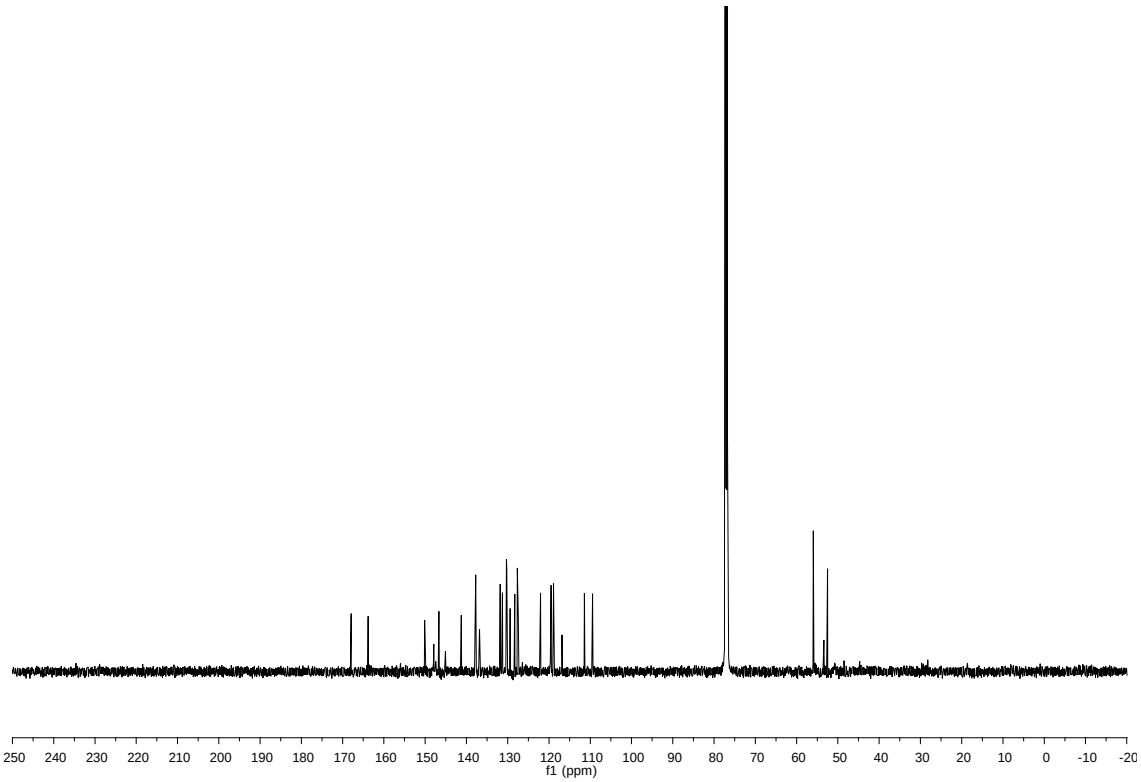
Methyl 4-(6-((6-methoxy-7-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 27



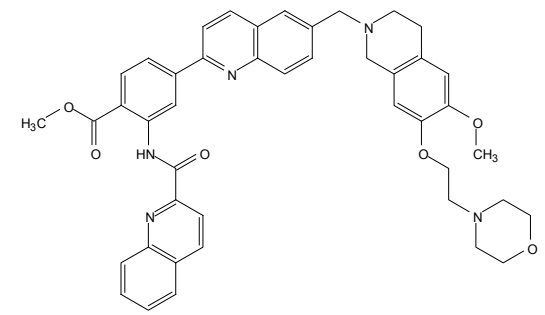
Methyl 4-(6-((6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 28

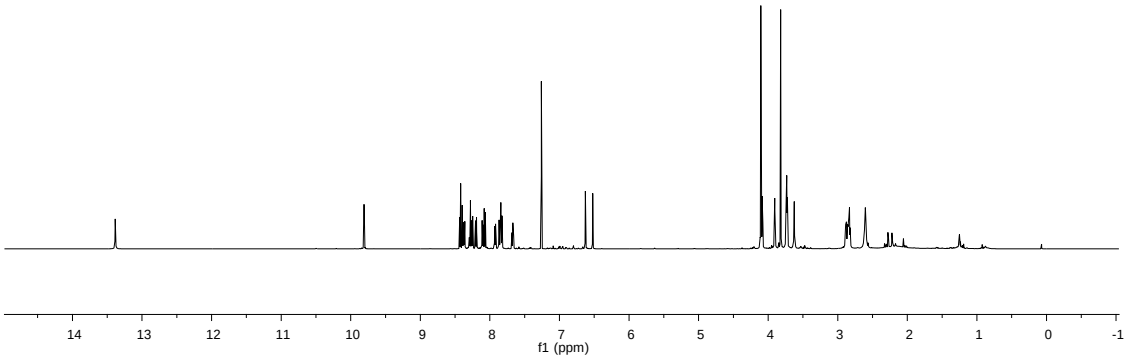


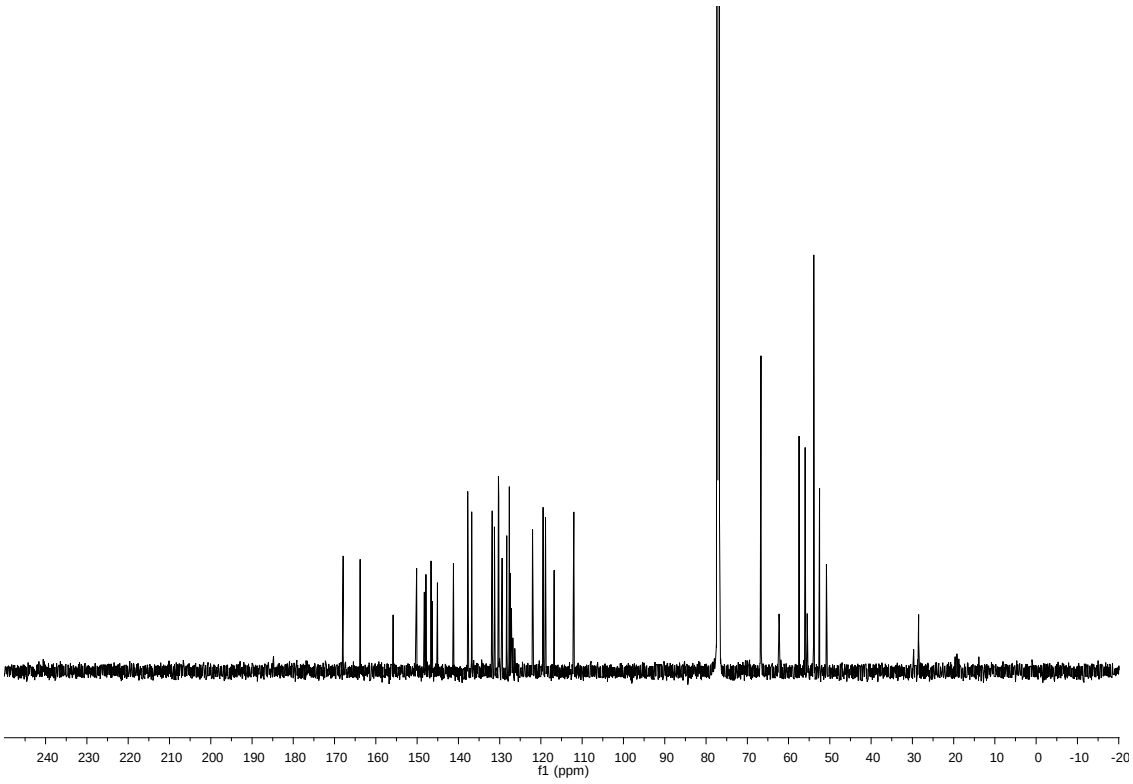




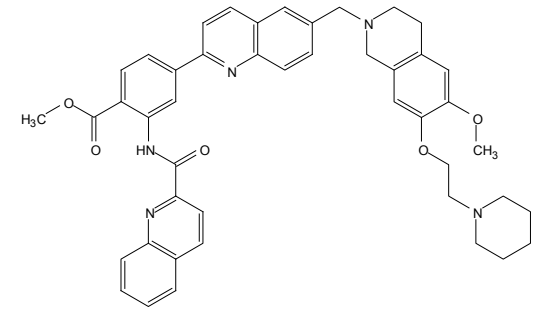
Methyl 4-(6-((6-methoxy-7-(2-morpholinoethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl) methyl) quinolin-2-yl)-2-(quinoline-2-carbonylamino) benzoate 42

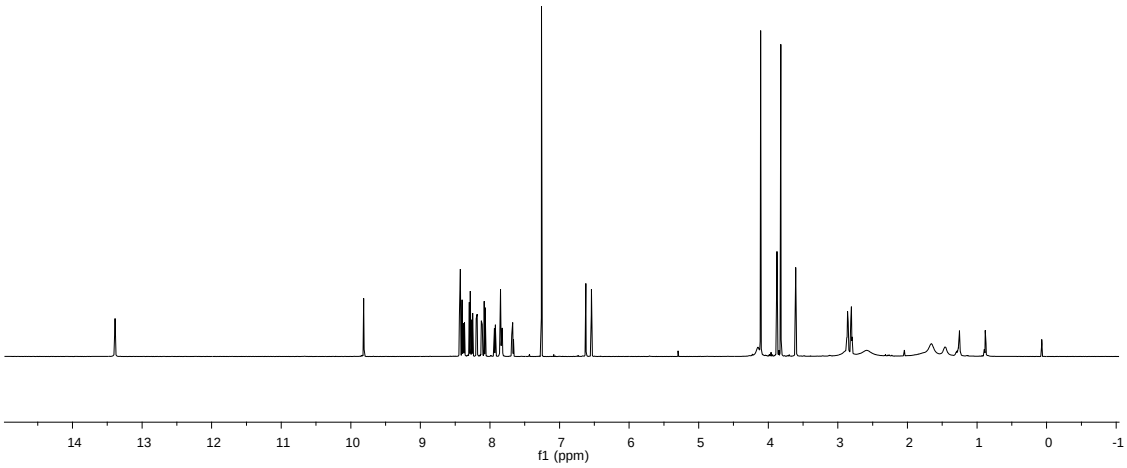


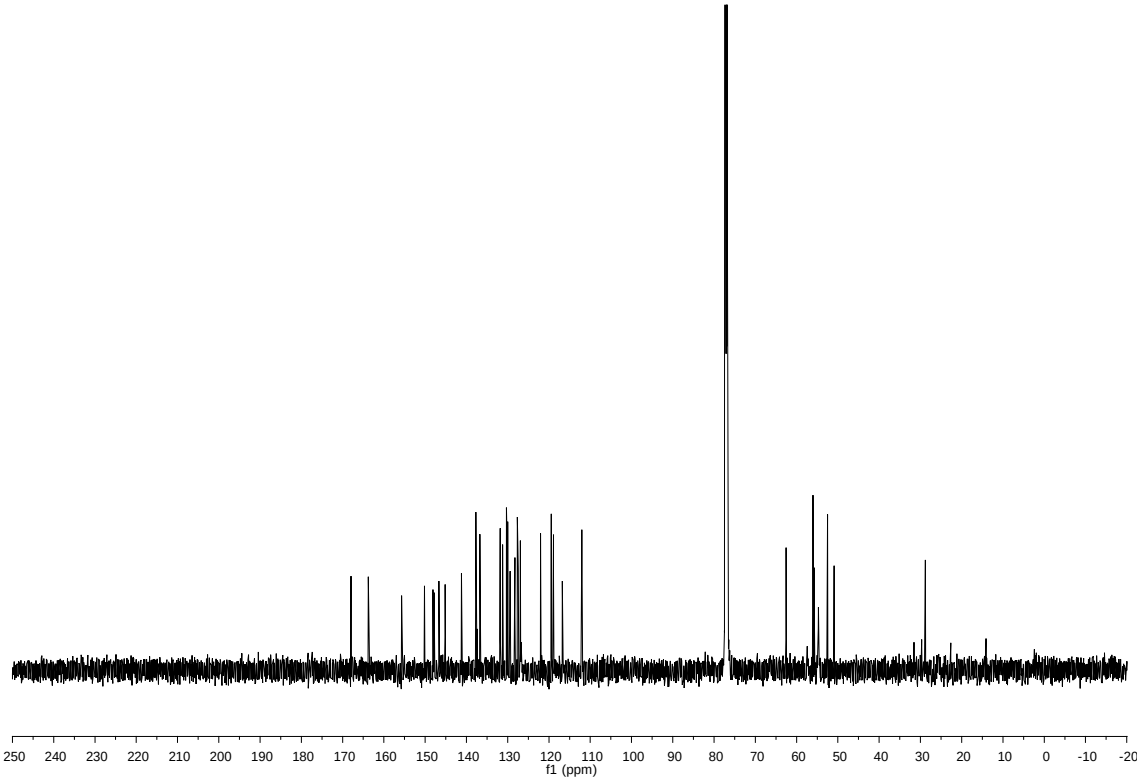




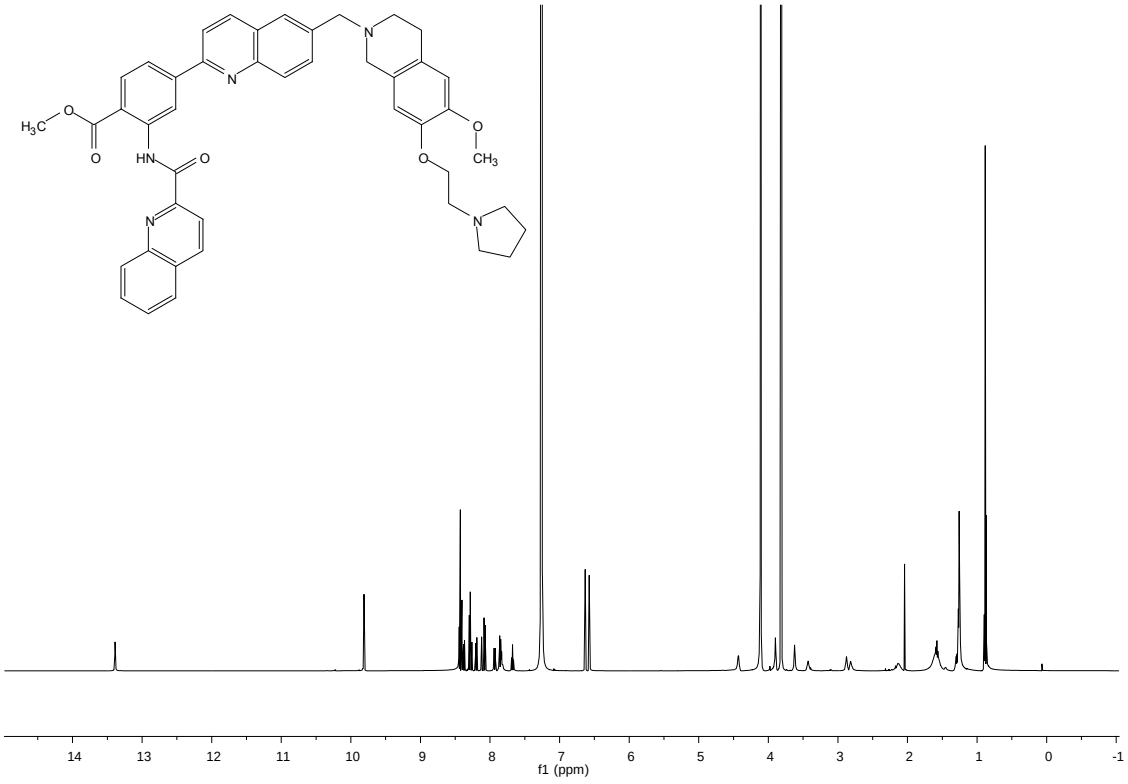
Methyl 4-(6-((6-methoxy-7-(2-(piperidin-1-yl)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino) benzoate 43

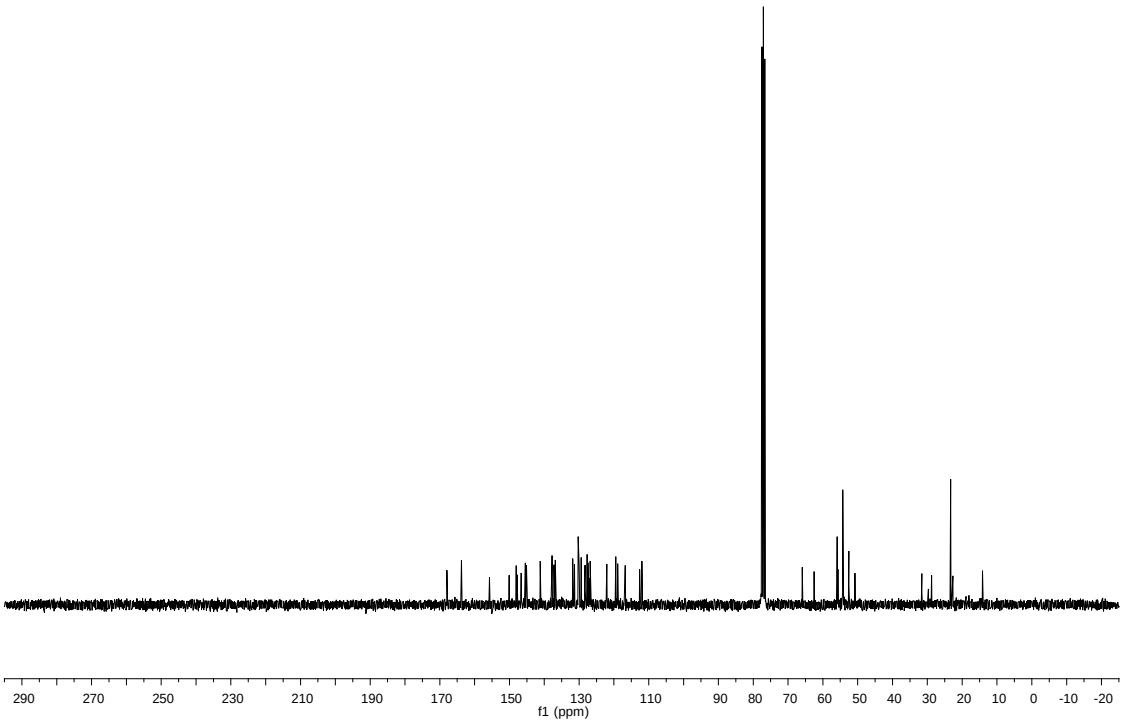




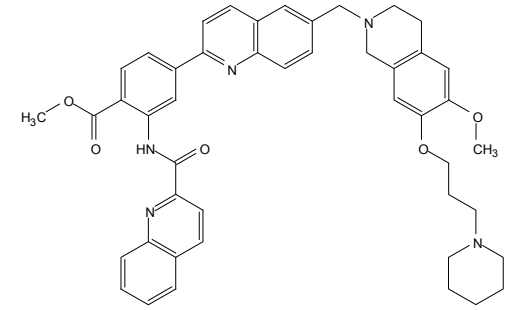


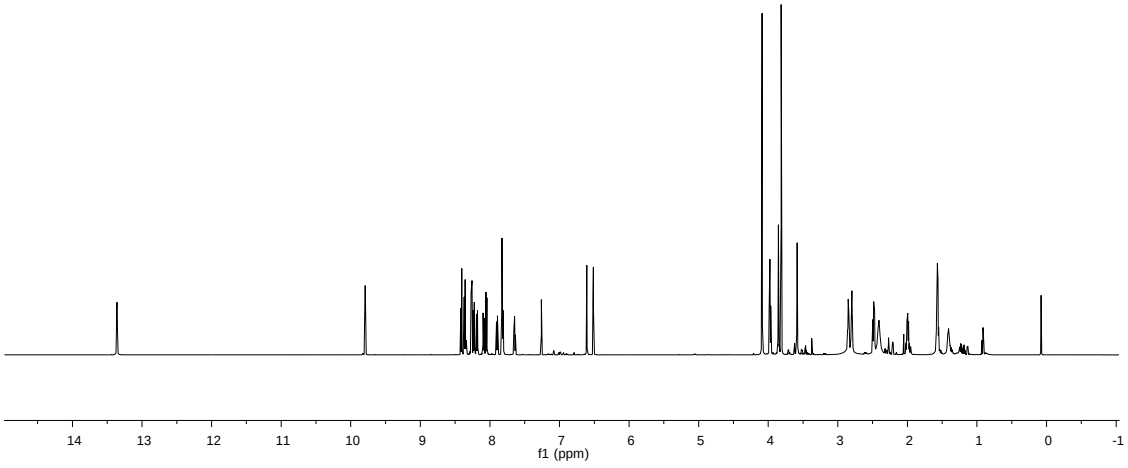
Methyl 4-(6-((6-methoxy-7-(2-(pyrrolidin-1-yl)ethoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 44

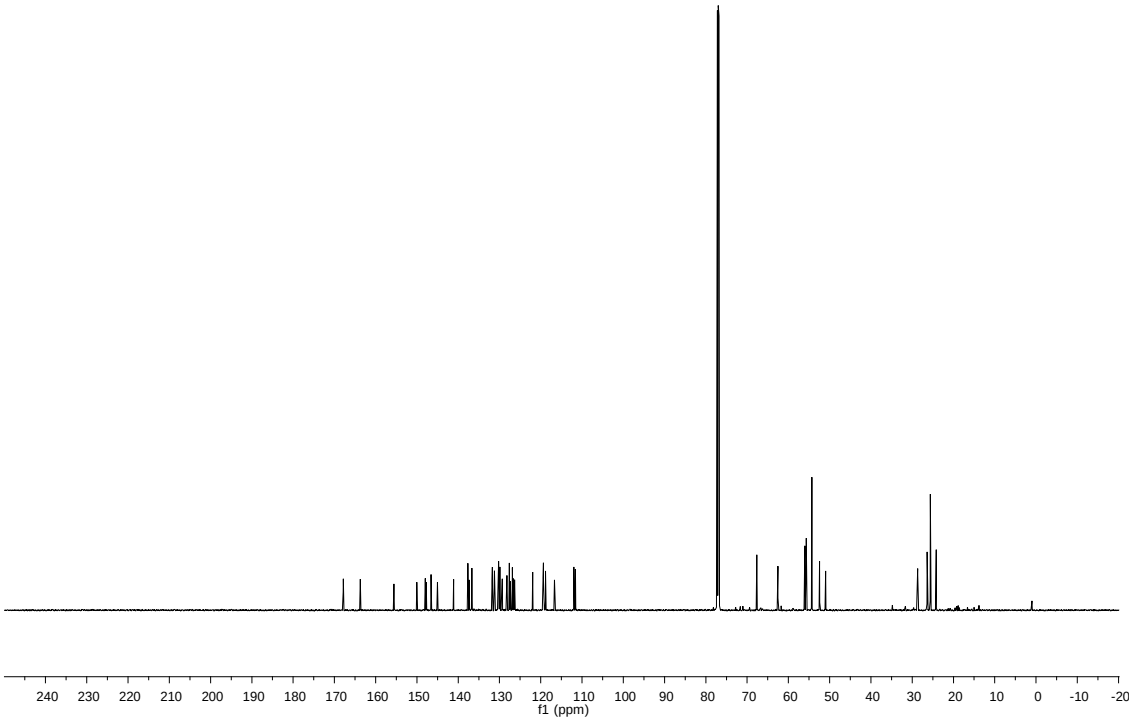




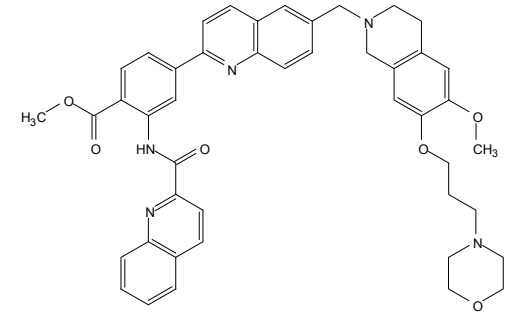
Methyl 4-(6-((6-methoxy-7-(3-(piperidin-1-yl)propoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 45

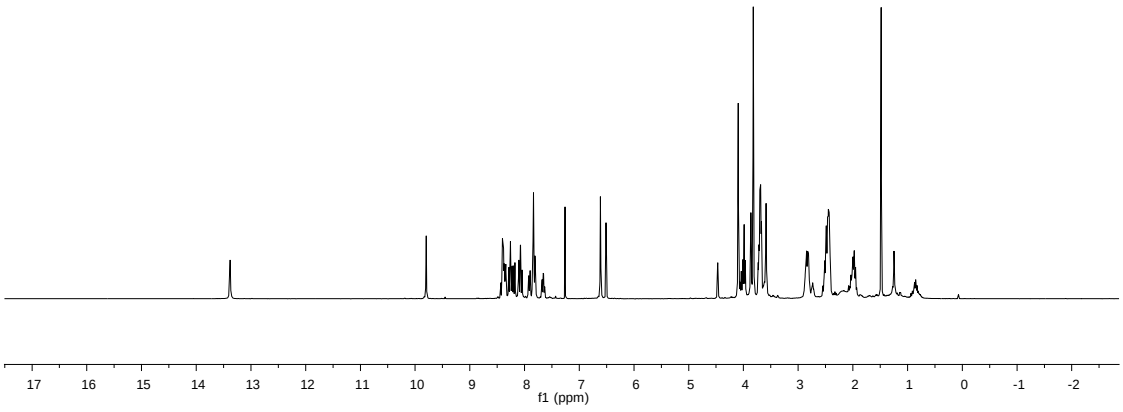


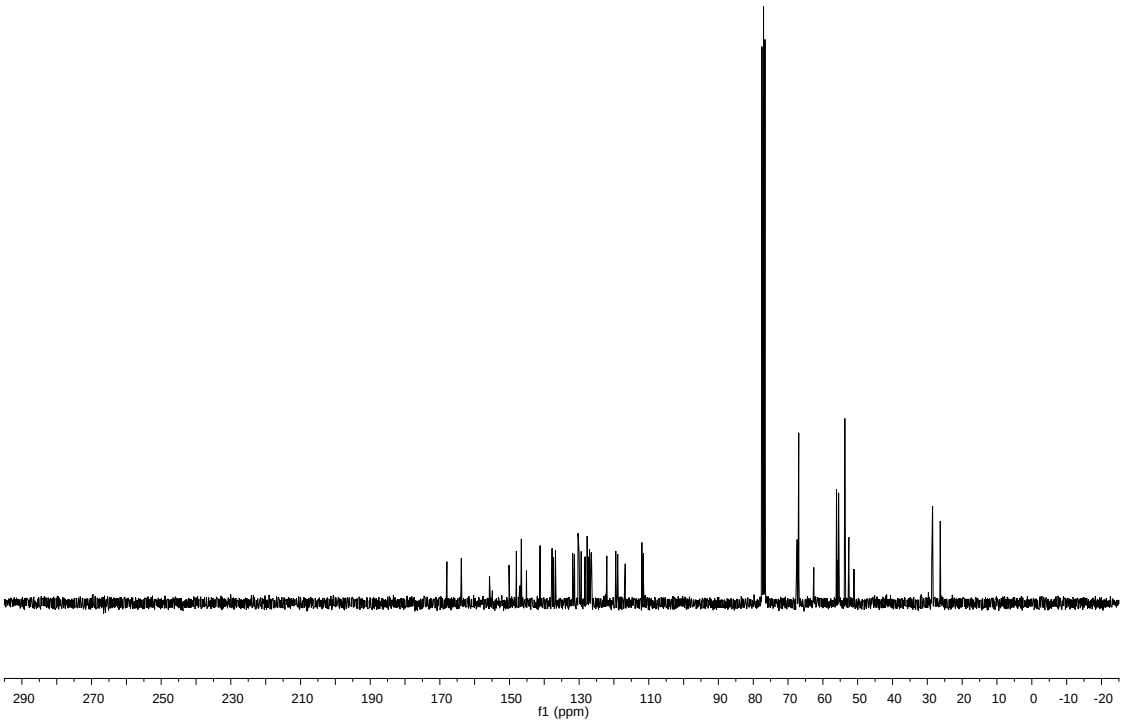




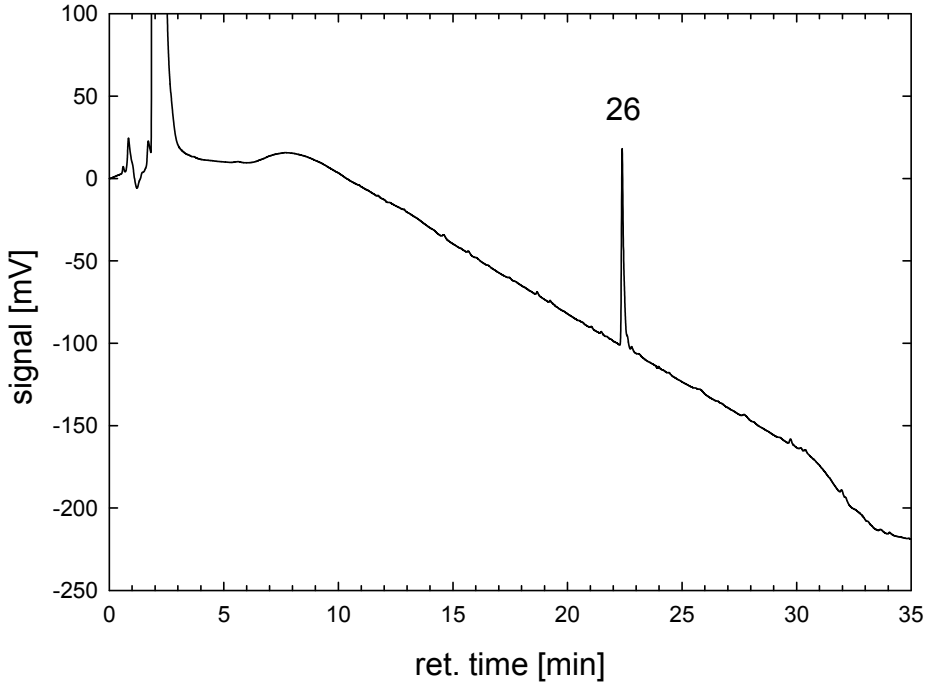
Methyl 4-(6-((6-methoxy-7-(3-morpholinopropoxy)-3,4-dihydroisoquinolin-2(1*H*)-yl)methyl)-quinolin-2-yl)-2-(quinoline-2-carbonylamino)benzoate 46

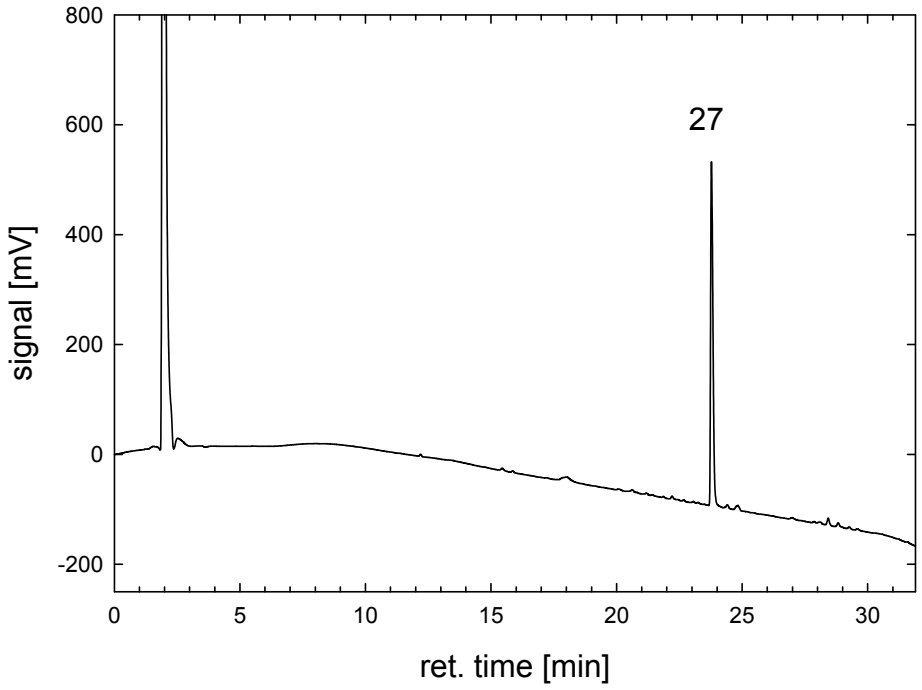






3.3 HPLC analysis of compounds 26-28





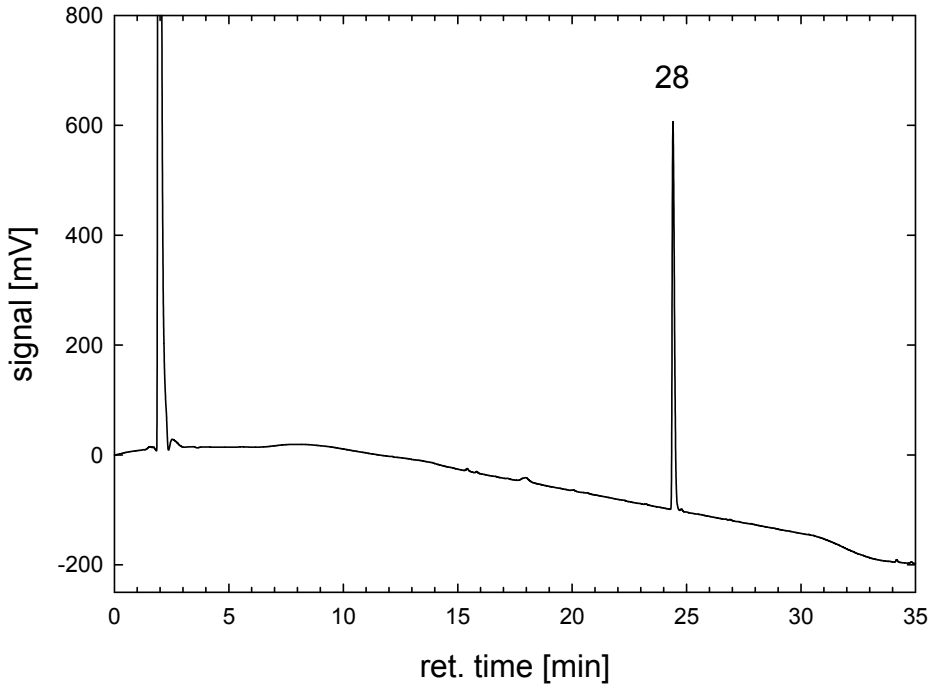


Figure 3. HPLC analysis of compounds **26-28** (UV-detection at 210 nm).

4 Assay protocol for the determination of ABCC1 inhibition

Drugs and chemicals used for assays. Calcein-AM (4 mM in anhydrous DMSO) and pluronic F127 were obtained from Biotium (Hayward, CA, USA). Bovine serum albumin (BSA) was purchased from Serva (Heidelberg, Germany. Reversan (Tocris Bioscience, Bristol, UK) was dissolved in DMSO and diluted to a concentration of 3 mM.
The test compounds were dissolved in DMSO at a concentration of 10 mM if possible, depending on the solubility of the compounds. All stock solutions were stored at -20 °C.
Loading buffer was made of 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2 \cdot 6\ H_2O$, 1.5 mM $CaCl_2 \cdot 2\ H_2O$, 25 mM HEPES, 10 mM glucose, pH 7.4.
PBS (phosphate buffered saline) was made of 8.0 g/L NaCl, 1.0 g/L $Na_2HPO_4 \cdot 2\ H_2O$, 0.20 g/L KCl, 0.20 g/L KH_2PO_4 and 0.15 g/L $NaH_2PO_4 \cdot H_2O$. The pH value was adjusted to 7.3 - 7.4. A solution of 4% (m/m) paraformaldeyde (PFA) in PBS was made by stirring 2 g of PFA per 50 g total solution while heating on a magnetic stirrer for approximately 30 min. If not otherwise stated, chemicals (p.a. quality) were obtained from Merck (Darmstadt, Germany). Purified water (Milli-Q system, Millipore, Eschborn, Germany) was used throughout.

Cell line and culture conditions. MDCKII-MRP1 cells: MDCKII cells (Madin-Darby Canine Kidney cells, strain II; an epithelial cell line; ATCC® CRL-2936), transfected with the gene encoding human ABCC1, were a kind gift from Prof. Dr. P. Borst (Netherland Cancer Institute, Amsterdam, NL).[11] The cells were cultured in Dulbecco's Minimum Essential Medium (DMEM; Sigma, Munich, Germany) supplemented with 10% fetal calf serum (FCS; Biochrom, Berlin, Germany), 3.7 g/L of sodium hydrogen carbonate and 110 mg/L of sodium pyruvate.

Calcein-AM (MRP1) standard protocol. MDCKII-MRP1 cells were seeded into flat-bottomed 96-well plates at a density of 20000-25000 cells per well. On the following day, cells were washed with loading buffer in order to remove unspecific serum esterases. Afterwards, cells were incubated with loading suspension (loading buffer, 5 mg/mL BSA, 1.25 µL/mL pluronic F127 (20% in DMSO)) containing 0.5 µM calcein-AM and the test compound at increasing concentrations (10 nM – 100 µM) for 60 min (37 °C / 5% CO_2). In general, test compounds were investigated in triplicate, controls in sextuplicate, respectively. Reversan served as positive control at a final concentration of 30 µM corresponding to 100% ABCC1 inhibition.
Subsequently, the loading suspension was discarded, and the cells were fixed with 4% PFA solution in PBS for 20 min. After three washing cycles (loading buffer), fixed cells were overlaid with loading buffer and relative fluorescence intensities were determined at 535/25 nm at a GENios Pro microplate reader (TECAN Deutschland GmbH, Crailsheim, Germany) after excitation at 485/20 nm.
TECAN instrument settings: Measurement mode: fluorescence top; number of reads: 10; integration time: 40 µs; lag time: 0 µs; mirror selection: Dichroic 3 (e.g. Fl.); plate definition file: GRE96ft.pdf; multiple reads per well (Circle): 3x3; time between move and flash: 100 ms.
The following cell quantification procedure was performed by analogy with the protocol for the Hoechst 33342 assay. All values were corrected by subtraction of the fluorescence intensity in the absence of ABCC1 modulators (DMSO control value) and the maximal response was referred to the signal caused by 30 µM of the reference compound reversan (100 %). IC_{50} values were calculated using SIGMA PLOT 11.0, "Four parameter logistic curve" fitting. Errors were expressed as standard error of the mean (SEM).

5 Chemical Stability in mouse plasma

Investigations were essentially performed according to a previously established procedure. The blood from NMRI (nu/nu) mice was collected by heart puncture in deep anesthesia using heparin-coated syringes. Samples were immediately centrifuged for 7 min at 4500 g (Eppendorf centrifuge 5415R, Eppendorf, Hamburg, Germany) and the supernatant was carefully removed. Stock solutions of the test compounds (3 mM) were prepared in DMSO. A 1:50 dilution of the substances in mouse plasma was prepared in 1.5-mL polypropylene reaction vessels (Eppendorf, Hamburg, Germany). The samples were shortly vortexed and incubated at 37 °C. At different periods of time, aliquots were taken, and the samples were deproteinated by mixing with two parts of ice-cold acetonitrile (MeCN). For quantitative precipitation, the samples were vortexed and stored at 4 °C for 30 min. Finally, samples were centrifuged for 5 min at 14000 g, using an Eppendorf MiniSpin plus centrifuge, and the supernatants were transferred into new reaction vessels. Prior to HPLC analysis, the samples were diluted (1:1) with acetonitrile and stored at -80 °C.
Subsequent RP-HPLC analysis was performed with a Waters (Eschborn, Germany) system composed of a 600S controller and pump, a Waters degasser, a temperature control module, a 717 plus autosampler and a 2487 UV-detector. A Luna RP-18 (Phenomenex, Aschaffenburg, Germany) analytical column (3 µm, 150 mm x 4.6 mm) thermostatted to 30 °C with a flow rate of 1.0 mL/min was used. Samples were thawed at room temperature, and 100 µL were injected. Gradient: MeCN/0.05% TFA (aq.): 0 min: 15/85, 25 min: 80/20, 26 min: 95/5, 36 min: 95/5, 37 min: 15/85, 45 min: 15/85 at a constant flow rate of 1.0 mL/min. UV-detection at 210 nm.
Cleavage products were identified by HPLC-MS analysis (Agilent 1100, Palo Alto, CA) using a Luna C18, 3 µm, 100 mm x 2 mm column (Phenomenex, Aschaffenburg, Germany) at 40 °C. Gradient elution with aqueous formic acid (0.1%) and acetonitrile (0 min: 3%; 15 min: 95%; 17 min: 95%; 17.5 min: 3%; 19 min: 3%) was performed at a flow rate of 0.4 mL/min with UV-detection at 220 nm.
Mass spectrometry: The HPLC was coupled to a Finnigan ThermoQuest TSQ (Triple-Stage-Quadrupol) 7000 ESI (Electron-Spray-Ionization) mass spectrometer, capillary temperature: 250 °C, spray voltage: 4.0 kV, sheath and auxiliary gas: on.

Compound UR-COP78 was completely enzymatically degraded within 30 minutes[1, 12] (**Figures 4-5**) giving the degradation products I-V. Structures I and II are the main cleavage products after hydrolysis of the central amide.

All indole-bearing compounds were hydrolyzed at the common ester giving the free carboxylic acid. Additionally, the quinoline carboxamide group was cleaved. Cleavage of the amide was not detectable for all of the investigated compounds via HPLC analysis (cf. **Figures 6-13**). However, it is assumed that, in general, the indole-type ABCG2 modulators are prone to hydrolysis at this position over a longer period of time, though to a different extent.

5.1 Enzymatic cleavage of compound UR-COP78

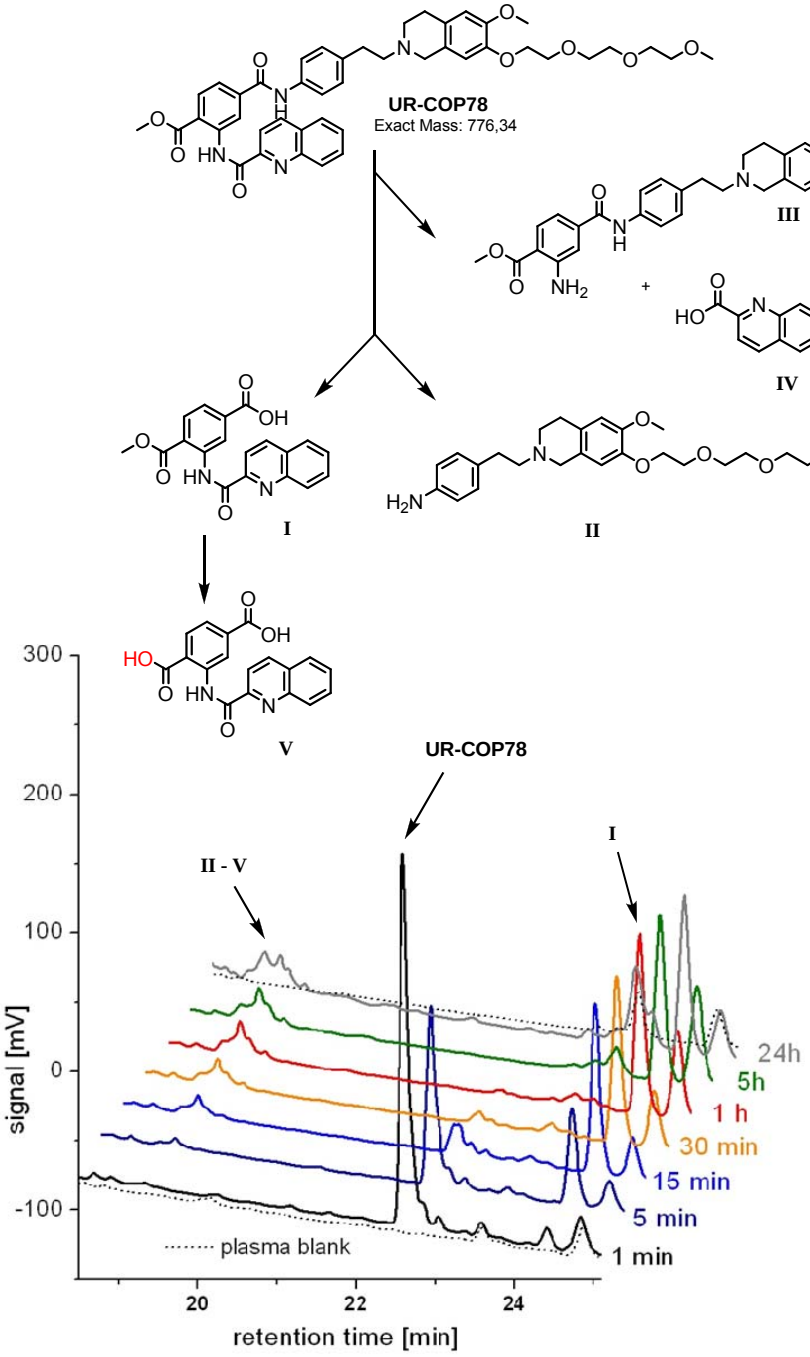


Figure 4. Enzymatic degradation of UR-COP78 when incubated in mouse plasma over a period of 24 h (HPLC analysis, UV detection at 210 nm). The cleavage products were identified by HPLC-MS analysis.

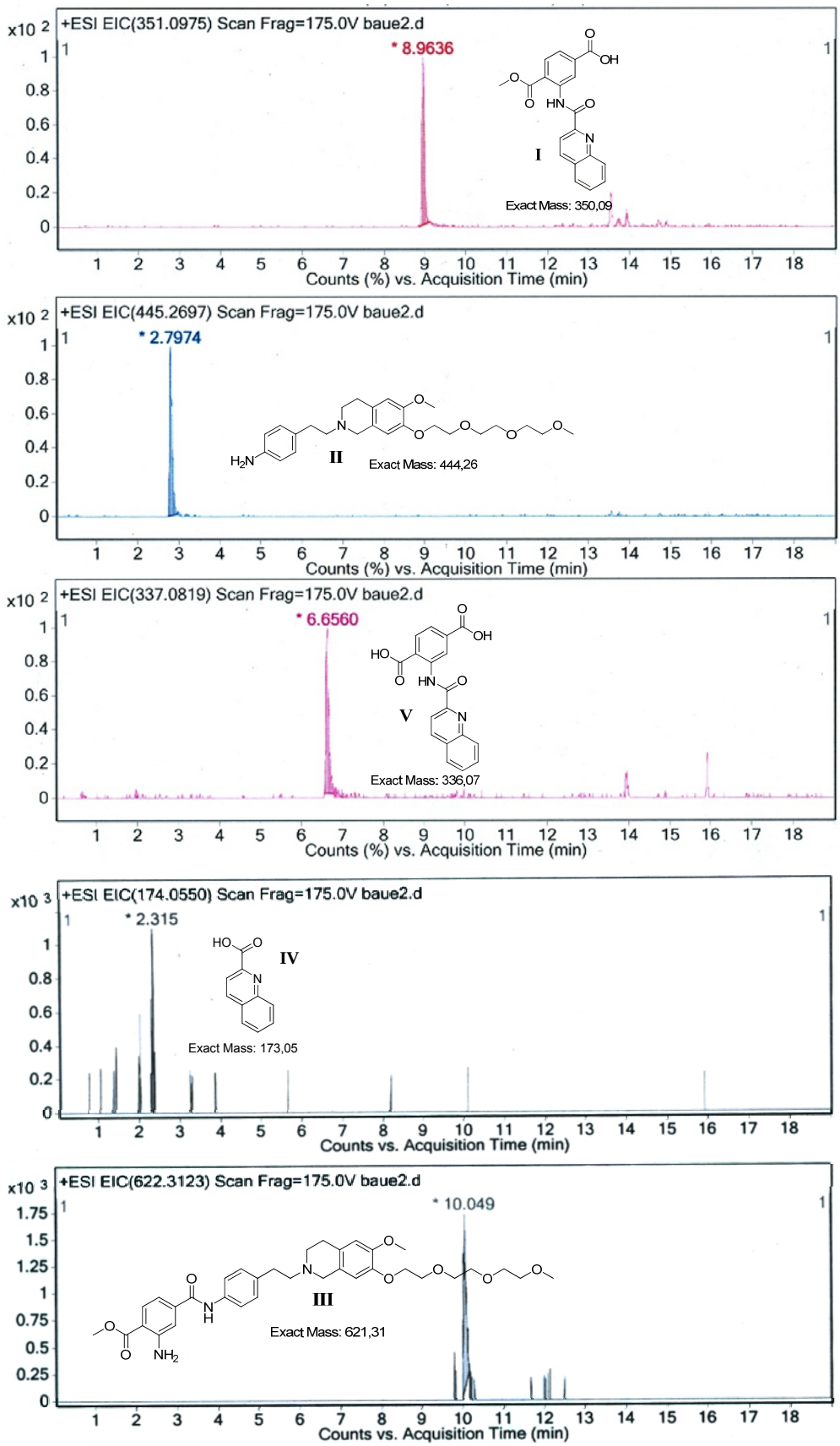


Figure 5. HPLC-MS analysis of compound UR-COP78 after incubation in mouse plasma: Detection of the cleavage products in plasma of NMRI mice (nu/nu), 24 h after incubation at 37°C.

5.2 Enzymatic cleavage of compound 25a (UR-COP240)

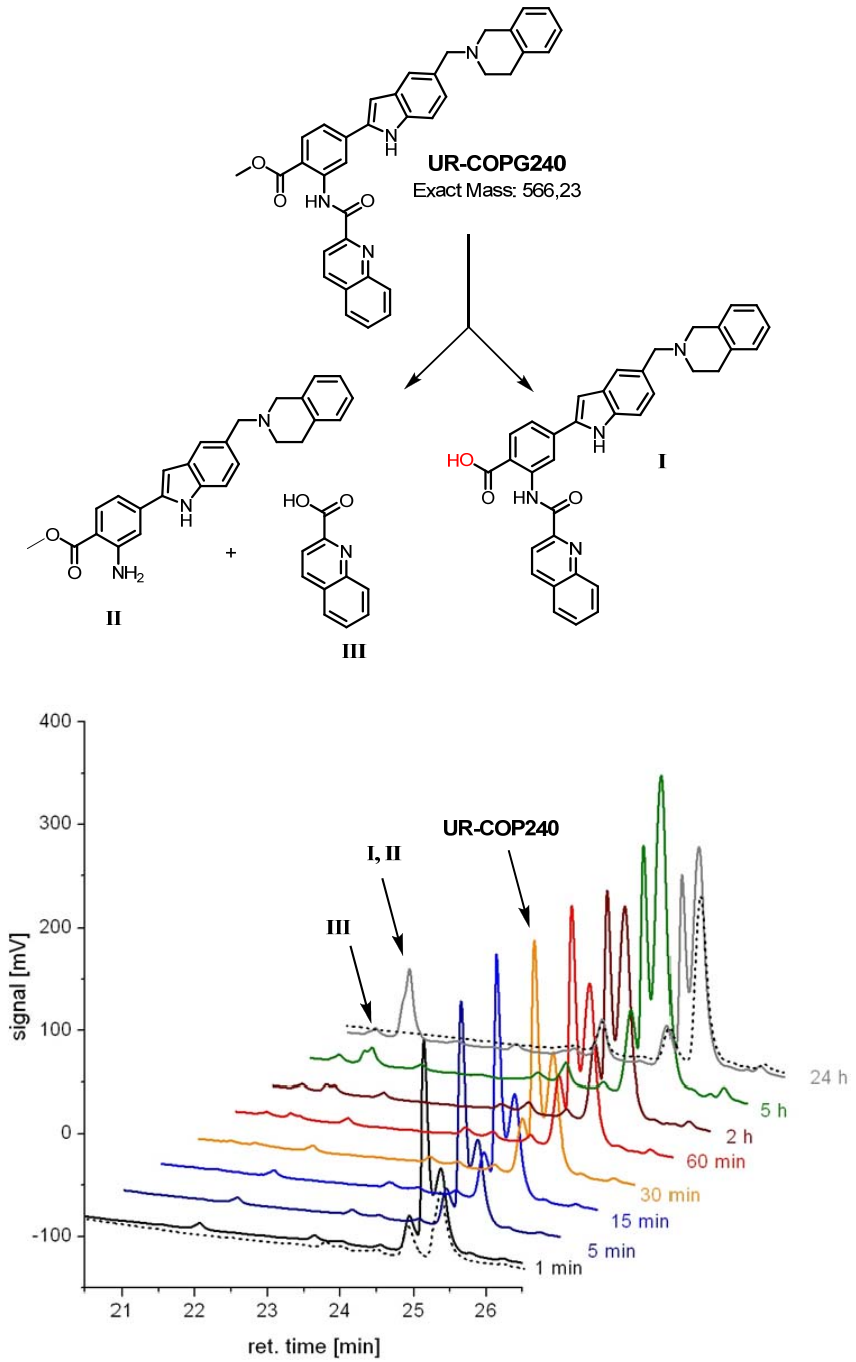


Figure 6. Enzymatic degradation of compound **25a** (UR-COP240) when incubated in mouse plasma over a period of 24 h (HPLC analysis, UV detection at 210 nm). The cleavage products were identified by HPLC-MS analysis.

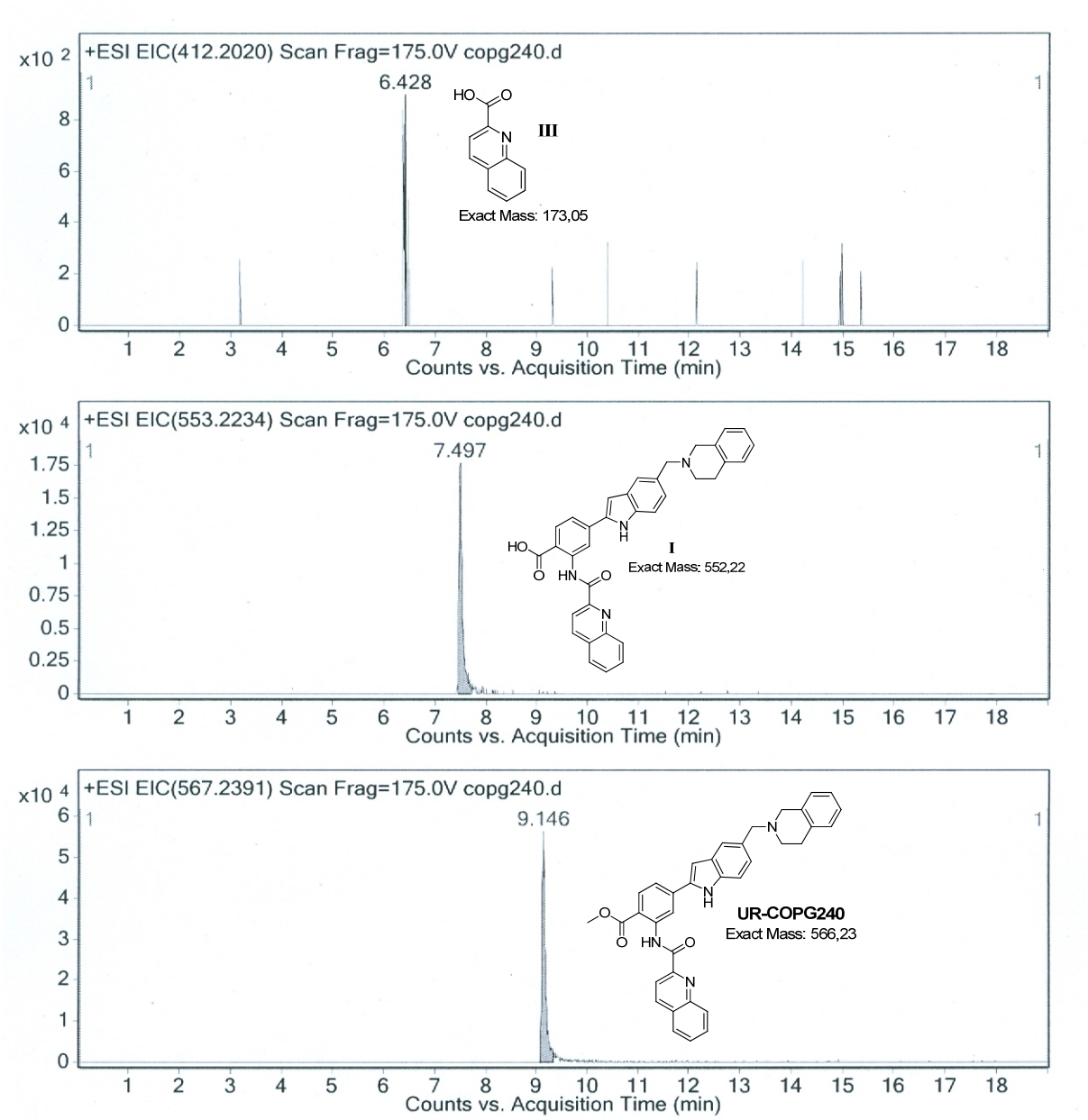


Figure 7. HPLC-MS analysis of compound **25a** (UR-COP240) after incubation in mouse plasma: Detection of the cleavage products in plasma of NMRI mice (nu/nu), 24 h after incubation at 37 °C.

5.3 Enzymatic cleavage of compound 25c (UR-COP251)

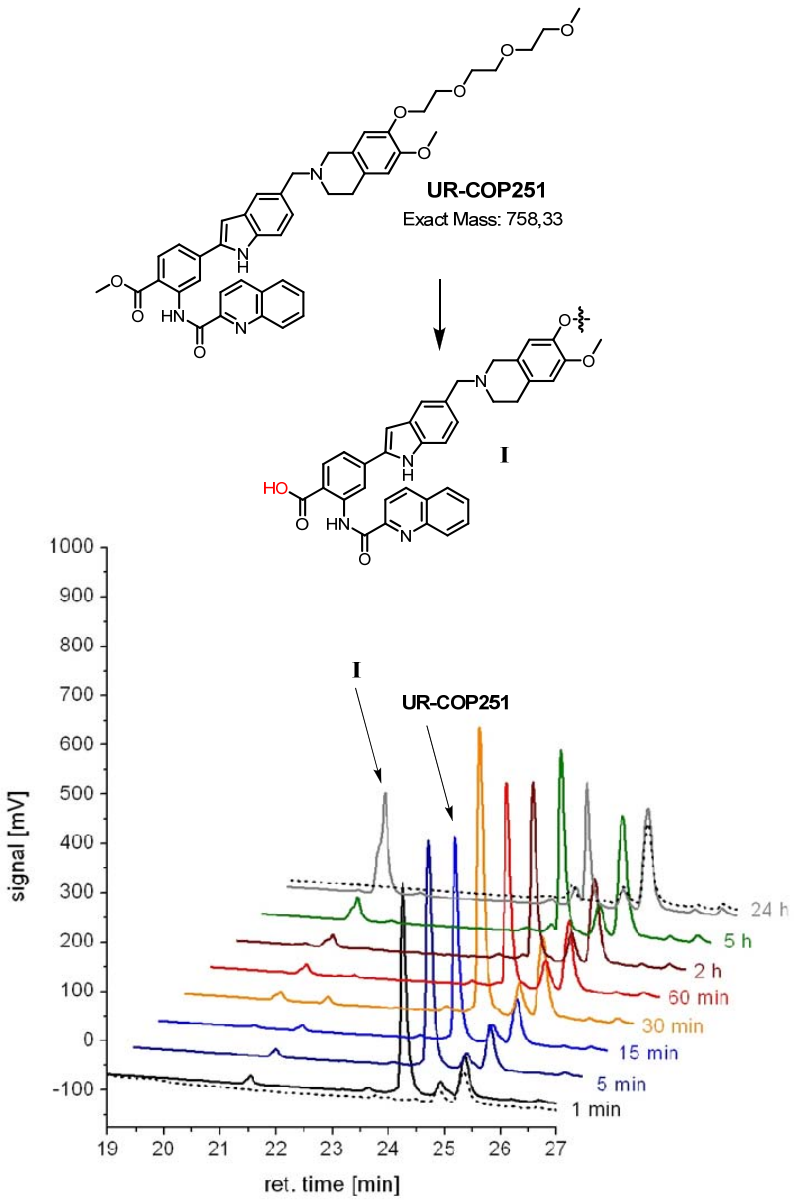


Figure 8. Enzymatic degradation of compound **25c** (UR-COP251) when incubated in mouse plasma over a period of 24 h (HPLC analysis, UV detection at 210 nm). The cleavage products were identified by HPLC-MS analysis.

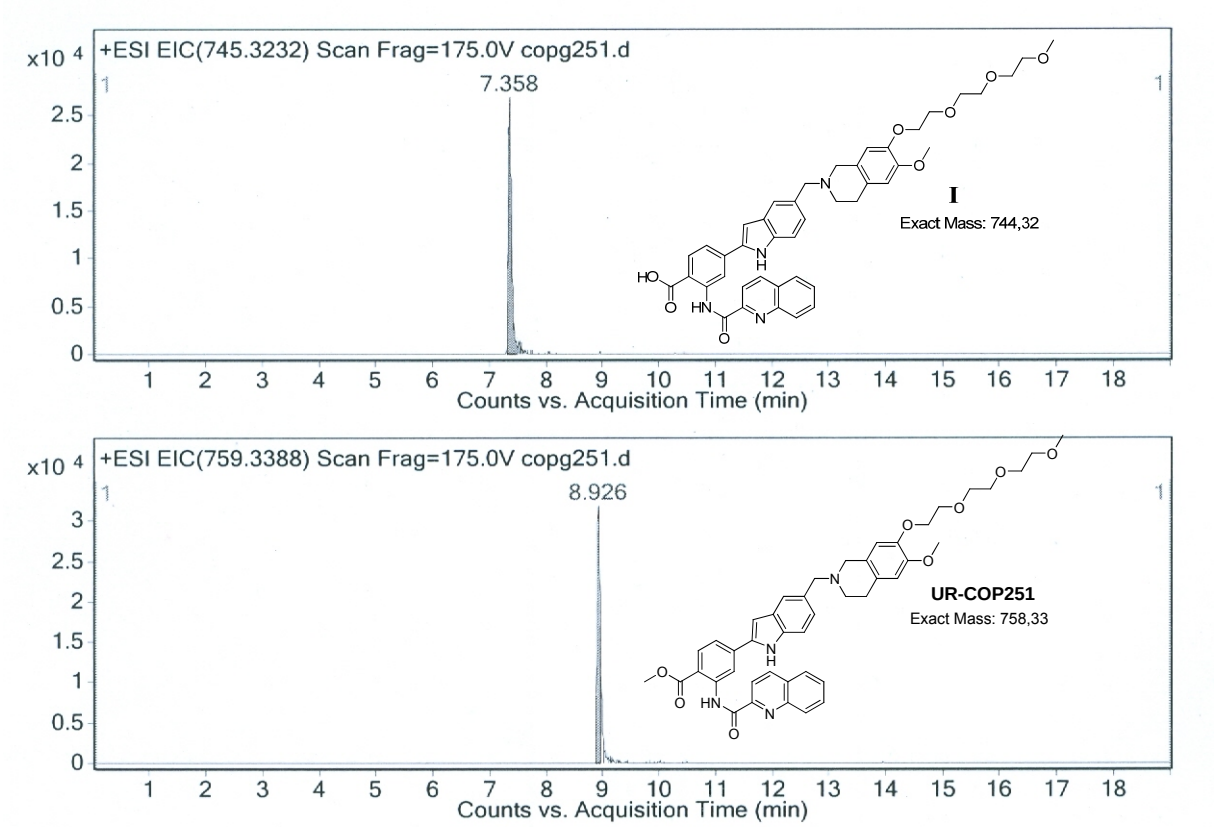


Figure 9. HPLC-MS analysis of compound **25c** (UR-COP251) after incubation in mouse plasma: Detection of the cleavage product in plasma of NMRI mice (nu/nu), 24 h after incubation at 37°C.

5.4 Enzymatic cleavage of compound 25g (UR-COP269)

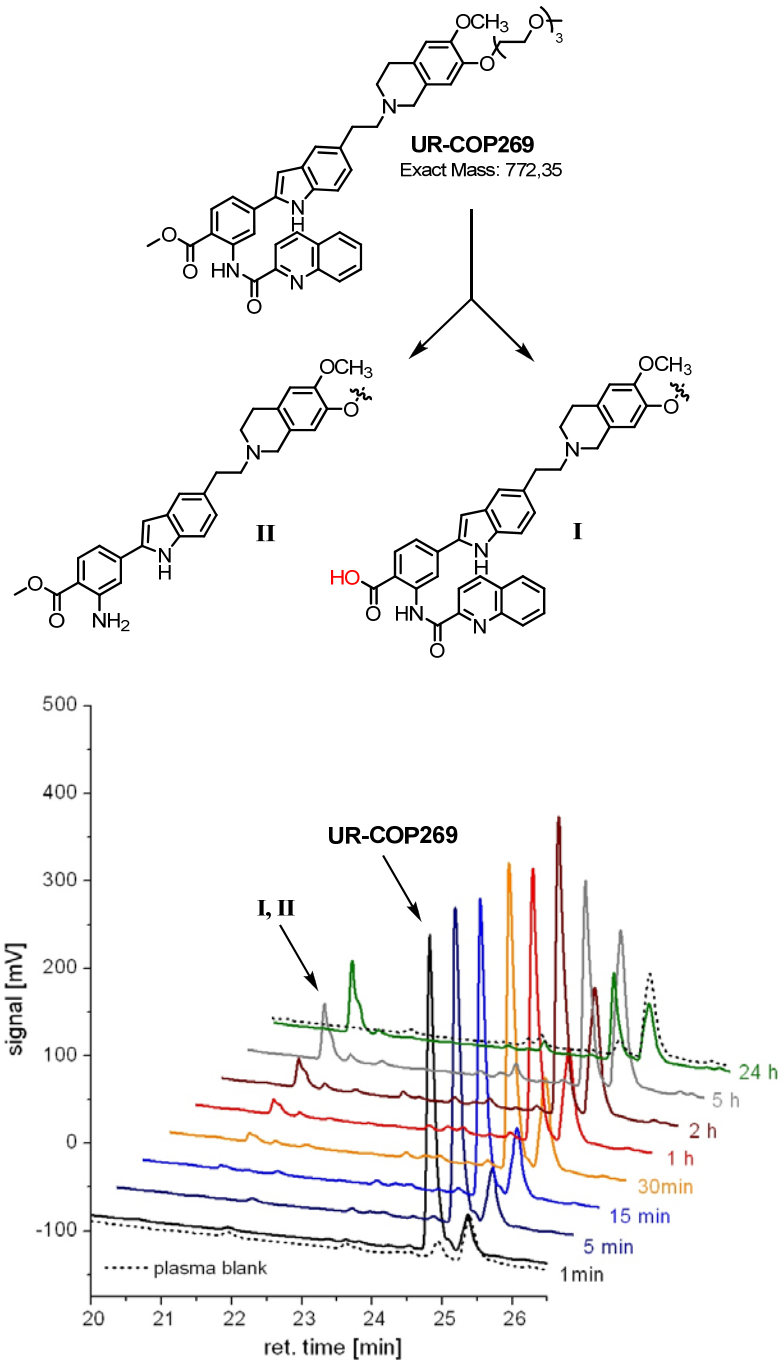


Figure 10. Enzymatic degradation of compound **25g** (UR-COP269) when incubated in mouse plasma over a period of 24 h (HPLC analysis, UV detection at 210 nm). The cleavage products were identified by HPLC-MS analysis.

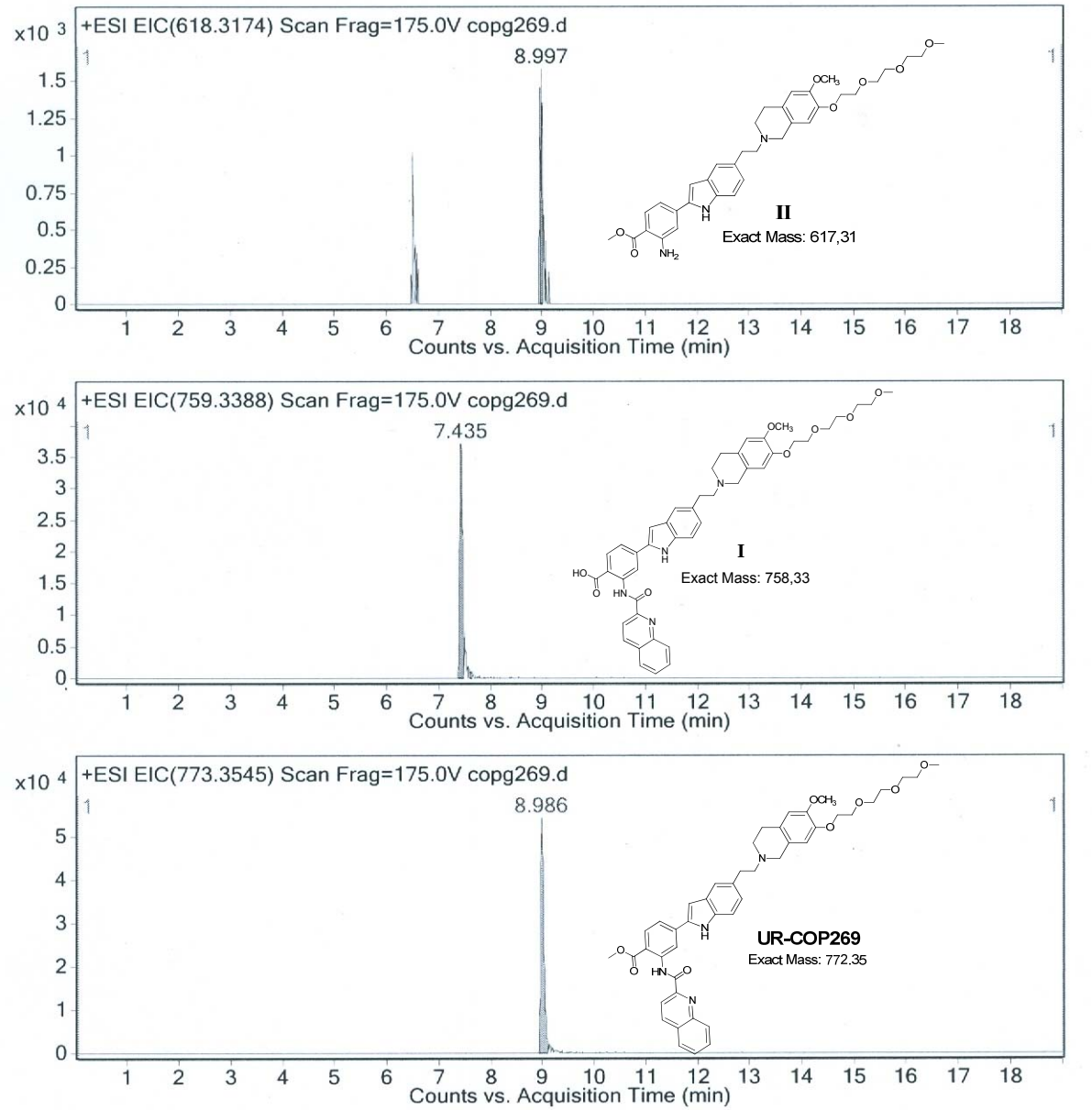


Figure 11. HPLC-MS analysis of compound **25g** (UR-COP269) after incubation in mouse plasma: Detection of the cleavage products in plasma of NMRI mice (nu/nu), 24 h after incubation at 37°C.

5.5 Enzymatic cleavage of compound 25h (UR-COP272)

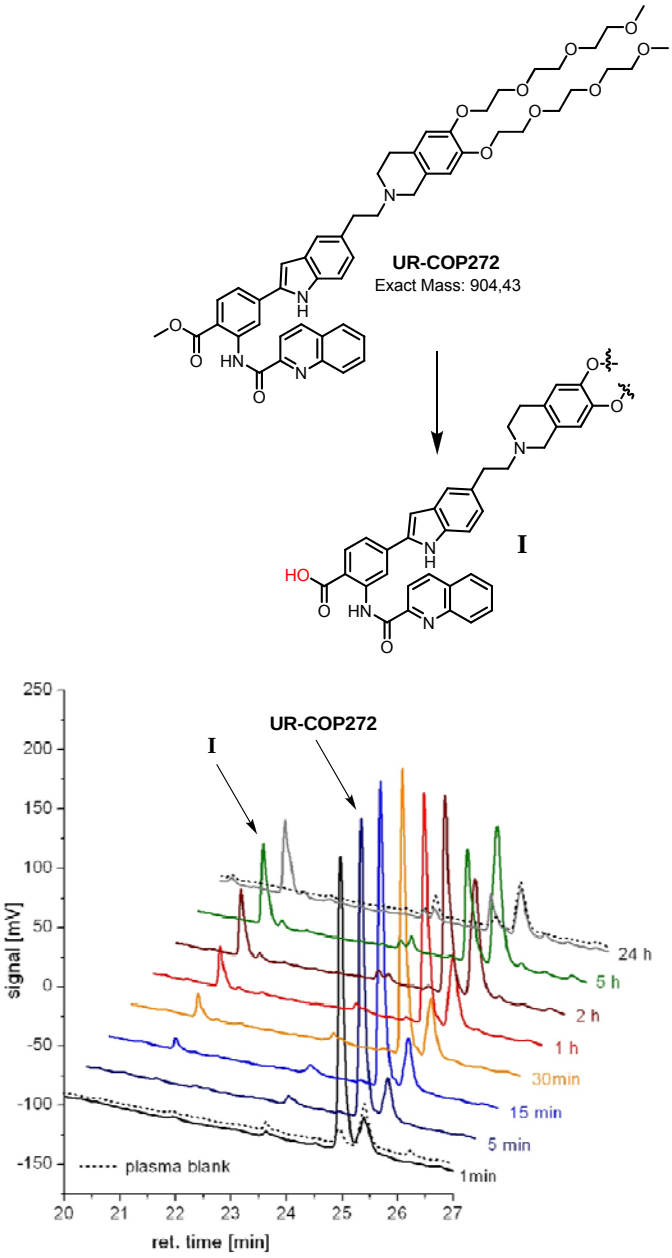


Figure 12. Enzymatic degradation of compound **25h** (UR-COP272) when incubated in mouse plasma over a period of 24 h (HPLC analysis, UV detection at 210 nm). The cleavage products were identified by HPLC-MS analysis.

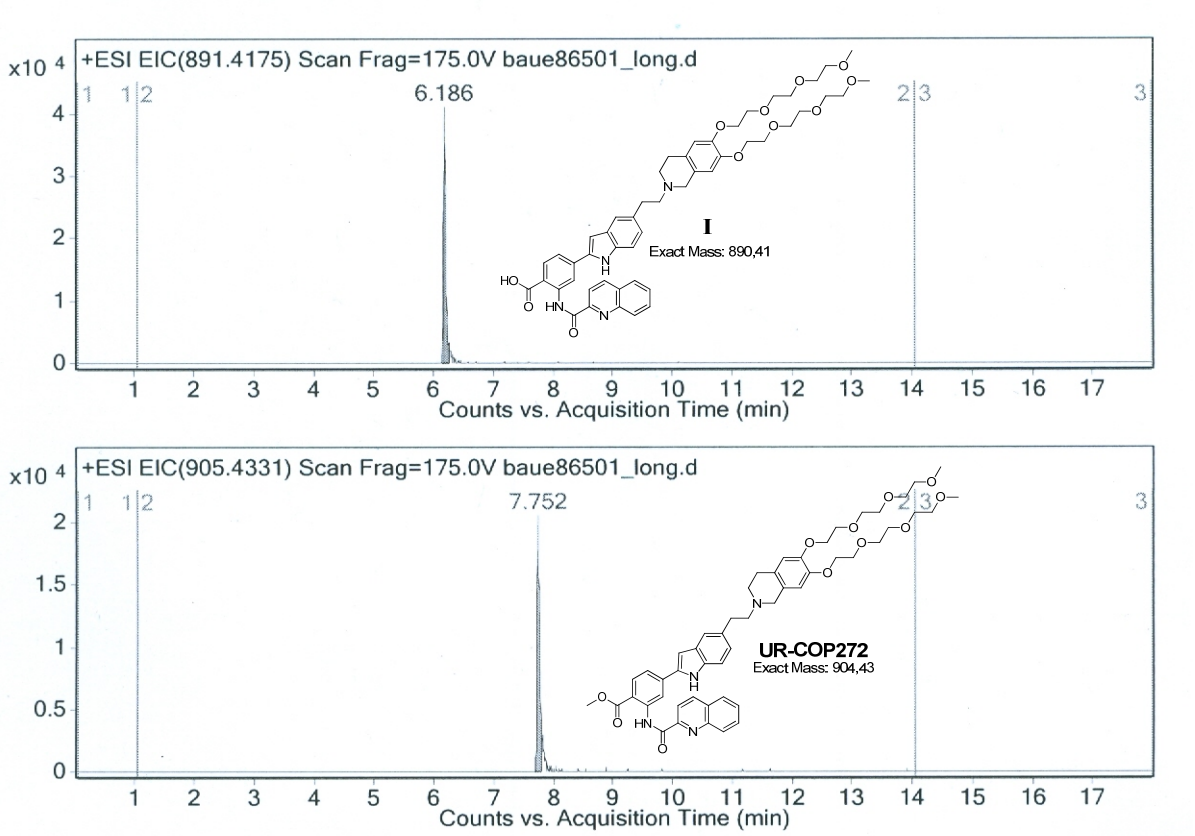


Figure 13. HPLC-MS analysis of compound **25h** (UR-COP272) after incubation in mouse plasma: Detection of the cleavage product in plasma of NMRI mice (nu/nu), 24 h after incubation at 37°C.

6 References

[1] C. O. Puentes, P. Höcherl, M. Kühnle, S. Bauer, K. Bürger, G. Bernhardt, A. Buschauer, B. König, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3654-3657.

[2] R. Xu, J. R. Lever, S. Z. Lever, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2594-2597.

[3] A. W. Snow, E. E. Foos, *Synthesis* **2003**, 509-512.

[4] P. Blurton, F. Burkamp, I. Churcher, T. Harrison, J. Neduvelil, **2006**, (Merck Sharp & Dohme, UK) WO2006008558; *Chem. Abstr.* 144:150126.

[5] R. Weinstain, A. Sagi, N. Karton, D. Shabat, *Chemistry* **2008**, *14*, 6857-6861.

[6] S. Ueda, T. Okada, H. Nagasawa, *Chem. Commun.* **2010**, *46*, 2462-2464.

[7] T. Manimaran, T. K. Thiruvengadam, V. T. Ramakrishnan, *Synthesis* **1975**, *1975*, 739-741.

[8] H. Fang, G. Kaur, J. Yan, B. Wang, *Tetrahedron Lett.* **2005**, *46*, 1671-1674.

[9] T. Watanabe, N. Miyaura, A. Suzuki, *Synlett* **1992**, 207-210.

[10] M. Tashiro, T. Yamato, *J. Org. Chem.* **1985**, *50*, 2939-2942.

[11] a) E. Bakos, R. Evers, G. Szakacs, G. E. Tusnady, E. Welker, K. Szabo, M. de Haas, L. van Deemter, P. Borst, A. Varadi, B. Sarkadi, *J. Biol. Chem.* **1998**, *273*, 32167-32175; b) R. Evers, M. Kool, L. van Deemter, H. Janssen, J. Calafat, L. C. Oomen, C. C. Paulusma, R. P. Oude Elferink, F. Baas, A. H. Schinkel, P. Borst, *J. Clin. Invest.* **1998**, *101*, 1310-1319.

[12] a) M. Kühnle, PhD thesis, University of Regensburg, Germany **2010**; b) C. O. Puentes, S. Bauer, M. Kühnle, G. Bernhardt, A. Buschauer, B. König, *ACS Med. Chem. Lett.* **2013**, *4*, 393-396.