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Expansion of the structure-activity relationships of BACE1 inhibitors by harnessing diverse building blocks prepared using a unified synthetic approach

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Supporting Information

Contents

1. Preparation of screening compounds

1.1. General experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Acros, Fluorochem and Alfa Aesar. Scaffolds **6b**–**i** (Figure 1) were synthesised according to literature procedures.[1] All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. All other solvents used were of chromatography or analytical grade. Petrol, TBD, DBU, TFA and NBS refers to petroleum spirit (b.p. 40–60 ℃), triazabicyclodecene, 1,8-diazabicyclo[5.4.0]undec-7-ene, trifluoroacetic acid and N-bromosuccinimide respectively. An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography was performed using silica gel 60 (35–70 μm particles) supplied by Merck. Strong cation exchange solid phase extraction (SCX-SPE) was performed using pre-packed Discovery DSC-SCX cartridges supplied by Supleco. Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Absorptions are reported in wavenumbers (cm^{-1}). Melting points (m.p.) were determined using Stuart melting point apparatus SMP3. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS).

Proton (^1H) and carbon (^{13}C) NMR data was collected on Bruker 300, 400 or 600 MHz spectrometers. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (J) are reported in

Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Assignments were made using COSY, DEPT, HMQC and NOESY experiments.

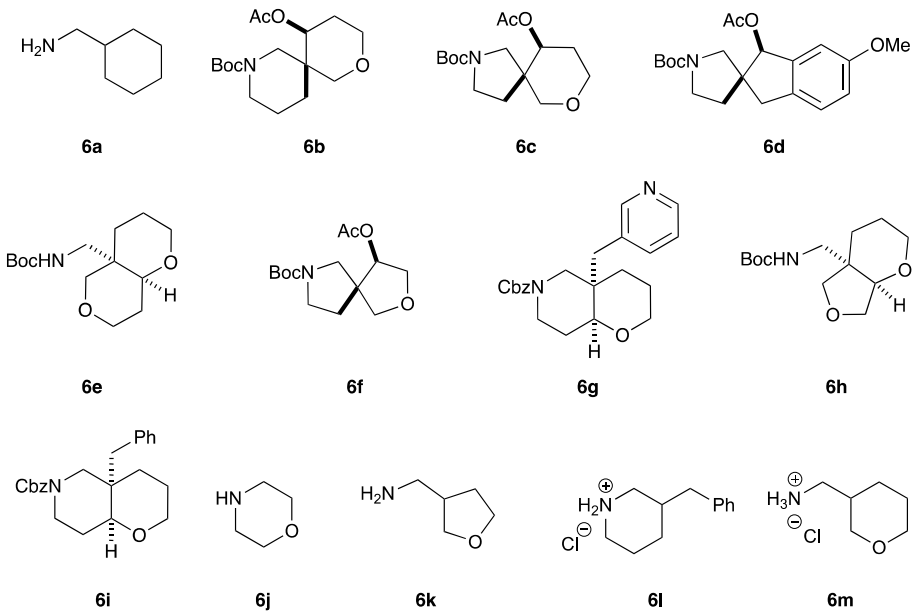


Figure 1: Building blocks used for the synthesis of screening compounds.

1.2. Preparation of thirteen initial screening compounds

1.2.1. Experimental for the preparation of the aminoquinoline ester

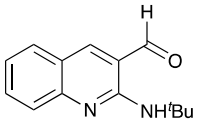
General Procedure A

By modification of an existing procedure,[2] LiCl (2.15 eq) was added to acetonitrile (0.23 M) and the resulting suspension was stirred overnight at rt. Subsequently, the aldehyde derivative **S1** (1.00 eq), the phosphonate derivative (1.32 eq) and DBU (1.10 eq) were added. After stirring the reaction mixture for 4 h at rt, a saturated aqueous solution of $NaHCO_3$ (9 mL per 1.00 mmol of the aldehyde derivative) and EtOAc (5 mL per 1.00 mmol of the aldehyde derivative) were added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × (2 mL per 1.00 mmol of the aldehyde derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure B

Hydrogen gas was passed through a mixture of the alkene derivative (1.00 eq) and Pd (0.05 eq of a 10% Pd/C) in EtOH (20.0 mL per 1.00 mmol of the alkene derivative) for the specified time at rt. Subsequently, the suspension was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give a crude material.

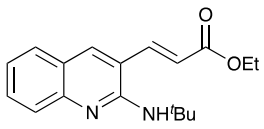
2-(tert-Butylamino)quinoline-3-carbaldehyde



S1

By modification of an existing procedure,[2] tert-butylamine (27.4 mL, 261 mmol) was added to a solution of 2- chloroquinoline- 3- carbaldehyde (5.00 g, 26.1 mmol) in N-methyl-2-pyrrolidone (141 mL) at rt. After stirring for 3 days at 130 ℃, the mixture was allowed to cool to rt and an aqueous solution of 1.0 M HCl (210 mL) was added. The mixture was stirred for 1.5 h and the resulting precipitate was removed by filtration. Subsequently, toluene (150 mL) and water (150 mL) were added. The phases were separated and the aqueous phase was extracted with toluene (10 × 100 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude material. The crude material was purified by flash column chromatography eluting with 5:95 EtOAc−hexane to yield the aldehyde derivative **S1** (3.10 g, 52%) as a bright yellow amorphous solid, R_f 0.57 (80:20 petrol−EtOAc); ν_{max}/cm^{-1} 3335, 2961, 2839, 2725, 1670, 1620, 1573, 1535, 1400, 1356, 1219; δ_H (400 MHz, $CDCl_3$) 9.93 (1H, s, CHO), 8.16 (1H, s, 4-H), 8.04 (1H, br. s, NH), 7.69-7.52 (3H, m, 5,7,8-H_3), 7.21-7.15 (1H, m, 6-H), 1.60 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 193.4 (CHO), 154.2 (C-2), 150.9 (C-8a), 148.7 (C-4), 133.3 (C-7), 129.2 (C-5), 126.9 (C-8), 122.2 (C-6), 121.5 (C-3), 117.8 (C-4a), 51.7 (^{t}Bu C_1), 29.1 (^{t}Bu C_3); HRMS found MH^+, 229.1336. $C_{14}H_{16}N_2O$ requires MH, 229.1340.

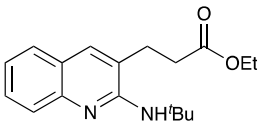
Ethyl (2E)-3-[2-(tert-butylamino)quinolin-3-yl]prop-2-enoate



S2

According to General Procedure A, the aldehyde derivative **S1** (2.00 g, 8.76 mmol) and triethyl phosphonoacetate (2.43 mL, 12.3 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the alkene derivative **S2** (2.58 g, 99%) as a yellow oil, R_f 0.27 (96:4 petrol−EtOAc); ν_{max}/cm^{-1} 3402, 3054, 2960, 1706, 1613, 1600, 1511, 1410, 1301, 1173, 1162; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, s, 4-H), 7.72 (1H, d, J 15.9, propenoate 3-H), 7.68 (1H, d, J 8.3. 8-H), 7.56 (1H, dd, J 8.0 and 1.5, 5-H), 7.53 (1H, ddd, J 8.3, 6.9 and 1.5. 7-H), 7.19 (1H, ddd, J 8.0, 6.9 and 1.2, 6-H), 6.46 (1H, d, J 15.9, propenoate 2-H), 4.60 (1H, br. s, NH), 4.31 (2H, q, J 7.1, ethyl 1-H_2), 1.60 (9H, s, ^{t}Bu), 1.37 (3H, t, J 7.1. ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 166.6 (propenoate C-1), 153.5 (C-2), 148.6 (C-8a), 139.7 (propenoate C-3), 135.6 (C-4), 130.2 (C-7), 127.8 (C-5), 126.7 (C-8), 122.6 (C-3), 122.4 (C-6), 121.9 (propenoate C-2), 119.2 (C-4a), 60.8 (ethyl C-1), 52.3 (^{t}Bu C_1), 29.3 (^{t}Bu C_3), 14.4 (ethyl C-2); HRMS found MH^+, 299.1751. $C_{18}H_{22}N_2O_2$ requires MH, 299.1759.

Ethyl 3-[2-(tert-butylamino)quinolin-3-yl]propanoate



5

According to General Procedure B, the alkene derivative **S2** (2.58 g, 8.64 mmol) was hydrogenated for 30 min to give a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the ester derivative **5** (2.53 g, 97%) as a light yellow amorphous solid, R_f 0.39 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3468, 2962, 2911,

2868, 1720, 1626, 1521, 1421, 1359, 1261, 1228, 1212, 1038; δ_H (300 MHz, $CDCl_3$) 7.71 (1H, d, J 8.3, 8-H), 7.55 (1H, s, 4-H), 7.53 (1H, dd, J 8.1 and 1.3, 5-H), 7.48 (1H, ddd, J 8.3, 7.3 and 1.3, 7-H), 7.18 (1H, ddd, J 8.1, 7.3 and 1.2, 6-H), 4.71 (1H, br. s, NH), 4.19 (2H, q, J 7.1, ethyl 1-H_2), 2.89-2.80 (2H, m, propanoate 3-H_2), 2.74-2.66 (2H, m, propanoate 2-H_2), 1.61 (9H, s, ^{t}Bu), 1.28 (3H, t, J 7.1, ethyl 2-H_3); δ_C (75 MHz, $CDCl_3$) 173.1 (propanoate C-1), 154.6 (C-2), 146.9 (C-8a), 134.2 (C-4), 128.5 (C-7), 126.8 (C-5), 126.5 (C-8), 123.1 (C-3), 122.6 (C-4a), 121.8 (C-6), 60.9 (ethyl C-1), 51.9 (^{t}Bu C_1), 33.0 (propanoate C-2), 29.4 (^{t}Bu C_3), 26.2 (propanoate C-3), 14.3 (ethyl C-2); HRMS found MH^+, 301.1907. $C_{18}H_{24}N_2O_2$ requires MH, 301.1916.

1.2.2. Experimental for the decoration of the scaffolds

General Procedure C (Method A in main text)

By modification of an existing procedure,[3] the respective amine (1.00 eq) and the specified amount of TBD were added to a solution of the ester derivative **5** (1.05 eq) in the specified amount of toluene. If an amine hydrochloride salt was used, Et_3N (17.0 eq) was also added. The reaction mixture was stirred for the specified time at 75 ℃. Subsequently, the solvent was removed under reduced pressure to yield a crude material.

General Procedure D (Method B in main text)

The specified amount of TFA was added to the respective amide derivative (1.00 eq) and the reaction was stirred for the specified time at 75 ℃ under air atmosphere. Subsequently, the mixture was concentrated under reduced pressure and it was loaded into a SCX pad, which was eluted with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a crude material or the respective amine derivative.

General Procedure E (Method C followed by D and A in main text)

By modification of existing procedures,[3,4] NaOMe (0.10 eq of a 0.5 M solution in MeOH) was added to a solution of the respective acetate derivative (1.00 eq) in MeOH (10.0 mL for each 1.00 mmol of the acetate derivative). After stirring for 45 min at rt, the solvent was removed under reduced pressure.

Subsequently, DCM (10.0 mL for each 1.00 mmol of the acetate derivative) and TFA (18.0 eq) were added, the mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (6.00 mL for each 1.00 mmol of the acetate derivative) and the ester derivative **5** (1.05 eq) were added. Subsequently, the specified amount of Et_3N and the specified amount of TBD were added and the reaction mixture was stirred for the indicated time at 75 ℃. Finally, the solvent was removed under reduced pressure to y ield a crude material

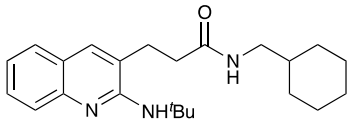
General Procedure F (Method D followed by A in main text)

By modification of an existing procedure,[3] TFA (17.0 eq) was added to a solution of the respective carbamate derivative (1.00 eq) in DCM (9.00 mL for each 1.00 mmol of the carbamate derivative). The mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (5.00 mL for each 1.00 mmol of the carbamate derivative), the specified amount of Et_3N, the specified amount of TBD and the ester derivative **5** (1.05 eq) were added and the reaction mixture was stirred for 4 days at 75 ℃. Finally, the solvent was removed under reduced pressure to yield a crude material

General Procedure G (Method E followed by A in main text)

By modification of an existing procedure,[3] hydrogen gas was passed through a mixture of the respective carbamate derivative (1.00 eq) and Pd (0.03 eq of a 10% Pd/C) in MeOH (7.30 mL for each 1.00 mmol of the carbamate derivative) for 1 h at rt. Subsequently, the suspension was filtered through a pad of celite and the solvent was removed under reduced pressure. Toluene (7.30 mL for each 1.00 mmol of the carbamate derivative), the ester derivative **5** (1.05 eq) and the specified amount of TBD were added and the reaction mixture was stirred for 2 days at 75 ℃. Finally, the solvent was removed under reduced pressure to yield a crude material

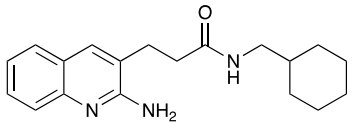
3-[2-(tert-Butylamino)quinolin-3-yl]-N-(cyclohexylmethyl)propanamide



S3

According to General Procedure C, the amine derivative **6a** (0.11 mL, 0.88 mmol), TBD (61.2 mg, 0.44 mmol) and toluene (1.00 mL) were stirred overnight to give a crude material. The crude material was purified by flash column chromatography eluting with 20:80 EtOAc−hexane to yield the amide derivative **S3**[2] (0.30 g, 98%) as a colourless amorphous solid, R_f 0.47 (60:40 petrol−EtOAc); ν_{max}/cm^{-1} 3423, 3252, 3083, 2948, 2923, 2850, 1621, 1524, 1449, 1413, 1352, 1271, 1222; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, J 8.2, quinolinyl 8-H), 7.50 (1H, s, quinolinyl 4-H), 7.49-7.40 (2H, m, quinolinyl 5,7-H_2), 7.15 (1H, ddd, J 7.9, 6.9 and 1.1, quinolinyl 6-H), 5.50 (1H, t, J 5.9, amide NH), 5.03 (1H, br. s, ^{t}Bu NH), 3.07 (2H, t, J 6.4, methylpropanamide 1-H_2), 2.87 (2H, t, J 7.1, propanamide 3-H_2), 2.48 (2H, t, J 7.1, propanamide 2-H_2), 1.81-1.61 (5H, m, 2-H_A, 6-H_A and 3,4,5-H_3), 1.58 (9H, s, ^{t}Bu), 1.36 (1H, app. dtp, J 14.1, 6.6 and 3.5, 1-H), 1.22-1.02 (3H, m, 3,4,5-H_3), 0.92-0.79 (2H, m, 2-H_B and 6-H_B); δ_C (100 MHz, $CDCl_3$) 172.0 (propanamide C-1), 154.8 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.4 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.4 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.6 (quinolinyl C-6), 51.8 (^{t}Bu C_1), 46.0 (methylpropanamide C-1), 37.9 (C-1), 35.7 (propanamide C-2), 30.9 (C_2-2,6), 29.3 (^{t}Bu C_3), 26.8 (propanamide C-3), 26.4 (C-4), 25.8 (C_2-3,5); HRMS found MH^+, 368.2695. $C_{23}H_{33}N_3O$ requires MH, 368.2701.

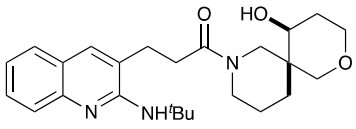
3-(2-Aminoquinolin-3-yl)-N-(cyclohexylmethyl)propanamide



2

According to General Procedure D, TFA (2.00 mL) and the amide derivative **S3** (0.10 g, 0.27 mmol) were stirred for 1.5 h to give the amine derivative **2**[2] (70.0 mg, 83%) as a colourless amorphous solid, R_f 0.37 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3461, 3314, 3059, 2915, 2843, 1640, 1539, 1500, 1437; δ_H (400 MHz, DMSO-d_6) 7.86 (1H, t, J 5.9, NH), 7.69 (1H, s, quinolinyl 4-H), 7.56 (1H, d, J 8.0, quinolinyl 5-H), 7.50-7.36 (2H, m, quinolinyl 7,8-H_2), 7.14 (1H, ddd, J 8.0, 6.4 and 1.6, quinolinyl 6-H), 6.40 (2H, br. s, NH_2), 2.88 (2H, app. t, J 6.3, methylpropanamide 1-H_2), 2.81 (2H, t, J 7.2, propanamide 3-H_2), 2.46 (2H, t, J 7.2, propanamide 2-H_2), 1.65-1.45 (5H, m, 2-H_A, 6-H_A and 3,4,5-H_3), 1.35-1.20 (1H, m, 1-H), 1.14-0.95 (3H, m, 3,4,5-H_3), 0.86-0.66 (2H, m, 2-H_B and 6-H_B); δ_C (100 MHz, DMSO-d_6) 171.2 (propanamide C-1), 156.9 (quinolinyl C-2), 146.1 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.3 (quinolinyl C-7), 126.8 (quinolinyl C-8), 124.3 (quinolinyl C-5), 123.3 (quinolinyl C-4a), 123.2 (quinolinyl C-3), 121.2 (quinolinyl C-6), 44.8 (methylpropanamide C-1), 37.4 (C-1), 33.9 (propanamide C-2), 30.3 (C_2-2,6), 26.3 (propanamide C-3), 26.0 (C-4), 25.3 (C_2-3,5); HRMS found MH^+, 312.2068. $C_{19}H_{25}N_3O$ requires MH, 312.2075.

3-[2-(tert-Butylamino)quinolin-3-yl]-1-[(5R*,6R*)-5-hydroxy-2-oxa-8-azaspiro[5.5] undecan-8-yl]propan-1-one

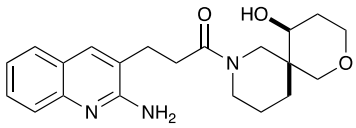


S4

According to General Procedure E, the acetate derivative **6b** (50.0 mg, 0.16 mmol), TBD (62.3 mg, 0.45 mmol) and Et_3N (0.75 mL, 5.40 mmol) were

stirred for 5 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 60:40→100:0 EtOAc−hexane to yield the amide derivative **S4** (14.0 mg, 21%, rotamers 78:22 by ^{1}H-NMR) as a colourless oil, R_f 0.48 (EtOAc); ν_{max}/cm^{-1} 3385, 2954, 2927, 2857, 1621, 1517, 1470, 1446, 1415, 1355, 1260, 1213, 1085; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, dd, J 8.5 and 2.6, quinolinyl 8-H), 7.54 (2H, s, quinolinyl 4-H), 7.50 (2H, dd, J 7.9 and 1.6, quinolinyl 5-H), 7.46 (2H, ddd, J 8.5, 7.0 and 1.6, quinolinyl 7-H), 7.15 (2H, app. td, J 7.4 and 3.3, quinolinyl 6-H), 5.07 (2H, br. s, NH), 4.29-4.19 (1H, m, 9-H_A^{minor}), 3.87-3.72 (2H, m, 3-H_A), 3.63-3.51 (6H, m, 1-H_A, 3-H_B and 7-H_A), 3.49 (2H, dd, J 7.6 and 3.9, 5-H), 3.42-3.29 (1H, m, 9-H_A^{major}), 3.28-3.22 (1H, m, 9-H_B^{major}), 3.15 (2H, d, J 13.6, 1-H_B), 3.10 (2H, d, J 11.9, 7-H_B), 2.99-2.81 (5H, m, propanone 3-H_2 and 9-H_B^{minor}), 2.79-2.56 (4H, m, propanone 2-H_2), 2.00-1.89 (2H, m, 4-H_A), 1.82 (2H, app. ddt, J 13.5, 8.6 and 4.0, 10-H_A), 1.71-1.61 (2H, m, 4-H_B), 1.58 (18H, s, ^{t}Bu), 1.55-1.38 (6H, m, 10-H_B and 11-H_2); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{minor}), 171.1 (propanone C-1^{major}), 155.0 (quinolinyl C_2-2), 147.0 (quinolinyl C_2-8a), 134.7 (quinolinyl C-4^{major}), 134.6 (quinolinyl C-4^{minor}), 128.5 (quinolinyl C-7^{major}), 128.4 (quinolinyl C-7^{minor}), 126.7 (quinolinyl C_2-5), 126.5 (quinolinyl C_2-8), 123.6 (quinolinyl C_2-3), 123.1 (quinolinyl C_2-4a), 121.7 (quinolinyl C-6^{major}), 121.6 (quinolinyl C-6^{minor}), 70.7 (C-1^{major}), 69.9 (C_2-5), 68.6 (C-1^{minor}), 65.2 (C-3^{major}), 64.3 (C-3^{minor}), 51.9 (^{t}Bu C_2), 50.3 (C-7^{minor}), 47.5 (C-7^{major}), 46.6 (C-9^{major}), 42.9 (C-9^{minor}), 38.9 (C_2-6), 32.0 (propanone C-2^{minor}), 31.7 (propanone C-2^{major}), 30.7 (C_2-4), 29.4 (^{t}Bu C_6), 26.9 (propanone C-3^{major}), 26.8 (propanone C-3^{minor}), 21.3 (C_2-10), 20.4 (C_2-11); HRMS found MH^{+}, 426.2748. $C_{25}H_{35}N_3O_3$ requires MH, 426.2756.

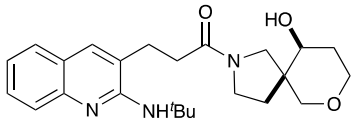
3-(2-Aminoquinolin-3-yl)-1-[(5R*,6R*)-5-hydroxy-2-oxa-8-azaspiro [5.5]undecan-8-yl]propan-1-one



7

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S4** (11.3 mg, 26.5 μmol) were stirred for 3 h to yield a crude material. The crude material was purified by flash column chromatography eluting with 93.9:5.42:0.68 DCM−EtOH−NH_4OH to yield the amine derivative **7** (9.80 mg, >99%, rotamers 78:22 by ^{1}H-NMR) as a pale yellow oil, R_f 0.68 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3337, 3200, 2929, 2854, 1617, 1498, 1468, 1432, 1260, 1233, 1132, 1083, 1002; δ_H (400 MHz, $CDCl_3$) 7.70 (2H, app. d, J 10.1, quinolinyl 4-H), 7.63 (2H, d, J 8.4, quinolinyl 8-H), 7.57 (2H, dd, J 8.0 and 1.6, quinolinyl 5-H), 7.50 (2H, ddd, J 8.4, 6.9 and 1.6, quinolinyl 7-H), 7.23 (2H, app. tt, J 8.0 and 1.3, quinolinyl 6-H), 5.39 (2H, br. s, NH_2^{minor}), 5.37 (2H, br. s, NH_2^{major}), 4.27 (1H, app. d, J 13.1, 9-H_A^{minor}), 3.85-3.75 (2H, m, 3-H_A), 3.74-3.62 (2H, m, 3-H_B), 3.60 (2H, d, J 11.9, 1-H_A), 3.56-3.50 (4H, m, 5-H and 7-H_A), 3.46-3.36 (1H, m, 9-H_A^{major}), 3.35-3.25 (1H, m, 9-H_B^{major}), 3.10 (2H, d, J 12.6, 7-H_B), 3.05-2.75 (7H, m, 1-H_B, 9-H_B^{minor} and propanone 3-H_2), 2.74-2.55 (4H, m, propanone 2-H_2), 2.12-1.81 (2H, m, 4-H_A), 1.75-1.65 (2H, m, 10-H_A), 1.64-1.44 (8H, m, 4-H_B, 10-H_B and 11-H_2); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{minor}), 171.1 (propanone C-1^{major}), 156.7 (quinolinyl C_2-2), 146.7 (quinolinyl C_2-8a), 136.7 (quinolinyl C_2-4), 129.2 (quinolinyl C_2-7), 127.0 (quinolinyl C_2-5), 125.5 (quinolinyl C_2-8), 124.3 (quinolinyl C_2-3), 123.5 (quinolinyl C_2-4a), 122.7 (quinolinyl C-6^{major}), 122.6 (quinolinyl C-6^{minor}), 70.6 (C-1^{major}), 69.8 (C-5^{major}), 69.7 (C-5^{minor}), 68.4 (C-1^{minor}), 65.3 (C-3^{minor}), 64.2 (C-3^{major}), 50.3 (C-7^{minor}), 47.6 (C-7^{major}), 46.6 (C-9^{major}), 42.9 (C-9^{minor}), 39.0 (C-6^{major}), 38.9 (C-6^{minor}), 32.4 (propanone C-2^{major}), 32.3 (propanone C-2^{minor}), 30.7 (C_2-4), 26.9 (propanone C-3^{minor}), 26.6 (propanone C-3^{major}), 21.3 (C_2-10), 20.5 (C_2-11); HRMS found MH^+, 370.2123. $C_{21}H_{27}N_3O_3$ requires MH, 370.2130.

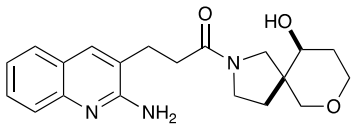
3-[2-(tert-Butylamino)quinolin-3-yl]-1-[(5R*,10R*)-10-hydroxy-7-oxa-2-azaspiro[4.5] decan-2-yl]propan-1-one



S5

According to General Procedure E, the acetate derivative **6c** (41.3 mg, 0.14 mmol), TBD (73.0 mg, 0.52 mmol) and Et_3N (0.75 mL, 5.40 mmol) were stirred for 4 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 90:10→100:0 EtOAc−hexane to yield the amide derivative **S5** (34.0 mg, 60%, rotamers >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.31 (EtOAc); ν_{max}/cm^{-1} 3360, 2954, 2862, 1621, 1518, 1447, 1416, 1355, 1213, 1082; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, J 8.3, quinolinyl 8-H), 7.52 (2H, app. d, J 5.9, quinolinyl 4-H), 7.49 (2H, dd, J 7.9 and 1.6, quinolinyl 5-H), 7.45 (2H, ddd, J 8.3, 6.9 and 1.6, quinolinyl 7-H), 7.14 (2H, app. t, J 7.4, quinolinyl 6-H), 5.10 (2H, br. s, NH), 3.91-3.78 (2H, m, 8-H_A), 3.72-3.52 (4H, m, 6-H_A and 10-H), 3.53-3.32 (6H, m, 1-H_A, 3-H_A and 8-H_B), 3.31-3.18 (4H, m, 1-H_B and 3-H_B), 3.11 (2H, d, J 11.5, 6-H_B), 2.87 (4H, t, J 7.4, propanone 3-H_2), 2.63-2.53 (4H, m, propanone 2-H_2), 2.12-2.00 (2H, m, 4-H_A), 1.93-1.82 (2H, m, 4-H_B), 1.82-1.72 (2H, m, 9-H_A), 1.70-1.58 (2H, m, 9-H_B), 1.57 (18H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.1 (propanone C_2-1), 154.8 (quinolinyl C_2-2), 146.9 (quinolinyl C_2-8a), 134.5 (quinolinyl C-4^{minor}), 134.4 (quinolinyl C-4^{major}), 128.5 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 123.7 (quinolinyl C_2-3), 123.0 (quinolinyl C_2-4a), 121.7 (quinolinyl C_2-6), 71.3 (C-6^{major}), 70.4 (C-6^{minor}), 69.7 (C-10^{major}), 69.5 (C-10^{minor}), 65.6 (C-8^{major}), 64.8 (C-8^{minor}), 51.8 (C-3^{minor}), 50.9 (C-3^{major}), 48.2 (^{t}Bu C_2), 46.5 (C_2-5), 45.5 (C-1^{major}), 44.5 (C-1^{minor}), 33.7 (propanone C_2-2), 33.3 (C_2-9), 32.3 (C-4^{major}), 32.1 (C-4^{minor}), 29.4 (^{t}Bu C_6), 26.4 (propanone C-3^{minor}), 26.3 (propanone C-3^{major}); HRMS found MH$^+$, 412.2598. $C_{24}H_{33}N_3O_3$ requires MH, 412.2600.

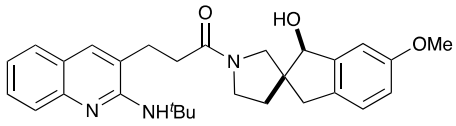
3-(2-Aminoquinolin-3-yl)-1-[(5R*,10R*)-10-hydroxy-7-oxa-2-azaspiro [4.5]decan-2-yl]propan-1-one



8

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S5** (10.0 mg, 24.3 μmol) were stirred for 3 h to give the amine derivative **8** (8.00 mg, 93%, rotamers >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.63 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3410, 3324, 3149, 2941, 2878, 2850, 1655, 1624, 1473, 1438, 1340, 1328, 1134, 1108, 1086, 1068; δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, J 5.3, quinolinyl 4-H), 7.62 (2H, d, J 8.4, quinolinyl 8-H), 7.55 (2H, d, J 8.0, quinolinyl 5-H), 7.50 (2H, ddd, J 8.4, 6.8 and 1.5, quinolinyl 7-H), 7.22 (2H, app. t, J 7.4, quinolinyl 6-H), 5.76 (2H, br. s, NH^{major}), 5.70 (2H, br. s, NH^{minor}), 3.93-3.81 (2H, m, 8-H_A), 3.74-3.65 (2H, m, 10-H), 3.63 (2H, d, J 12.5, 6-H_A), 3.56-3.45 (4H, m, 3-H_A and 8-H_B), 3.44-3.33 (4H, m, 1-H_A and 3-H_B), 3.32-3.24 (2H, m, 1-H_B), 3.19-3.10 (2H, app. dd, J 11.6 and 2.4, 6-H_B), 2.98 (4H, t, J 6.8, propanone 3-H_2), 2.62 (4H, t, J 6.8, propanone 2-H_2), 2.08 (2H, app. dt, J 12.9 and 9.1, 4-H_A), 1.98-1.86 (2H, m, 4-H_B), 1.85-1.75 (2H, m, 9-H_A), 1.69-1.55 (2H, m, 9-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C-1^{major}), 171.1 (propanone C-1^{minor}), 156.7 (quinolinyl C_2-2), 146.0 (quinolinyl C-8a^{minor}), 145.8 (quinolinyl C-8a^{major}), 137.0 (quinolinyl C_2-4), 129.4 (quinolinyl C_2-7), 127.0 (quinolinyl C_2-5), 124.9 (quinolinyl C-8^{minor}), 124.8 (quinolinyl C-8^{major}), 124.1 (quinolinyl C-3^{minor}), 124.0 (quinolinyl C-3^{major}), 123.8 (quinolinyl C-4a^{major}), 123.7 (quinolinyl C-4a^{minor}), 122.8 (quinolinyl C_2-6), 71.4 (C-6^{major}), 70.6 (C-6^{minor}), 69.8 (C-10^{major}), 69.5 (C-10^{minor}), 65.7 (C-8^{major}), 65.0 (C-8^{minor}), 51.8 (C-3^{minor}), 51.1 (C-3^{major}), 48.5 (C-5^{minor}), 46.5 (C-5^{major}), 45.6 (C-1^{major}), 44.7 (C-1^{minor}), 34.1 (propanone C_2-2), 33.9 (C_2-9), 32.4 (C-4^{major}), 32.3 (C-4^{minor}), 26.1 (propanone C-3^{minor}), 26.0 (propanone C-3^{major}); HRMS found MH^+, 356.1971. $C_{20}H_{25}N_3O_3$ requires MH, 356.1974.

3-[2-(tert-Butylamino)quinolin-3-yl]-1-[(2R*,3R*)-3-hydroxy-5-methoxy-1,3-dihydrospiro[indene-2,3'-pyrrolidin]-1'-yl]propan-1-one

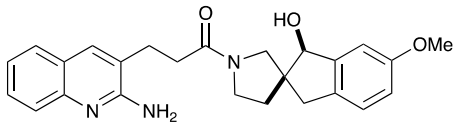


S6

According to General Procedure E, the acetate derivative **6d** (50.0 mg, 0.14 mmol), TBD (73.0 mg, 0.52 mmol) and Et_3N (0.75 mL, 5.40 mmol) were stirred for 4 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 70:30→100:0 EtOAc−hexane to yield the amide derivative **S6** (49.0 mg, 75%, rotamers 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.56 (EtOAc); ν_{max}/cm^{-1} 3338, 2956, 1619, 1517, 1487, 1445, 1414, 1387, 1354, 1270, 1248, 1213, 1147, 1028; δ_H (400 MHz, $CDCl_3$) 7.69 (2H, app. t, J 9.3, quinolinyl 8-H), 7.57-7.41 (6H, m, quinolinyl 4,5,7-H_3), 7.21-7.09 (2H, m, quinolinyl 6-H), 7.04-6.97 (2H, m, 7-H), 6.92-6.83 (2H, m, 4-H), 6.78 (2H, app. dt, J 8.3 and 2.4, 6-H), 5.14 (2H, br. s, NH), 4.61 (1H, s, 3-H^{minor}), 4.58 (1H, d, J 2.5, 3-H^{major}), 3.77 (3H, s, methoxy^{major}), 3.76 (3H, s, methoxy^{minor}), 3.71-3.59 (2H, m, 5'-H_A), 3.56-3.43 (2H, m, 5'-H_B), 3.35-3.23 (2H, m, 2'-H_A), 3.14 (2H, app. t, J 9.7, 2'-H_B), 2.96-2.84 (4H, m, propanone 3-H_2), 2.83-2.74 (2H, m, 1-H_A), 2.65-2.55 (4H, m, propanone 2-H_2), 2.54-2.46 (2H, m, 1-H_B), 2.29 (1H, app. dt, J 12.4 and 7.4, 4'-H_A^{major}), 2.18 (1H, app. dt, J 12.6 and 7.7, 4'-H_A^{minor}), 1.97-1.80 (1H, m, 4'-H_B^{major}), 1.79-1.70 (1H, m, 4'-H_B^{minor}), 1.58 (9H, s, ^{t}Bu^{major}), 1.57 (9H, s, ^{t}Bu^{minor}); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C-1^{major}), 171.1 (propanone C-1^{minor}), 159.3 (C-5^{major}), 159.2 (C-5^{minor}), 155.0 (quinolinyl C-2^{major}), 154.9 (quinolinyl C-2^{minor}), 147.0 (quinolinyl C-8a^{major}), 146.9 (quinolinyl C-8a^{minor}), 145.0 (C-3a^{major}), 144.9 (C-3a^{minor}), 134.7 (quinolinyl C-4^{major}), 134.5 (quinolinyl C-4^{minor}), 133.0 (C-7a^{minor}), 132.8 (C-7a^{major}), 128.5 (quinolinyl C-7^{major}), 128.4 (quinolinyl C-7^{minor}), 126.7 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.9 (C-7^{major}), 125.7 (C-7^{minor}), 123.7 (quinolinyl C-3^{major}), 123.6 (quinolinyl C-3^{minor}), 123.0 (quinolinyl C-4a^{major}), 122.9 (quinolinyl C-4a^{minor}), 121.7 (quinolinyl C-6^{major}), 121.6 (quinolinyl C-6^{minor}), 115.1 (C-6^{minor}), 115.0 (C-6^{major}), 110.0 (C-4^{minor}), 109.7

(C-4^{major}), 79.3 (C-3^{minor}), 79.1 (C-3^{major}), 56.7 (C-2'^{major}), 55.6 (methoxy), 55.4 (C-2'^{minor}), 54.0 (C_2-2), 53.9 (^{t}Bu C_2), 46.1 (C-5'^{minor}), 45.3 (C-5'^{major}), 40.3 (C-1^{major}), 40.0 (C-1^{minor}), 35.7 (C_2-4'), 34.3 (propanone C-2^{major}), 33.6 (propanone C-2^{minor}), 29.4 (^{t}Bu C_6), 26.6 (propanone C-3^{major}), 26.4 (propanone C-3^{minor}); HRMS found MH^+, 474.2757. $C_{29}H_{35}N_3O_3$ requires MH, 474.2756.

3-(2-Aminoquinolin-3-yl)-1-[(2R*,3R*)-3-hydroxy-5-methoxy-1,3-dihydros piro[indene-2,3'-pyrrolidin]-1'-yl]propan-1-one

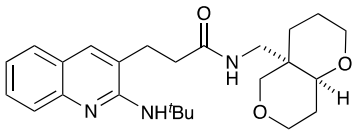


9

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S6** (18.0 mg, 38.0 μmol) were stirred for 3 h to yield a crude material. The crude material was purified by flash column chromatography eluting with 95.4:4.08:0.52 DCM−EtOH−NH_4OH to yield the amine derivative **9** (5.00 mg, 32%, rotamers 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.27 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3341, 3214, 3057, 2960, 2921, 1613, 1490, 1432, 1259, 1095, 1019; δ_H (400 MHz, $CDCl_3$) 7.75-7.45 (8H, m, quinolinyl 4,5,7,8-H_4), 7.23-7.15 (2H, m, quinolinyl 6-H), 7.07-7.00 (2H, m, 7-H), 6.88 (2H, app. ddd, J 9.4, 7.2 and 2.5, 4-H), 6.79 (2H, dd, J 8.3 and 2.6, 6-H), 5.51 (2H, br. s, NH^{minor}), 5.47 (2H, br. s, NH^{major}), 4.64 (1H, s, 3-H^{major}), 4.50 (1H, s, 3-H^{minor}), 3.78 (3H, methoxy^{minor}), 3.77 (3H, methoxy^{major}), 3.75-3.63 (2H, m, 5'-H_A), 3.61-3.49 (2H, m, 5'-H_B), 3.42-3.23 (2H, m, 2'-H_A), 3.22-3.11 (2H, m, 2'-H_B), 3.10-2.95 (4H, m, propanone 3-H_2), 2.94-2.81 (2H, m, 1-H_A), 2.73-2.61 (4H, m, propanone 2-H_2), 2.60-2.49 (2H, m, 1-H_B), 2.37-2.28 (1H, m, 4'-H_A^{minor}), 2.27-2.18 (1H, m, 4'-H_A^{major}), 1.96-1.84 (1H, m, 4'-H_B^{minor}), 1.83-1.65 (1H, m, 4'-H_B^{major}); δ_C (100 MHz, $CDCl_3$) 171.3 (propanone C-1^{major}), 171.2 (propanone C-1^{minor}), 159.4 (C-5^{major}), 159.3 (C-5^{minor}), 156.8 (quinolinyl C_2-2), 146.7 (quinolinyl C-8a^{minor}), 146.6 (quinolinyl C-8a^{major}), 145.0 (C-3a^{major}), 144.9 (C-3a^{minor}), 136.8 (quinolinyl C-4^{major}), 136.7 (quinolinyl C-4^{minor}), 133.1

(C-7a^{minor}), 132.9 (C-7a^{major}), 129.3 (quinolinyl C-7^{major}), 129.2 (quinolinyl C-7^{minor}), 127.0 (quinolinyl C_2-5), 126.0 (C-7^{minor}), 125.8 (C-7^{major}), 125.5 (quinolinyl C-8^{major}), 125.3 (quinolinyl C-8^{minor}), 124.3 (quinolinyl C_2-3), 123.6 (quinolinyl C_2-4a), 122.7 (quinolinyl C-6^{minor}), 122.6 (quinolinyl C-6^{major}), 115.2 (C-6^{minor}), 115.1 (C-6^{major}), 109.8 (C-4^{major}), 109.7 (C-4^{minor}), 80.0 (C-3^{major}), 79.4 (C-3^{minor}), 56.7 (C_2-2'), 55.6 (methoxy), 54.1 (C-2^{major}), 53.9 (C-2^{minor}), 46.3 (C-5'^{major}), 45.3 (C-5'^{minor}), 40.3 (C-1^{minor}), 40.0 (C-1^{major}), 36.0 (C_2-4'), 34.4 (propanone C-2^{major}), 33.9 (propanone C-2^{minor}), 26.4 (propanone C-3^{minor}), 26.2 (propanone C-3^{major}); HRMS found MH$^+$, 418.2125. $C_{25}H_{27}N_3O_3$ requires MH, 418.2130.

N-{[(4aR*,8aR*)-Octahydropyrano[4,3-b]pyran-4a-yl]methyl}-3-[2-(tert-butylamino) quinolin-3-yl]propanamide

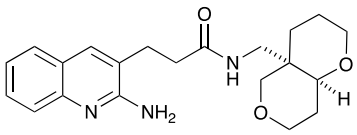


S7

According to General Procedure F, the carbamate derivative **6e** (50.0 mg, 0.18 mmol), TBD (76.5 mg, 0.55 mmol) and Et_3N (0.55 mL, 3.94 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 60:40→100:0 EtOAc−hexane to yield the amide derivative **S7** (22.0 mg, 28%) as a colourless oil, R_f 0.50 (EtOAc); ν_{max}/cm^{-1} 3314, 2952, 2926, 2859, 1648, 1623, 1516, 1486, 1447, 1415, 1355, 1274, 1259, 1214, 1098, 1080, 1024; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, J 8.3 and 1.2, quinolinyl 8-H), 7.53 (1H, s, quinolinyl 4-H), 7.48 (1H, dd, J 8.0 and 1.5, quinolinyl 5-H), 7.44 (1H, ddd, J 8.3, 6.9 and 1.5, quinolinyl 7-H), 7.14 (1H, ddd, J 8.0, 6.9 and 1.2, quinolinyl 6-H), 5.92 (1H, t, J 6.4, amide NH), 4.96 (1H, br. s, ^{t}Bu NH), 3.93-3.86 (1H, m, 2-H$_A$), 3.82 (1H, d, J 11.7, 5-H$_A$), 3.64 (2H, app. dd, J 9.3 and 2.2, 7-H$_2$), 3.40 (1H, dd, J 13.9 and 6.4, methylpropanamide 1-H$_A$), 3.30 (1H, app. s, 8a-H), 3.28-3.24 (1H, m, 2-H$_B$), 3.24-3.19 (1H, m, methylpropanamide 1-H$_B$), 3.22 (1H, dd, J 11.7 and 1.7, 5-H$_B$), 2.89 (2H, t, J 7.1, propanamide 3-H$_2$), 2.54 (2H, td, J 7.1 and 1.8,

propanamide 2-H_2), 1.95 (1H, app. dtd, J 14.8, 9.1 and 3.2, 8-H_A), 1.59-1.50 (1H, m, 3-H_A), 1.58 (9H, s, ^{t}Bu), 1.48-1.38 (1H, m, 8-H_B), 1.31-1.15 (3H, m, 3-H_B and 4-H_2); δ_C (100 MHz, $CDCl_3$) 172.3 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.1 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 74.8 (C-8a), 68.0 (C-5), 67.6 (C-2), 63.4 (C-7), 51.9 (^{t}Bu C_1), 45.2 (methylpropanamide C-1), 36.2 (C-4a), 35.7 (propanamide C-2), 29.4 (^{t}Bu C_3), 28.8 (C-4), 28.7 (C-8), 26.8 (propanamide C-3), 22.1 (C-3); HRMS found MH^+, 426.2753. $C_{25}H_{35}N_3O_3$ requires MH, 426.2756.

N-{[(4aR*,8aR*)-Octahydropyrano[4,3-b]pyran-4a-yl]methyl}-3-(2-aminoquinolin-3-yl)propanamide

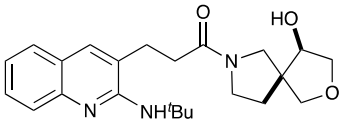


10

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S7** (11.7 mg, 27.5 μmol) were stirred for 3 h to give the amine derivative **10** (10.0 mg, 98%) as a colourless oil, R_f 0.43 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3316, 3209, 3058, 2930, 2859, 1632, 1555, 1498, 1433, 1258, 1235, 1097, 1078, 1024; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, quinolinyl 4-H), 7.62 (1H, dd, J 8.3 and 1.2, quinolinyl 8-H), 7.55 (1H, dd, J 8.1 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, J 8.3, 6.9 and 1.5, quinolinyl 7-H), 7.22 (1H, ddd, J 8.1, 6.9 and 1.2, quinolinyl 6-H), 6.03 (1H, t, J 6.3, amide NH), 5.29 (2H, br. s, NH_2), 3.92-3.84 (1H, m, 2-H_A), 3.80 (1H, d, J 11.7, 5-H_A), 3.66-3.59 (2H, m, 7-H_2), 3.37 (1H, dd, J 13.9 and 6.7, methylpropanamide 1-H_A), 3.32-3.24 (2H, m, 8a-H and methylpropanamide 1-H_B), 3.23-3.15 (1H, m, 2-H_B), 3.21 (1H, d, J 11.7, 5-H_B), 2.99 (2H, t, J 7.1, propanamide 3-H_2), 2.58 (2H, t, J 7.1, propanamide 2-H_2), 2.03-1.88 (1H, m, 8-H_A), 1.62-1.49 (1H, m, 3-H_A), 1.48-1.40 (1H, m, 8-H_B), 1.31-1.12 (3H, m, 3-H_B and 4-H_2); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 156.4 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 136.8 (quinolinyl C-4), 129.3 (quinolinyl C-7), 127.0

(quinolinyl C-5), 125.5 (quinolinyl C-8), 124.3 (quinolinyl C-3), 122.8 (quinolinyl C-6), 122.7 (quinolinyl C-4a), 74.7 (C-8a), 67.8 (C-5), 67.6 (C-2), 63.4 (C-7), 45.1 (methylpropanamide C-1), 36.3 (C-4a), 36.0 (propanamide C-2), 28.7 (C-4), 28.6 (C-8), 26.9 (propanamide C-3), 22.1 (C-3); HRMS found MH^+, 370.2120. $C_{21}H_{27}N_3O_3$ requires MH, 370.2130.

3-[2-(tert-Butylamino)quinolin-3-yl]-1-[(4R*,5S*)-4-hydroxy-2-oxa-7-azaspiro[4.4]nonan-7-yl]propan-1-one

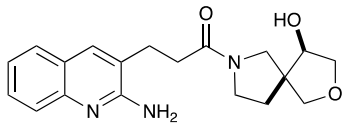


S8

According to General Procedure E, the acetate derivative **6f** (0.10 g, 0.35 mmol), TBD (0.12 mg, 0.87 mmol) and Et_3N (0.50 mL, 3.60 mmol) were stirred for 2 days to yield a crude material. The crude material was purified by flash column chromatography eluting with 80:20→100:0 EtOAc−hexane to yield the amide derivative **S8** (0.10 g, 72%, rotamers 53:47 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.34 (EtOAc); ν_{max}/cm^{-1} 3278, 2950, 2914, 2866, 1625, 1517, 1453, 1418, 1353, 1216, 1054; δ_H (400 MHz, DMSO-d_6) 7.66 (2H, s, quinolinyl 4-H), 7.56 (2H, dd, J 8.0 and 1.5, quinolinyl 5-H), 7.50 (2H, d, J 8.4, quinolinyl 8-H), 7.42 (2H, ddd, J 8.4, 6.8 and 1.5, quinolinyl 7-H), 7.13 (2H, ddd, J 8.0, 6.8 and 1.3, quinolinyl 6-H), 5.88 (1H, br. s, NH^{minor}), 5.82 (1H, br. s, NH^{major}), 5.18 (2H, app. t, J 4.1, OH), 3.95-3.81 (2H, m, 4-H), 3.59-3.35 (12H, m, 1,3,8-H_6), 3.24 (2H, app. s, 6-H_A), 3.19 (2H, app. s, 6-H_B), 2.84 (4H, td, J 6.9 and 4.0, propanone 3-H_2), 2.59 (4H, app. q, J 6.4, propanone 2-H_2), 2.15 (1H, ddd, J 12.7, 7.9 and 6.3, 9-H_A^{minor}), 2.05 (1H, ddd, J 13.0, 7.7 and 5.9, 9-H_A^{major}), 1.75-1.65 (1H, m, 9-H_B^{minor}), 1.59 (1H, app. dt, J 13.0 and 7.7, 9-H_B^{major}), 1.53 (18H, s, ^{t}Bu); δ_C (100 MHz, DMSO-d_6) 170.2 (propanone C-1^{minor}), 170.1 (propanone C-1^{major}), 155.0 (quinolinyl C_2-2), 146.1 (quinolinyl C_2-8a), 134.2 (quinolinyl C_2-4), 128.1 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 125.5 (quinolinyl C_2-8), 125.0 (quinolinyl C_2-3), 124.8 (quinolinyl C_2-4a), 121.2 (quinolinyl C_2-6), 74.5 (C-3^{minor}), 74.4 (C-3^{major}), 73.8

(C-4^{major}), 73.7 (C-1^{major}), 73.6 (C-4^{minor}), 73.5 (C-1^{minor}), 54.2 (C-6^{minor}), 54.1 (C-5^{majoror}), 53.6 (C-6^{major}), 52.2 (C-5^{minor}), 51.1 (^{t}Bu C_2), 45.1 (C-8^{minor}), 44.6 (C-8^{major}), 32.9 (propanone C-2^{major}), 32.6 (propanone C-2^{minor}), 28.9 (^{t}Bu C_6), 27.5 (C-9^{minor}), 25.7 (C-9^{major}), 25.3 (propanone C-3^{minor}), 25.1 (propanone C-3^{major}); HRMS found MH^+, 398.2435. $C_{23}H_{31}N_3O_3$ requires MH, 398.2443.

3-(2-Aminoquinolin-3-yl)-1-[(4R*,5S*)-4-hydroxy-2-oxa-7-azaspiro [4.4]nonan-7-yl]propan-1-one

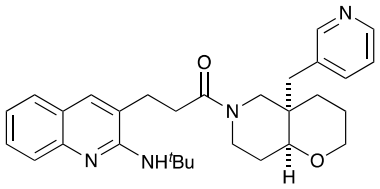


11

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S8** (20.0 mg, 50.3 μmol) were stirred for 3 h to give the amine derivative **11** (17.1 mg, >99%, rotamers 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.51 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3326, 3148, 2919, 2872, 1625, 1567, 1471, 1431, 1362, 1327, 1216, 1124, 1054; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, s, quinolinyl 4-H), 7.59 (2H, dd, J 8.4 and 5.2, quinolinyl 8-H), 7.55 (2H, d, J 8.0, quinolinyl 5-H), 7.49 (2H, app. ddt, J 8.4, 6.8 and 1.6, quinolinyl 7-H), 7.21 (2H, ddd, J 8.0, 6.8 and 1.2, quinolinyl 6-H), 5.61 (4H, br. s, NH_2), 4.01-3.87 (2H, m, 4-H), 3.81-3.69 (6H, m, 1-H_2 and 3-H_A), 3.68-3.55 (2H, m, 3-H_B), 3.54-3.44 (2H, m, 8-H_A), 3.43-3.38 (2H, m, 8-H_B), 3.21 (2H, d, J 10.3, 6-H_A), 3.08 (2H, d, J 10.3, 6-H_B), 3.05-2.86 (4H, m, propanone 3-H_2), 2.66-2.50 (4H, m, propanone 2-H_2), 2.31 (1H, ddd, J 13.2, 7.8 and 5.7, 9-H_A^{major}), 2.22 (1H, ddd, J 13.2, 7.6 and 5.8, 9-H_A^{minor}), 1.80 (1H, app. dt, J 12.9 and 7.6, 9-H_B^{major}), 1.71 (1H, app. dt, J 13.0 and 7.8, 9-H_B^{minor}); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.7 (quinolinyl C_2-2), 146.2 (quinolinyl C_2-8a), 137.1 (quinolinyl C-4^{minor}), 137.0 (quinolinyl C-4^{major}), 129.5 (quinolinyl C-7^{minor}), 129.4 (quinolinyl C-7^{major}), 127.1 (quinolinyl C_2-5), 125.0 (quinolinyl C-8^{major}), 124.9 (quinolinyl C-8^{minor}), 124.1 (quinolinyl C-3^{major}), 124.0 (quinolinyl C-3^{minor}), 123.5 (quinolinyl C_2-4a), 122.9 (quinolinyl C-6^{minor}), 122.8 (quinolinyl C-6^{major}), 75.3 (C_2-1), 74.9 (C_2-4), 74.4 (C_2-3), 55.5 (C-6^{minor}), 54.7 (C-5^{minor}), 54.4 (C-6^{major}), 52.7 (C-5^{major}), 46.1 (C-8^{major}), 45.3 (C-8^{minor}), 34.3 (propanone

C-2^{minor}), 33.7 (propanone C-2^{major}), 28.3 (C_2-9), 26.3 (propanone C-3^{major}), 26.2 (propanone C-3^{minor}); HRMS found MH^+, 342.1807. $C_{19}H_{23}N_3O_3$ requires MH, 342.1817.

1-[(4aR*,8aR*)-4a-[(Pyridin-3-yl)methyl]-octahydro-2H-pyrano[3,2-c]pyridin-6-yl]-3-[2-(tert-butylamino)quinolin-3-yl]propan-1-one

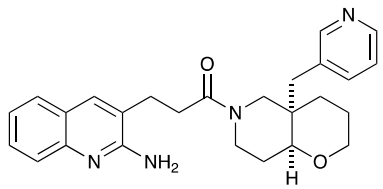


S9

According to General Procedure G, the carbamate derivative **6g** (50.0 mg, 0.14 mmol) and TBD (43.4 mg, 0.31 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 90:10→100:0 EtOAc−hexane to yield the amide derivative **S9** (13.0 mg, 20%, rotamers 80:20 by ^{1}H-NMR) as a colourless oil, R_f 0.17 (EtOAc); ν_{max}/cm^{-1} 3312, 2926, 2852, 1622, 1518, 1474, 1447, 1415, 1354, 1272, 1213, 1118, 1091; δ_H (400 MHz, $CDCl_3$) 8.46 (2H, br. s, pyridinyl 6-H), 8.33 (1H, br. s, pyridinyl 2-H^{major}), 8.26 (1H, br. s, pyridinyl 2-H^{minor}), 7.71-7.61 (4H, m, pyridinyl 4-H and quinolinyl 8-H), 7.56 (2H, s, quinolinyl 4-H), 7.42 (2H, ddd, J 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.38 (2H, dd, J 8.1 and 1.5, quinolinyl 5-H), 7.25-7.19 (2H, m, pyridinyl 5-H), 7.07 (2H, ddd, J 8.1, 6.9 and 1.2, quinolinyl 6-H), 5.16 (1H, br. s, NH^{minor}), 5.05 (1H, br. s, NH^{major}), 4.43 (1H, app. d, J 13.0, 7-H$_A$^{minor}), 4.13 (1H, d, J 13.3, 5-H$_A$^{major}), 3.91 (2H, dd, J 11.4 and 4.5, 2-H$_A$), 3.72-3.61 (1H, m, 7-H$_A$^{major}), 3.48 (1H, d, J 13.3, 5-H$_A$^{minor}), 3.37-3.27 (3H, m, 2-H$_B$ and 7-H$_B$^{major}), 3.25 (2H, s, 8a-H), 3.10 (2H, d, J 13.3, 5-H$_B$), 3.04-2.82 (5H, m, 7-H$_B$^{minor} and propanone 3-H$_2$), 2.78-2.68 (4H, m, propanone 2-H$_2$), 2.64 (1H, d, J 13.8 pyridinylmethyl 1-H$_A$^{minor}), 2.52 (1H, d, J 13.6, pyridinylmethyl 1-H$_A$^{major}), 2.27 (1H, d, J 13.8 pyridinylmethyl 1-H$_B$^{minor}), 2.09 (1H, d, J 13.6, pyridinylmethyl 1-H$_B$^{major}), 2.05-1.97 (1H, m, 8-H$_A$^{minor}), 1.80-1.70 (1H, m, 8-H$_A$^{major}), 1.69-1.60 (2H, m, 8-H$_B$), 1.59 (9H, s, ^{t}Bu^{major}), 1.54 (9H, s, ^{t}Bu^{minor}), 1.55-1.50 (2H, m, 3-H$_A$), 1.39-1.32 (2H, m, 3-H$_B$), 1.30-1.23

(2H, m, 4-H_A), 1.10-1.00 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 154.8 (quinolinyl C_2-2), 151.6 (pyridinyl C_2-2), 147.7 (quinolinyl C_2-8a), 147.0 (pyridinyl C_2-6), 138.3 (pyridinyl C_2-4), 134.9 (quinolinyl C_2-4), 132.4 (pyridinyl C_2-3), 128.5 (quinolinyl C_2-7), 126.7 (quinolinyl C_2-5), 126.5 (quinolinyl C_2-8), 123.4 (quinolinyl C_2-3), 123.0 (quinolinyl C_2-4a), 121.8 (quinolinyl C_2-6), 121.7 (pyridinyl C_2-5), 77.2 (C-8a^{major}), 74.8 (C-8a^{minor}), 67.9 (C_2-2), 51.9 (^{t}Bu C_2), 43.1 (C_2-5), 41.0 (C_2-7), 38.2 (pyridinylmethyl C_2-1), 36.4 (C_2-4a), 31.8 (propanone C_2-2), 30.8 (C_2-4), 29.4 (^{t}Bu C_3^{major}), 29.3 (^{t}Bu C_3^{minor}), 28.1 (C_2-8), 27.1 (propanone C_2-3), 22.1 (C_2-3); HRMS found MH^+, 487.3071. $C_{30}H_{38}N_4O_2$ requires MH, 487.3073.

1-[(4aR*,8aR*)-4a-[(Pyridin-3-yl)methyl]-octahydro-2H-pyrano[3,2-c]pyridin-6-yl]-3-(2-aminoquinolin-3-yl)propan-1-one

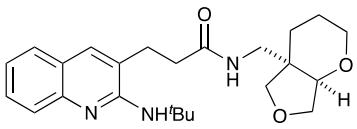


12

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S9** (10.3 mg, 21.2 μmol) were stirred for 3 h to give the amine derivative **12** (9.00 mg, 99%, rotamers 80:20 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.43 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3332, 3173, 3048, 2929, 2852, 1619, 1471, 1432, 1272, 1259, 1118, 1089; δ_H (400 MHz, $CDCl_3$) 8.46 (2H, dd, J 4.8 and 1.7, pyridinyl 6-H), 8.33 (1H, d, J 2.3, pyridinyl 2-H^{major}), 8.30 (1H, d, J 2.3, pyridinyl 2-H^{minor}), 7.72 (1H, s, quinolinyl 4-H^{major}), 7.70 (1H, s, quinolinyl 4-H^{minor}), 7.64-7.57 (4H, m, pyridinyl 4-H and quinolinyl 8-H), 7.53-7.40 (4H, m, quinolinyl 5,7-H_2), 7.25-7.11 (4H, m, quinolinyl 6-H and pyridinyl 5-H), 5.46 (4H, br. s, NH_2), 4.39 (1H, app. d, J 13.2, 7-H_A^{minor}), 4.13 (1H, d, J 13.2, 5-H_A^{major}), 3.94 (2H, dd, J 11.3 and 4.7, 2-H_A), 3.67 (1H, ddd, J 11.0, 5.0 and 2.6, 7-H_A^{major}), 3.56 (1H, d, J 13.3, 5-H_A^{minor}), 3.37-3.29 (3H, m, 2-H_B and 7-H_B^{major}), 3.28 (2H, s, 8a-H), 3.10 (2H, d, J 13.2, 5-H_B), 3.07-2.98 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.96-2.71 (4H, m,

propanone 2-H_2), 2.70 (1H, d, J 13.6, pyridinylmethyl 1-H_A^{minor}), 2.55 (1H, d, J 13.6, pyridinylmethyl 1-H_A^{major}), 2.37 (1H, d, J 13.6, pyridinylmethyl 1-H_B^{minor}), 2.13 (1H, d, J 13.6, pyridinylmethyl 1-H_B^{major}), 2.10-2.00 (1H, m, 8-H_A^{minor}), 1.85 (1H, app. tdd, J 13.2, 5.0 and 2.9, 8-H_A^{major}), 1.74-1.59 (4H, m, 3-H_A and 8-H_B), 1.43-1.27 (4H, m, 3-H_B and 4-H_A), 1.10-1.00 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.5 (quinolinyl C_2-2), 151.6 (pyridinyl C_2-2), 147.9 (pyridinyl C_2-6 and quinolinyl C_2-8a), 138.2 (pyridinyl C_2-4), 136.8 (quinolinyl C_2-4), 132.3 (pyridinyl C_2-3), 129.3 (quinolinyl C_2-7), 126.9 (quinolinyl C_2-5), 125.4 (quinolinyl C_2-8), 124.2 (quinolinyl C_2-3), 123.4 (quinolinyl C_2-4a), 123.3 (pyridinyl C_2-5), 122.7 (quinolinyl C_2-6), 77.3 (C-8a^{major}), 74.9 (C-8a^{minor}), 68.0 (C_2-2), 43.1 (C_2-5), 41.0 (C_2-7), 38.3 (pyridinylmethyl C_2-1), 36.5 (C_2-4a), 32.5 (propanone C_2-2), 30.8 (C_2-4), 28.1 (C_2-8), 26.7 (propanone C_2-3), 22.2 (C_2-3); HRMS found MH^+, 431.2438. $C_{26}H_{30}N_4O_2$ requires MH, 431.2447.

N-{[(4aR*,7aS*)-Hexahydro-2H-furo[3,4-b]pyran-4a-yl]methyl}-3-[2-(tert-butylamino)quinolin-3-yl]propanamide

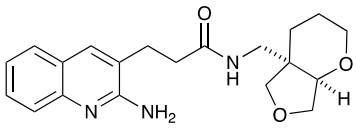


S10

According to General Procedure F, the carbamate derivative **6h** (0.10 g, 0.39 mmol), TBD (0.13 g, 0.93 mmol) and Et_3N (0.50 mL, 3.58 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 70:30→100:0 EtOAc−hexane to yield the amide derivative **S10** (50.0 mg, 31%) as a colourless amorphous solid, R_f 0.53 (EtOAc); ν_{max}/cm^{-1} 3410, 3336, 2959, 2943, 2908, 2875, 1653, 1621, 1549, 1520, 1488, 1450, 1417, 1355, 1277, 1263, 1214, 1189; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, app. d, J 8.3, quinolinyl 8-H), 7.54 (1H, s, quinolinyl 4-H), 7.49 (1H, dd, J 8.0 and 1.4, quinolinyl 5-H), 7.47-7.42 (1H, m, quinolinyl 7-H), 7.15 (1H, ddd, J 8.0, 6.9 and 1.2, quinolinyl 6-H), 5.66 (1H, t, J 6.3, amide NH), 4.94 (1H, br. s, ^{t}Bu NH), 4.02 (1H, dd, J 10.1 and 4.1, 7-H_A), 3.84-3.77 (1H, m, 2-H_A), 3.81 (1H, d,

J 8.6, 5-H_A), 3.74 (1H, d, J 10.1, 7-H_B), 3.61 (1H, d, J 4.1, 7a-H), 3.46 (1H, d, J 8.6, 5-H_B), 3.27 (1H, dd, J 14.0 and 6.3, methylpropanamide 1-H_A), 3.15 (1H, app. td, J 11.5 and 2.4, 2-H_B), 3.11 (1H, dd, J 14.0 and 6.3, methylpropanamide 1-H_B), 2.90 (2H, t, J 7.0, propanamide 3-H_2), 2.56 (2H, t, J 7.0, propanamide 2-H_2), 1.58 (9H, s, ^{t}Bu), 1.49 (1H, app. dd, J 11.2 and 4.3, 3,4-H_A), 1.48-1.46 (1H, m, 3,4-H_B), 1.39-1.30 (1H, m, 3,4-H_C), 1.28-1.21 (1H, m, 3,4-H_D); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.7 (quinolinyl C-4), 128.6 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.0 (quinolinyl C-3), 121.8 (quinolinyl C_2-4a,6), 80.3 (C-7a), 74.2 (C-7), 71.1 (C-5), 66.0 (C-2), 51.9 (^{t}Bu C_1), 45.5 (C-4a), 45.4 (methylpropanamide C-1), 35.6 (propanamide C-2), 29.4 (^{t}Bu C_3), 26.8 (propanamide C-3), 24.4 (C-4), 21.5 (C-3); HRMS found MH^+, 412.2594. $C_{24}H_{33}N_3O_3$ requires MH, 412.2600.

N-{[(4aR*,7aS*)-Hexahydro-2H-furo[3,4-b]pyran-4a-yl]methyl}-3-(2-aminoquinolin-3-yl)propanamide

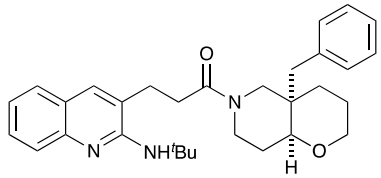


13

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S10** (11.0 mg, 26.7 μmol) were stirred for 3 h to give the amine derivative **13** (10.0 mg, >99%) as a pale yellow oil, R_f 0.65 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3322, 3206, 3055, 2927, 2876, 1632, 1550, 1498, 1472, 1433, 1262, 1097, 1082, 1055; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, s, quinolinyl 4-H), 7.62 (1H, d, J 8.4, quinolinyl 8-H), 7.55 (1H, dd, J 8.0 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, J 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.23 (1H, ddd, J 8.0, 6.9 and 0.9, quinolinyl 6-H), 6.12 (1H, t, J 5.3, amide NH), 5.51 (2H, br. s, NH_2), 4.00 (1H, dd, J 10.1 and 4.1, 7-H_A), 3.78 (1H, d, J 8.5, 5-H_A), 3.82-3.75 (1H, m, 2-H_A), 3.71 (1H, d, J 10.1, 7-H_B), 3.60 (1H, d, J 4.0, 7a-H), 3.46 (1H, d, J 8.5, 5-H_B), 3.24 (1H, dd, J 13.9 and 6.2, methylpropanamide 1-H_A), 3.17-3.05 (2H, m, 2-H_B and methylpropanamide 1-H_B), 3.00 (2H, t, J 7.0,

propanamide 3-H_2), 2.59 (2H, t, J 7.0, propanamide 2-H_2), 1.65-1.52 (1H, m, 3-H_A), 1.51-1.44 (2H, m, 4-H_2), 1.36-1.27 (1H, m, 3-H_B); δ_C (100 MHz, $CDCl_3$) 172.7 (propanamide C-1), 156.2 (quinolinyl C-2), 145.9 (quinolinyl C-8a), 137.2 (quinolinyl C-4), 129.6 (quinolinyl C-7), 127.1 (quinolinyl C-5), 125.0 (quinolinyl C-8), 124.1 (quinolinyl C-3), 123.0 (quinolinyl C-6), 122.7 (quinolinyl C-4a), 80.3 (C-7a), 74.2 (C-7), 71.1 (C-5), 66.1 (C-2), 53.5 (C-4a), 45.5 (methylpropanamide C-1), 35.8 (propanamide C-2), 26.9 (propanamide C-3), 24.5 (C-4), 21.5 (C-3); HRMS found MH^+, 356.1968. $C_{20}H_{25}N_3O_3$ requires MH, 356.1974.

1-[(4aR*,8aR*)-4a-Benzyl-octahydro-2H-pyrano[3,2-c]pyridin-6-yl]-3-[2-(tert- butylamino)quinolin-3-yl]propan-1-one

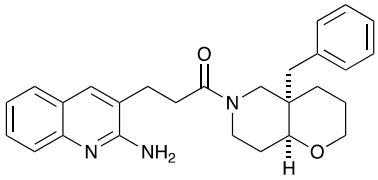


S11

According to General Procedure G, the carbamate derivative **6i** (50.0 mg, 0.14 mmol) and TBD (29.5 mg, 0.21 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 30:70 EtOAc−hexane to yield the amide derivative **S11** (15.0 mg, 23%, rotamers 65:35 by ^{1}H-NMR) as a colourless oil, R_f 0.44 (50:50 EtOAc−petrol); ν_{max}/cm^{-1} 3305, 2951, 2925, 2868, 1634, 1622, 1582, 1543, 1447, 1419, 1352, 1272, 1227, 1212, 1116, 1090; δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, J 8.6, quinolinyl 8-H), 7.58 (2H, s, quinolinyl 4-H), 7.47-7.40 (4H, m, quinolinyl 5,7-H_2), 7.31-7.15 (8H, m, phenyl 2,6-H_2^{major} and phenyl 3,4,5-H_3), 7.12 (2H, app. q, J 6.9, quinolinyl 6-H), 7.07-7.00 (2H, m, phenyl 2,6-H_2^{minor}), 5.14 (2H, br. s, NH), 4.42 (1H, app. d, J 13.1, 7-H_A^{minor}), 4.18 (1H, d, J 13.2, 5-H_A^{major}), 3.95-3.81 (2H, m, 2-H_A), 3.70-3.61 (1H, m, 7-H_A^{major}), 3.46 (1H, d, J 13.2, 5-H_A^{minor}), 3.40-3.20 (5H, m, 2-H_B, 7-H_B^{major} and 8a-H), 3.14 (1H, d, J 13.2, 5-H_B^{major}), 3.07 (1H, d, J 13.2, 5-H_B^{minor}), 3.00-2.89 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.86-2.71 (5H, m, phenylmethyl 1-H_A^{minor} and propanone 2-H_2), 2.63 (1H, d, J 13.4, phenylmethyl 1-H_A^{major}), 2.47 (1H, d, J 13.4, phenylmethyl 1-H_B^{minor}),

2.25 (1H, d, J 13.4, phenylmethyl 1-H_B^{major}), 2.17-2.07 (1H, m, 8-H_A^{minor}), 1.94-1.81 (1H, m, 8-H_A^{major}), 1.78-1.61 (4H, m, 3-H_A and 8-H_B), 1.60 (9H, s, $^tBu^{major}$), 1.56 (9H, s, $^tBu^{minor}$), 1.59-1.52 (2H, m, 3-H_B), 1.41-1.37 (2H, m, 4-H_A), 1.17-1.05 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.8 (propanone C-1^{minor}). 171.2 (propanone C-1^{major}), 154.9 (quinolinyl C_2-2), 147.0 (quinolinyl C_2-8a), 136.8 (phenyl C_2-1), 134.6 (quinolinyl C-4^{major}), 134.5 (quinolinyl C-4^{minor}), 131.0 (phenyl C_2-2,6^{major}), 130.7 (phenyl C_2-2,6^{minor}), 128.4 (quinolinyl C-7^{major}), 128.3 (quinolinyl C-7^{minor}), 128.1 (phenyl C_4-3,5), 126.7 (quinolinyl C_2-5), 126.5 (quinolinyl C_2-8), 126.4 (phenyl C_2-4), 123.6 (quinolinyl C_2-3), 123.1 (quinolinyl C_2-4a), 121.7 (quinolinyl C_2-6), 77.1 (C-$8a^{major}$), 75.4 (C-$8a^{minor}$), 67.8 (C-2^{major}), 67.2 (C-2^{minor}), 51.9 (^tBu C_1^{major}), 51.8 (^tBu C_1^{minor}), 48.7 (C-5^{minor}), 43.6 (C-5^{major}), 41.4 (phenylmethyl C_2-1), 41.0 (C-7^{major}), 37.4 (C-$4a^{minor}$), 37.3 (C-$4a^{major}$), 36.5 (C-7^{minor}), 32.1 (propanone C_2-2), 30.6 (C_2-4), 29.4 (^tBu C_3^{major}), 29.3 (^tBu C_3^{minor}), 28.0 (C_2-8), 27.0 (propanone C_2-3), 22.3 (C-3^{major}), 22.2 (C-3^{minor}); HRMS found MH^+, 486.3116. $C_{31}H_{39}N_3O_2$ requires MH, 486.3120.

1-[(4aR*,8aR*)-4a-Benzyl-octahydro-2H-pyrano[3,2-c]pyridin-6-yl]-3-(2-aminoquinolin-3-yl)propan-1-one

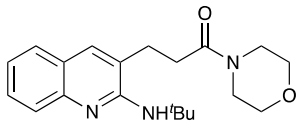


14

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S11** (10.5 mg, 21.6 μmol) were stirred for 3 h to give the amine derivative **14** (9.20 mg, >99%, rotamers 69:31 by ^{1}H-NMR) as a pale yellow oil, R_f 0.27 (EtOAc); ν_{max}/cm^{-1} 3329, 3177, 3052, 3026, 2932, 2852, 1620, 1497, 1470, 1431, 1264, 1118, 1091, 1075; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, s, quinolinyl 4-H^{major}), 7.67 (2H, s, quinolinyl 4-H^{minor}), 7.63 (2H, d, J 8.4, quinolinyl 8-H), 7.54 (2H, dd, J 8.2 and 1.4, quinolinyl 5-H), 7.49 (2H, ddd, J 8.4, 6.9 and 1.4, quinolinyl 7-H), 7.31-7.19 (8H, m, phenyl 3,4,5-H_3 and quinolinyl 6-H), 7.18-7.13 (2H, m, phenyl 2,6-H_2^{major}), 7.07-7.01 (2H, m, phenyl 2,6-H_2^{minor}), 5.43 (4H, br. s, NH_2), 4.39 (1H, app. d, J 13.3, 7-H_A^{minor}), 4.17 (1H, d, J 13.2, 5-

H_A^{major}), 3.96-3.82 (2H, m, 2-H_A), 3.71-3.60 (1H, m, 7-H_A^{major}), 3.54 (1H, d, J 13.2, 5-H_A^{minor}), 3.40-3.21 (5H, m, 2-H_B, 7-H_B^{major} and 8a-H), 3.13 (2H, d, J 13.2, 5-H_B), 3.10-2.97 (5H, m, 7-H_B^{minor} and propanone 3-H_2), 2.94-2.71 (5H, m, phenylmethyl 1-H_A^{minor} and propanone 2-H_2), 2.64 (1H, d, J 13.4, phenylmethyl 1-H_A^{major}), 2.48 (1H, d, J 13.4, phenylmethyl 1-H_B^{minor}), 2.26 (1H, d, J 13.4, phenylmethyl 1-H_B^{major}), 2.15-2.06 (1H, m, 8-H_A^{minor}), 2.00-1.85 (1H, m, 8-H_A^{major}), 1.80-1.53 (4H, m, 3-H_A and 8-H_B), 1.49-1.31 (4H, m, 3-H_B and 4-H_A), 1.18-1.05 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.2 (propanone C_2-1), 156.6 (quinolinyl C_2-2), 146.6 (quinolinyl C_2-8a), 136.7 (phenyl C_2-1), 136.6 (quinolinyl C_2-4), 130.9 (phenyl C_2-2,6^{major}), 130.7 (phenyl C_2-2,6^{minor}) 129.2 (quinolinyl C_2-7), 128.3 (phenyl C_2-3,5^{minor}), 128.1 (phenyl C_2-3,5^{major}), 127.0 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.5 (phenyl C_2-4), 124.3 (quinolinyl C_2-3), 123.6 (quinolinyl C-4a^{minor}), 123.5 (quinolinyl C-4a^{major}), 122.7 (quinolinyl C_2-6), 77.2 (C-8a^{major}), 75.4 (C-8a^{minor}), 67.9 (C_2-2), 48.7 (C-5^{minor}), 43.6 (C-5^{major}), 41.4 (phenylmethyl C_2-1), 40.9 (C-7^{major}), 37.3 (C-7^{minor}), 36.6 (C_2-4a), 32.7 (propanone C_2-2), 30.7 (C_2-4), 28.0 (C_2-8), 26.7 (propanone C_2-3), 22.3 (C_2-3); HRMS found MH^+, 430.2488. $C_{27}H_{31}N_3O_2$ requires MH, 430.2494.

3-[2-(tert-Butylamino)quinolin-3-yl]-1-(morpholin-4-yl)propan-1-one

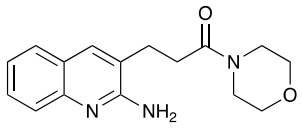


S12

According to General Procedure C, the amine derivative **6j** (71.6 µL, 0.83 mmol), TBD (57.7 mg, 0.41 mmol) and toluene (1.00 mL) were stirred for 4 days to give a crude material. The crude material was purified by flash column chromatography eluting with 50:50 EtOAc−hexane to yield the amide derivative **S12** (0.16 g, 56%) as a pale yellow oil, R_f 0.36 (40:60 petrol−EtOAc); ν_{max}/cm^{-1} 3452, 3391, 2954, 2915, 2860, 2242, 1639, 1624, 1515, 1419, 1354, 1272, 1216, 1116; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, J 8.3, quinolinyl 8-H), 7.52 (1H, s, quinolinyl 4-H), 7.50 (1H, dd, J 8.0 and 1.5,

quinolinyl 5-H), 7.46 (1H, ddd, J 8.3, 7.0 and 1.5, quinolinyl 7-H), 7.16 (1H, ddd, J 8.0, 7.0 and 1.2, quinolinyl 6-H), 5.09 (1H, br. s, NH), 3.63 (4H, app. s, 2-H_A, 3-H_A, 5-H_A and 6-H_A), 3.55-3.49 (2H, m, 2-H_B and 6-H_B), 3.42-3.36 (2H, m, 3-H_B and 5-H_B), 2.92 (2H, t, J 7.1, propanone 3-H_2), 2.65 (2H, t, J 7.1, propanone 2-H_2), 1.58 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.8 (propanone C-1), 154.8 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.6 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.6 (quinolinyl C-5), 126.5 (quinolinyl C-8), 123.5 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 66.9 (C_A-2,6), 66.5 (C_B-2,6), 51.8 (^{t}Bu C_1), 46.0 (C_A-3,5), 42.2 (C_B-3,5), 31.8 (propanone C-2), 29.3 (^{t}Bu C_3), 26.6 (propanone C-3); HRMS found MH^+, 342.2179. $C_{20}H_{27}N_3O_2$ requires MH, 342.2181.

3-(2-Aminoquinolin-3-yl)-1-(morpholin-4-yl)propan-1-one

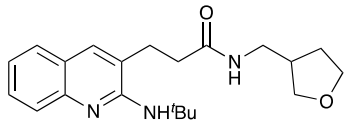


15

According to General Procedure D, TFA (8.00 mL) and the amide derivative **S12** (0.12 g, 0.35 mmol) were stirred for 2 h to give a crude material. The crude material was purified by flash column chromatography eluting with 95.4:4.08:0.52 DCM−EtOH−NH_4OH to yield the amine derivative **15** (93.0 mg, 93%) as colourless crystals, m.p. (DCM), 183–193 °C; R_f 0.31 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3315, 3133, 2965, 2899, 2853, 1628, 1614, 1461, 1428, 1408, 1240, 1228, 1108; δ_H (400 MHz, DMSO-d_6) 7.71 (1H, s, quinolinyl 4-H), 7.58 (1H, d, J 7.9, quinolinyl 8-H), 7.48-7.35 (2H, m, quinolinyl 5,7-H_2), 7.12 (1H, t, J 7.2, quinolinyl 6-H), 6.29 (2H, br. s, NH_2), 3.51-3.45 (4H, m, 2,6-H_4), 3.45-3.39 (4H, m, 3,5-H_4), 2.82 (2H, t, J 7.4, propanone 3-H_2), 2.67 (2H, t, J 7.4, propanone 2-H_2); δ_C (75 MHz, DMSO-d_6) 170.2 (propanone C-1), 157.1 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 134.8 (quinolinyl C-4), 128.2 (quinolinyl C-7), 126.8 (quinolinyl C-8), 124.7 (quinolinyl C-5), 123.4 (quinolinyl C-3), 123.3 (quinolinyl C-4a), 121.2 (quinolinyl C-6), 45.3 (C_2-2,6), 41.5 (C_2-3,5), 30.7 (propanone C-2), 25.9

(propanone C-3); HRMS found MH^+, 286.1550. $C_{16}H_{19}N_3O_2$ requires MH, 286.1555.

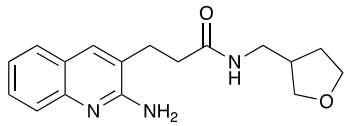
3-[2-(tert-Butylamino)quinolin-3-yl]-N-[(oxolan-3-yl)methyl]propanamide



S13

According to General Procedure C, the amine derivative **6k** (0.10 g, 0.98 mmol), TBD (68.2 mg, 0.49 mmol) and toluene (1.00 mL) were stirred overnight to give a crude material. The crude material was purified by flash column chromatography eluting with 50:50→100:0 EtOAc−hexane to yield the amide derivative **S13** (0.32 g, 90%) as a yellow oil, R_f 0.45 (EtOAc); ν_{max}/cm^{-1} 3307, 2959, 2928, 2866, 1644, 1623, 1516, 1485, 1448, 1414, 1355, 1273, 1212; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, d, J 8.3, quinolinyl 8-H), 7.51 (1H, s, quinolinyl 4-H), 7.49-7.42 (2H, m, quinolinyl 5,7-H_2), 7.16 (1H, t, J 7.4, quinolinyl 6-H), 5.71 (1H, t, J 6.1, amide NH), 5.01 (1H, br. s, ^{t}Bu NH), 3.79 (1H, app. td, J 8.3 and 5.3, 5-H_A), 3.74-3.60 (2H, m, 2-H_A and 5-H_B), 3.45 (1H, dd, J 8.8 and 5.1, 2-H_B), 3.23 (2H, t, J 6.4, methylpropanamide 1-H_2), 2.87 (2H, t, J 7.1, propanamide 3-H_2), 2.49 (2H, t, J 7.1, propanamide 2-H_2), 2.37 (1H, app. hept, J 6.6, 3-H), 1.98-1.84 (1H, m, 4-H_A), 1.59 (9H, s, ^{t}Bu), 1.54-1.41 (1H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.3 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.2 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 71.3 (C-2), 67.7 (C-5), 51.9 (^{t}Bu C_1), 42.6 (methylpropanamide C-1), 39.0 (C-3), 35.6 (propanamide C-2), 29.8 (C-4), 29.3 (^{t}Bu C_3), 26.7 (propanamide C-3); HRMS found MH^+, 356.2334. $C_{21}H_{29}N_3O_2$ requires MH, 356.2338.

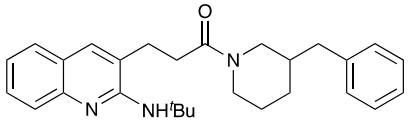
3-(2-Aminoquinolin-3-yl)-N-[(oxolan-3-yl)methyl]propanamide



16

According to General Procedure D, TFA (2.00 mL) and the amide derivative **S13** (0.10 g, 0.28 mmol) were stirred for 1.5 h to yield a crude material. The crude material was purified by flash column chromatography eluting with 92.4:6.76:0.84→84.7:13.6:1.70 DCM−EtOH−NH_4OH to yield the amine derivative **16** (40.0 mg, 47%) as a colourless amorphous solid, R_f 0.61 (84.7:13.6:1.70 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3476, 3329, 3083, 2965, 2924, 2840, 1637, 1618, 1529, 1501, 1477, 1438, 1260, 1069; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, app. d, J 7.9, quinolinyl 8-H), 7.56 (1H, s, quinolinyl 4-H), 7.50 (1H, dd, J 8.1 and 1.5, quinolinyl 5-H), 7.45 (1H, ddd, J 8.4, 6.9 and 1.5, quinolinyl 7-H), 7.18 (1H, ddd, J 8.1, 6.9 and 1.2, quinolinyl 6-H), 6.32 (1H, t, J 6.0, amide NH), 5.36 (2H, br. s, NH_2), 3.71 (1H, app. td, J 8.3 and 5.3, 5-H_A), 3.64-3.50 (2H, m, 2-H_A and 5-H_B), 3.38 (1H, dd, J 8.8 and 5.1, 2-H_B), 3.25-3.08 (2H, m, methylpropanamide 1-H_2), 2.89 (2H, t, J 7.1, propanamide 3-H_2), 2.47 (2H, t, J 7.1, propanamide 2-H_2), 2.31 (1H, app. ddt, J 8.3, 6.9 and 5.3, 3-H), 1.83 (1H, app. dtd, J 13.2, 8.1 and 5.3, 4-H_A), 1.42 (1H, dddd, J 12.6, 8.0, 7.1 and 5.7, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.5 (propanamide C-1), 156.5 (quinolinyl C-2), 146.6 (quinolinyl C-8a), 136.4 (quinolinyl C-4), 129.2 (quinolinyl C-7), 127.0 (quinolinyl C-5), 125.3 (quinolinyl C-8), 124.2 (quinolinyl C-3), 122.7 (quinolinyl C-4a), 122.6 (quinolinyl C-6), 71.1 (C-2), 67.7 (C-5), 42.5 (methylpropanamide C-1), 39.0 (C-3), 35.5 (propanamide C-2), 29.8 (C-4), 26.8 (propanamide C-3); HRMS found MH^+, 300.1703. $C_{17}H_{21}N_3O_2$ requires MH, 300.1712.

1-(3-Benzylpiperidin-1-yl)-3-[2-(tert-butylamino)quinolin-3-yl]propan-1-one

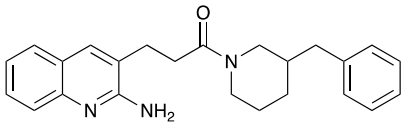


S14

According to General Procedure C, the amine hydrochloride derivative **6l** (67.1 mg, 0.32 mmol), TBD (0.10 g, 0.72 mmol) and toluene (2.00 mL) were stirred for 2 days to give a crude material. The crude material was purified by flash column chromatography eluting with 20:80 EtOAc−hexane to yield the amide derivative **S14** (50.0 mg, 37%, rotamers 51:49 by ^{1}H-NMR) as a colourless oil, R_f 0.37 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3455, 2942, 2923, 2869, 2848, 1645, 1623, 1517, 1489, 1449, 1437, 1420, 1353, 1278, 1215, 1194, 1175; δ_H (400 MHz, $CDCl_3$) 7.71 (2H, dd, J 8.3 and 3.7, quinolinyl 8-H), 7.57-7.38 (6H, m, quinolinyl 4,5,7-H_3), 7.33-7.06 (12H, phenyl and quinolinyl 6-H), 5.19 (1H, br. s, NH^{minor}), 5.17 (1H, br. s, NH^{major}), 4.55 (1H, ddt, J 12.9, 3.8 and 1.7, phenylmethyl 1-H_A^{minor}), 4.44 (1H, app. dt, J 12.9 and 3.8, phenylmethyl 1-H_A^{major}), 3.74 (1H, app. dt, J 12.4 and 4.2, phenylmethyl 1-H_B^{minor}), 3.66-3.59 (1H, m, phenylmethyl 1-H_B^{major}), 2.97 (2H, app. dd, J 12.0 and 2.8, 6-H_2^{minor}), 2.93 (2H, t, J 7.2, propanone 3-H_2^{minor}), 2.84 (2H, t, J 7.2, propanone 3-H_2^{major}), 2.78-2.70 (2H, m, 6-H_2^{major}), 2.69-2.62 (4H, m, 2-H_2^{major} and propanone 2-H_2^{minor}), 2.55-2.48 (2H, m, propanone 2-H_2^{major}), 2.47-2.38 (2H, m, 2-H_2^{minor}), 1.86-1.62 (6H, m, 3-H, 4-H_A and 5-H_A), 1.60 (18H, s, ^{t}Bu), 1.49-1.07 (4H, m, 4-H_B and 5-H_B); δ_C (100 MHz, $CDCl_3$) 170.5 (propanone C-1^{minor}), 170.4 (propanone C-1^{major}), 154.9 (quinolinyl C_2-2), 147.0 (quinolinyl C_2-8a), 139.5 (phenyl C-1^{minor}), 139.3 (phenyl C-1^{major}), 134.5 (quinolinyl C-4^{major}), 134.3 (quinolinyl C-4^{minor}), 129.1 (phenyl C_2-2,6^{minor}), 128.8 (phenyl C_2-2,6^{major}), 128.6 (quinolinyl C_2-7), 128.4 (phenyl C_2-3,5^{major}), 128.3 (phenyl C_2-3,5^{minor}), 126.6 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 126.1 (phenyl C_2-4), 124.0 (quinolinyl C-3^{major}), 123.8 (quinolinyl C-3^{minor}), 123.1 (quinolinyl C_2-4a), 121.6 (quinolinyl C_2-6), 51.8 (^{t}Bu C_2), 51.3 (C-2^{major}), 48.0 (C-2^{minor}), 46.4 (phenylmethyl C-1^{minor}), 42.9 (phenylmethyl C-1^{major}), 40.3 (C-6^{minor}), 40.0 (C-6^{major}), 38.8 (phenylmethyl C-3^{major}), 37.8 (phenylmethyl C-3^{minor}), 32.2 (propanone C-2^{minor}), 31.9 (propanone C-2^{major}), 30.9 (C-4^{major}), 30.8 (C-4^{minor}),

29.4 (^{t}Bu C_6), 26.7 (propanone C-3^{minor}), 26.5 (propanone C-3^{major}), 25.8 (C-5^{minor}), 24.7 (C-5^{major}); HRMS found MH^+, 430.2858. $C_{28}H_{35}N_3O$ requires MH, 430.2858.

3-(2-Aminoquinolin-3-yl)-1-(3-benzylpiperidin-1-yl)propan-1-one

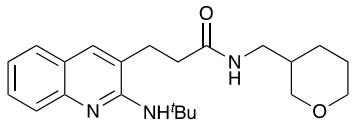


17

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S14** (13.0 mg, 30.3 μmol) were stirred for 3 h to give the amine derivative **17** (11.3 mg, >99%, rotamers 51:49 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.45 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3369, 3338, 3128, 2942, 2917, 2865, 2847, 1665, 1619, 1499, 1476, 1452, 1434, 1330, 1279, 1218, 1143, 1111; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, s, quinolinyl 4-H^{minor}), 7.65 (2H, dd, J 8.4 and 2.6, quinolinyl 8-H), 7.59 (2H, dd, J 8.0 and 1.6, quinolinyl 5-H), 7.57 (1H, s, quinolinyl 4-H^{major}), 7.53-7.46 (2H, m, quinolinyl 7-H), 7.33-7.23 (6H, m, phenyl 3,4,5-H_3), 7.24-7.17 (2H, m, quinolinyl 6-H), 7.13 (2H, d, J 7.1, phenyl 2,6-H_A), 7.07 (2H, d, J 7.1, phenyl 2,6-H_B), 5.41 (2H, br. s, NH^{minor}), 5.35 (2H, br. s, NH^{major}), 4.50 (1H, ddt, J 12.9, 3.8 and 1.7, phenylmethyl 1-H_A^{minor}), 4.42 (1H, app. dt, J 13.3 and 4.2, phenylmethyl 1-H_A^{major}), 3.72 (1H, app. dt, J 13.5 and 4.1, phenylmethyl 1-H_B^{minor}), 3.63 (1H, ddt, J 13.3, 3.7 and 1.6, phenylmethyl 1-H_B^{major}), 3.02 (4H, t, J 7.0, 6-H_2^{major} and propanone 3-H_2^{minor}), 2.93 (2H, t, J 7.0, propanone 3-H_2^{major}), 2.72 (2H, t, J 7.0, propanone 2-H_2^{minor}), 2.70-2.63 (4H, m, 2-H_2^{minor} and 6-H_2^{minor}), 2.55 (2H, t, J 7.0, propanone 2-H_2^{major}), 2.48-2.34 (2H, m, 2-H_2^{major}), 1.85-1.73 (2H, m, 4-H_A), 1.75-1.59 (4H, m, 3-H and 5-H_A), 1.48-1.33 (2H, m, 5-H_B), 1.29-1.04 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 170.6 (propanone C-1^{major}), 170.5 (propanone C-1^{minor}), 156.6 (quinolinyl C_2-2), 146.7 (quinolinyl C_2-8a), 139.5 (phenyl C-1^{minor}), 139.3 (phenyl C-1^{major}), 136.5 (quinolinyl C-4^{minor}), 136.4 (quinolinyl C-4^{major}), 129.2 (phenyl C_2-2,6^{major}), 129.1 (phenyl C_2-2,6^{minor}), 128.9 (quinolinyl C_2-7), 128.6 (phenyl C_2-3,5^{major}), 128.4 (phenyl C_2-3,5^{minor}),

127.0 (quinolinyl C_2-5), 126.4 (quinolinyl C_2-8), 125.6 (phenyl C-4^{major}), 125.5 (phenyl C-4^{minor}), 124.3 (quinolinyl C_2-3), 123.6 (quinolinyl C-4a^{minor}), 123.5 (quinolinyl C-4a^{major}), 122.6 (quinolinyl C_2-6), 51.4 (C-2^{major}), 48.1 (C-2^{minor}), 46.4 (phenylmethyl C-1^{minor}), 43.0 (phenylmethyl C-1^{major}), 40.4 (quinolinyl C-6^{minor}), 40.1 (quinolinyl C-6^{major}), 38.8 (quinolinyl C-3^{major}), 37.7 (quinolinyl C-3^{minor}), 32.7 (propanone C-2^{minor}), 32.4 (propanone C-2^{major}), 31.0 (C-4^{major}), 30.4 (C-4^{minor}), 26.6 (propanone C_2-3), 25.7 (C-5^{minor}), 24.7 (C-5^{major}); HRMS found MH^+, 374.2233. $C_{24}H_{27}N_3O$ requires MH, 374.2232.

3-[2-(tert-Butylamino)quinolin-3-yl]-N-[(oxan-3-yl)methyl]propanamide

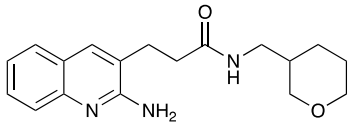


S15

According to General Procedure C, the amine hydrochloride derivative **6m** (48.1 mg, 0.32 mmol), TBD (0.10 g, 0.72 mmol) and toluene (2.00 mL) were stirred for 2 days to give a crude material. The crude material was purified by flash column chromatography eluting with 60:40 EtOAc−hexane to yield the amide derivative **S15** (50.0 mg, 43%) as a colourless oil, R_f 0.45 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3429, 3294, 3089, 2953, 2920, 2843, 1641, 1622, 1557, 1518, 1448, 1413, 1354, 1212, 1089; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, dd, J 8.4 and 1.2, quinolinyl 8-H), 7.49 (1H, s, quinolinyl 4-H), 7.48-7.42 (2H, m, quinolinyl 5,7-H_2), 7.14 (1H, ddd, J 8.0, 7.0 and 1.2, quinolinyl 6-H), 5.61 (1H, t, J 6.2, amide NH), 5.00 (1H, br. s, ^{t}Bu NH), 3.81-3.72 (2H, m, 2-H_A and 6-H_A), 3.35 (1H, ddd, J 11.2, 9.7 and 3.3, 6-H_B), 3.14-3.11 (1H, m, 2-H_B), 3.10 (2H, t, J 6.2, methylpropanamide 1-H_2), 2.85 (2H, t, J 7.1, propanamide 3-H_2), 2.47 (2H, t, J 7.1, propanamide 2-H_2), 1.76-1.63 (2H, m, 3-H and 4-H_A), 1.58 (9H, s, ^{t}Bu), 1.55-1.45 (2H, m, 5-H_2), 1.16 (1H, app. dtd, J 13.7, 10.5 and 4.6, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.2 (propanamide C-1), 154.7 (quinolinyl C-2), 147.0 (quinolinyl C-8a), 134.5 (quinolinyl C-4), 128.5 (quinolinyl C-7), 126.7 (quinolinyl C-5), 126.4 (quinolinyl C-8), 123.3 (quinolinyl C-3), 123.0 (quinolinyl C-4a), 121.7 (quinolinyl C-6), 71.1 (C-2), 68.5 (C-6), 51.9 (^{t}Bu C_1),

41.7 (methylpropanamide C-1), 36.3 (C-3), 35.5 (propanamide C-2), 29.3 (^{t}Bu C_3), 27.3 (C-4), 26.7 (propanamide C-3), 25.0 (C-5); HRMS found MH^+, 370.2488. $C_{22}H_{31}N_3O_2$ requires MH, 370.2494.

3-(2-Aminoquinolin-3-yl)-N-[(oxan-3-yl)methyl]propanamide



18

According to General Procedure D, TFA (0.50 mL) and the amide derivative **S15** (11.0 mg, 29.7 μmol) were stirred for 3 h to give the amine derivative **18** (9.30 mg, >99%) as a colourless oil, R_f 0.28 (92.4:6.76:0.84 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3397, 3277, 3148, 3083, 2948, 2930, 2916, 2850, 1654, 1627, 1565, 1501, 1477, 1154; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, s, quinolinyl 4-H), 7.63 (1H, dd, J 8.5 and 1.2, quinolinyl 8-H), 7.53 (1H, dd, J 8.1 and 1.5, quinolinyl 5-H), 7.50 (1H, ddd, J 8.5, 6.9 and 1.5, quinolinyl 7-H), 7.23 (1H, ddd, J 8.1, 6.9 and 1.2, quinolinyl 6-H), 5.81 (1H, t, J 5.2, amide NH), 5.35 (2H, s, NH_2), 3.83-3.61 (2H, m, 2-H_A and 6-H_A), 3.35 (1H, ddd, J 11.2, 9.6 and 3.3, 6-H_B), 3.14-3.06 (1H, m, 2-H_A), 3.11 (2H, t, J 6.5, methylpropanamide 1-H_2), 2.97 (2H, t, J 7.0, propanamide 3-H_2), 2.54 (2H, t, J 7.0, propanamide 2-H_2), 1.78-1.62 (2H, m, 3-H and 4-H_A), 1.60-1.40 (2H, m, 5-H_2), 1.15 (1H, app. dtd, J 12.7, 10.1, 9.6 and 4.6, 4-H_B); δ_C (100 MHz, $CDCl_3$) 172.4 (propanamide C-1), 156.4 (quinolinyl C-2), 146.4 (quinolinyl C-8a), 136.8 (quinolinyl C-4), 129.3 (quinolinyl C-7), 127.0 (quinolinyl C-5), 125.3 (quinolinyl C-8), 124.2 (quinolinyl C-3), 122.9 (quinolinyl C-4a), 122.8 (quinolinyl C-6), 71.0 (C-2), 68.5 (C-6), 41.7 (methylpropanamide C-1), 36.2 (C-3), 35.8 (propanamide C-2), 27.3 (C-4), 26.9 (propanamide C-3), 24.9 (C-5); HRMS found MH^+, 314.1867. $C_{18}H_{23}N_3O_2$ requires MH, 314.1868.

1.3. Preparation of the nine optimised screening compounds

1.3.1. Experimental for the preparation of the aminoquinoline esters

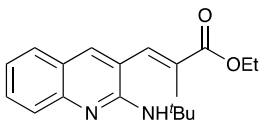
General Procedure H

NBS (1.00 eq) was added to a solution of the respective ester derivative (1.00 eq) in THF (0.33 M) and the reaction mixture was stirred for the specified time at rt. The solution was concentrated under reduced pressure to give a crude material.

General Procedure I

According to a modified procedure,[5] 2-methylbenzeneboronic acid (1.10 eq) and Na_2CO_3 (2.00 eq from a 1.00 M aqueous solution) were added to a solution of the respective brominated derivative (1.00 eq) in 1:2 ethanol:toluene (0.31 M). Subsequently, $Pd(PPh_3)_4$ (0.05 eq) was added and the reaction mixture was stirred at 80 ℃. After 1.5 h, the mixture was allowed to cool to room temperature and water (2 mL per 1.00 mmol of the brominated derivative) and EtOAc (2 mL per 1.00 mmol of the brominated derivative) were added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × (2 mL per 1.00 mmol of the brominated derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

Ethyl (2E)-3-[2-(tert-butylamino)quinolin-3-yl]-2-methylprop-2-enoate

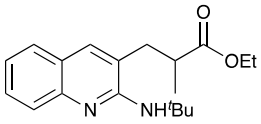


S16

According to General Procedure A, the aldehyde derivative **S1** (1.00 g, 4.38 mmol) and ethyl-2-(diethylphosphono)propanoate (1.17 mL, 5.47 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 10:90 EtOAc−hexane to yield the alkene derivative **S16** (1.37 g, >99%) as a yellow oil, R_f 0.74 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3376, 2958, 1692, 1600, 1519, 1409, 1358, 1264, 1223, 1122, 1107; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, dd J 8.4 and 1.2, 8-H), 7.60 (1H, s, 4-H), 7.56

(1H, dd, J 8.1 and 1.5, 5-H), 7.53 (1H, app. dt, J 8.4 and 1.5, 7-H), 7.50 (1H, app. t, J 1.5, propenoate 3-H), 7.19 (1H, ddd, J 8.1, 6.9 and 1.2, 6-H), 4.39 (1H, br. s, NH), 4.32 (2H, q, J 7.1, ethyl 1-H_2), 2.03 (3H, d, J 1.5, methyl), 1.58 (9H, s, ^{t}Bu), 1.38 (3H, t, J 7.1, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 167.9 (propenoate C-1) 153.6 (C-2), 147.8 (C-8a), 135.9 (C-4), 133.6 (propenoate C-3), 133.0 (propenoate C-2), 129.5 (C-7), 127.5 (C-5), 126.7 (C-8), 122.3 (C-6), 122.1 (C-3), 119.9 (C-4a), 61.2 (ethyl C-1), 52.1 (^{t}Bu C_1), 29.3 (^{t}Bu C_3), 14.5 (ethyl C-2), 14.4 (methyl); HRMS found MH^+, 313,1909. $C_{19}H_{24}N_2O_2$ requires MH, 313.1916.

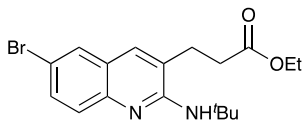
Ethyl 3-[2-(tert-butylamino)quinolin-3-yl]-2-methylpropanoate



19

According to General Procedure B, the alkene derivative **S16** (1.33 g, 4.25 mmol) was hydrogenated for 1 h to give a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the ester derivative **19** (1.32 g, 99%) as a yellow oil, R_f 0.74 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2960, 1727, 1623, 1516, 1448, 1415, 1387, 1208, 1173; δ_H (400 MHz, $CDCl_3$) 7.70 (1H, d, J 8.3, 8-H), 7.55 (1H, s, 4-H), 7.53 (1H, dd, J 8.0 and 1.5, 5-H), 7.48 (1H, ddd, J 8.3, 6.9 and 1.5, 7-H), 7.18 (1H, ddd, J 8.0, 6.9 and 1.2, 6-H), 4.75 (1H, br. s, NH), 4.16 (2H, q, J 7.1, ethyl 1-H_2), 3.00 (1H, dd, J 14.7 and 6.1, propanoate 3-H_A), 2.79 (1H, app. h, J 6.9, propanoate 2-H), 2.53 (1H, dd, J 14.7 and 7.5, propanoate 3-H_B), 1.61 (9H, s, ^{t}Bu), 1.26 (3H, d, J 6.9, methyl), 1.25 (3H, t, J 7.1, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 176.0 (propanoate C-1), 154.7 (C-2), 147.1 (C-8a), 135.7 (C-4), 128.6 (C-7), 126.8 (C-5), 126.5 (C-8), 123.0 (C-4a and C-3), 121.8 (C-6), 60.8 (ethyl C-1), 51.9 (^{t}Bu C_1), 38.7 (propanoate C-2), 35.9 (propanoate C-3), 29.3 (^{t}Bu C_3), 17.1 (methyl), 14.3 (ethyl C-2); HRMS found MH^+, 315.2069. $C_{19}H_{26}N_2O_2$ requires MH, 315.2072.

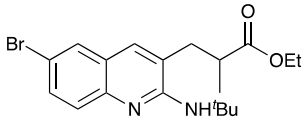
Ethyl 3-[6-bromo-2-(tert-butylamino)quinolin-3-yl]propanoate



S17

According to General Procedure H, the ester derivative **5** (0.65 g, 2.16 mmol) was stirred for 2 h to give a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the ester derivative **S17** (0.46 g, 56%) as a light brown amorphous solid, R_f 0.38 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3465, 2977, 2957, 1730, 1625, 1510, 1416, 1272, 1145; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, d, J 2.1, 5-H), 7.56-7.50 (2H, m, 7,8-H_2), 7.43 (1H, s, 4-H), 4.77 (1H, br. s, NH), 4.18 (2H, q, J 7.1, ethyl 1-H_2), 2.82 (2H, t, J 7.4, propanoate 3-H_2), 2.68 (2H, t, J 7.4, propanoate 2-H_2), 1.58 (9H, s, ^{t}Bu), 1.27 (3H, t, J 7.1, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 172.9 (propanoate C-1), 154.7 (C-2), 145.6 (C-8a), 133.1 (C-4), 131.6 (C-7), 128.8 (C-5), 128.2 (C-8), 124.3 (C-3), 123.6 (C-4a), 114.4 (C-6), 61.0 (ethyl C-1), 52.0 (^{t}Bu C_1), 32.8 (propanoate C-2), 29.3 (^{t}Bu C_3), 26.1 (propanoate C-3), 14.3 (ethyl C-2); HRMS found MH^+, 379.1012. $C_{18}H_{23}BrN_2O_2$ requires MH, 379.1021.

Ethyl 3-[6-bromo-2-(tert-butylamino)quinolin-3-yl]-2-methylpropanoate

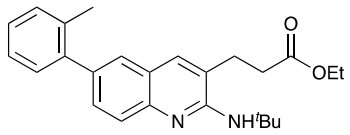


S18

According to General Procedure H, the ester derivative **19** (0.65 g, 2.06 mmol) was stirred for 1 h to give a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the ester derivative **S18** (0.53 g, 65%) as a yellow oil, R_f 0.42 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3446, 2971, 2934, 1725, 1621, 1512, 1450, 1411, 1347, 1269, 1210, 1192, 1174; δ_H (400 MHz, $CDCl_3$) 7.64 (1H, d, J 2.1, 5-H),

7.56-7.49 (2H, m, 7,8-H_2), 7.43 (1H, s, 4-H), 4.81 (1H, br. s, NH), 4.15 (2H, q, J 7.1, ethyl 1-H_2), 2.97 (1H, dd, J 14.7 and 6.3, propanoate 3-H_A), 2.75 (1H, app. h, J 6.9, propanoate 2-H), 2.50 (1H, dd, J 14.7 and 7.3, propanoate 3-H_B), 1.57 (9H, s, ^{t}Bu), 1.24 (3H, d, J 6.9, methyl), 1.23 (3H, t, J 7.1, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 175.9 (propanoate C-1), 154.8 (C-2), 145.8 (C-8a), 134.5 (C-4), 131.7 (C-7), 128.8 (C-5), 128.2 (C-8), 124.2 (C-3), 122.7 (C-4a), 114.4 (C-6), 60.9 (ethyl C-1), 52.0 (^{t}Bu C_1), 38.6 (propanoate C-2), 35.8 (propanoate C-3), 29.3 (^{t}Bu C_3), 17.2 (methyl), 14.3 (ethyl C-2); HRMS found MH^+, 393.1168. $C_{19}H_{25}BrN_2O_2$ requires MH, 393.1177.

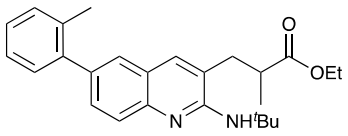
Ethyl 3-[2-(tert-butylamino)-6-(2-methylphenyl)quinolin-3-yl]propanoate



20

According to General Procedure I, the brominated derivative **S17** (0.46 g, 1.21 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 5:95 EtOAc−hexane to yield the ester derivative **20** (0.40 g, 85%) as a light brown amorphous solid, R_f 0.40 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3457, 2957, 1734, 1514, 1502, 1429, 1416, 1175, 1160; δ_H (400 MHz, $CDCl_3$) 7.72-7.20 (8H, m, Ar), 4.71 (1H, br. s, NH), 4.15 (2H, q, J 7.2, ethyl 1-H_2), 2.83 (2H, t, J 7.4, propanoate 3-H_2), 2.68 (2H, t, J 7.4, propanoate 2-H_2), 2.28 (3H, s, methyl), 1.58 (9H, s, ^{t}Bu), 1.24 (3H, t, J 7.2, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 173.1 (propanoate C-1), 154.7 (Ar C_1), 145.9 (Ar C_1), 142.2 (Ar C_1), 135.7 (Ar C_1), 135.5 (Ar C_1), 134.3 (Ar C_1), 130.4 (Ar C_1), 130.3 (Ar C_1), 130.1 (Ar C_1), 127.1 (Ar C_1), 126.9 (Ar C_1), 126.0 (Ar C_1), 125.8 (Ar C_1), 123.0 (Ar C_1), 122.7 (Ar C_1), 60.9 (ethyl C-1), 51.9 (^{t}Bu C_1), 33.0 (propanoate C-2), 29.4 (^{t}Bu C_3), 26.3 (propanoate C-3), 20.7 (methyl), 14.3 (ethyl C-2); HRMS found MH^+, 391.2385. $C_{25}H_{30}N_2O_2$ requires MH, 391.2385.

Ethyl 3-[2-(tert-butylamino)-6-(2-methylphenyl)quinolin-3-yl]-2-methyl propanoate



21

According to General Procedure I, the brominated derivative **S18** (0.53 g, 1.34 mmol) gave a crude material. The crude material was purified by flash column chromatography eluting with 4:96 EtOAc−hexane to yield the ester derivative **21** (0.52 g, 96%) as a yellow oil, R_f 0.46 (90:10 petrol−EtOAc); ν_{max}/cm^{-1} 3447, 2959, 1727, 1624, 1514, 1500, 1451, 1412, 1264, 1218, 1173, 1146; δ_H (400 MHz, $CDCl_3$) 7.72-7.20 (8H, m, Ar), 4.76 (1H, br. s, NH), 4.13 (2H, q, J 7.1, ethyl 1-H_2), 2.98 (1H, dd, J 14.7 and 6.1, propanoate 3-H_A), 2.76 (1H, app. h, J 7.0, propanoate 2-H), 2.50 (1H, dd, J 14.7 and 7.4, propanoate 3-H_B), 2.28 (3H, s, methylphenyl), 1.58 (9H, s, ^{t}Bu), 1.22 (3H, d, J 7.0, methylpropanoate), 1.21 (3H, t, J 7.1, ethyl 2-H_3); δ_C (100 MHz, $CDCl_3$) 176.1 (propanoate C-1), 154.8 (Ar C_1), 146.1 (Ar C_1), 142.1 (Ar C_1), 135.7 (Ar C_1), 135.7 (Ar C_1), 135.5 (Ar C_1), 130.4 (Ar C_1), 130.3 (Ar C_1), 130.1 (Ar C_1), 127.1 (Ar C_1), 126.9 (Ar C_1), 126.0 (Ar C_1), 125.8 (Ar C_1), 122.7 (Ar C_1), 122.0 (Ar C_1), 60.9 (ethyl C-1), 51.9 (^{t}Bu C_1), 38.8 (propanoate C-2), 35.9 (propanoate C-3), 29.3 (^{t}Bu C_3), 20.7 (methylphenyl), 17.1 (methylpropanoate), 14.3 (ethyl C-2); HRMS found MH^+, 405.2533. $C_{26}H_{32}N_2O_2$ requires MH, 405.2542.

1.3.2. Experimental for the decoration of the scaffolds

General Procedure J (Method D followed by A and B in main text)

By modification of an existing procedure,[3] TFA (17.0 eq) was added to a solution of the carbamate derivative **6e** (1.00 eq) in DCM (9.00 mL for each 1.00 mmol of the carbamate derivative **6e**). The mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (8.00 mL for each 1.00 mmol of the carbamate derivative **6e**), Et_3N (18.0 eq), TBD (0.50 eq) and the specified ester derivative (1.05 eq) were added and the reaction mixture was stirred for 18 h at 75 ℃. Finally, the solvent was removed under reduced pressure to yield an intermediate crude material,

which was loaded into a silica pad, eluted with the specified eluent and concentrated under reduced pressure. The resulting product was treated with TFA (0.50 mL) and stirred at 75 °C for 3 h under air atmosphere. Subsequently, the mixture was concentrated under reduced pressure and it was loaded into a SCX pad, which was eluted with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a final crude material.

General Procedure K (Method C followed by D, A and B in main text)

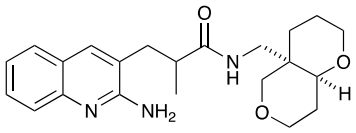
By modification of existing procedures,[3,4] NaOMe (0.10 eq of a 0.5 M solution in MeOH) was added to a solution of the acetate derivative **6d** (1.00 eq) in MeOH (10.0 mL for each 1.00 mmol of the acetate derivative **6d**). After stirring for 45 min at rt, the solvent was removed under reduced pressure. Subsequently, DCM (10.0 mL for each 1.00 mmol of the acetate derivative **6d**) and TFA (24.0 eq) were added, the mixture was stirred at rt for 1 h and it was concentrated under reduced pressure. Afterwards, toluene (9.00 mL for each 1.00 mmol of the acetate derivative **6d**) and the specified ester derivative (1.05 eq) were added. Subsequently, Et_3N (26.0 eq) and TBD (0.50 eq) were added and the reaction mixture was stirred for 18 h at 75 °C. The solvent was removed under reduced pressure to yield an intermediate crude material, which was loaded into a silica pad, eluted with the specified eluent and concentrated under reduced pressure. The resulting product was treated with TFA (0.50 mL) and stirred at 75 °C for 3 h under air atmosphere. Subsequently, the mixture was concentrated under reduced pressure and it was loaded into a SCX pad, which was eluted with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a final crude material.

General Procedure L (Method E followed by A and B in main text)

By modification of an existing procedure,[3] hydrogen gas was passed through a mixture of the carbamate derivative **6i** (1.00 eq) and Pd (0.03 eq of a 10% Pd/C) in MeOH (9.00 mL for each 1.00 mmol of the carbamate derivative **6i**)

for 1 h at rt. Subsequently, the suspension was filtered through a pad of celite and the solvent was removed under reduced pressure. Toluene (9.00 mL for each 1.00 mmol of the carbamate derivative **6i**), the specified ester derivative (1.05 eq) and TBD (0.50 eq) were added and the reaction mixture was stirred for 18 h at 75 ℃. Finally, the solvent was removed under reduce d pressure to yield an intermediate crude material, which was loaded into a silica pad, eluted with the specified eluent and concentrated under reduced pressure. The resulting product was treated with TFA (0.50 mL) and stirred at 75 ℃ for 3 h under air atmosphere. Subsequently, the mixture was concentrated under reduced pressure and it was loaded into a SCX pad, which was eluted with MeOH and with a solution of saturated NH_3 in MeOH. The fraction containing the saturated solution of NH_3 in MeOH was collected and concentrated under reduced pressure to yield a final crude material.

N- {[(4aR*,8aR*)- Octahydropyrano[4,3- b]pyran- 4a- yl]methyl}- 3- (2- aminoquinolin- 3- yl)- 2- methylpropanamide

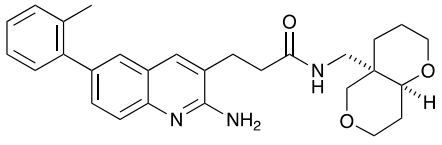


22

According to General Procedure J, the carbamate derivative **6e** (20.0 mg, 73.0 μmol) and the ester derivative **19** (24.3 mg, 77.0 μmol) gave an intermediate crude material that was eluted with 70:30 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 93.9:5.3:0.7 DCM−EtOH–NH_4OH to yield the amine derivative **22** (10.5 mg, 43%, dr 50:50 by ^{1}H-NMR) as a colourless oil, R_f 0.22 (92.4:6.8:0.8 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3324, 2933, 2864, 1648, 1552, 1435, 1098; δ_H (400 MHz, $CDCl_3$) 7.69 (1H, s, quinolinyl 4-H^{diastA}), 7.68 (1H, s, quinolinyl 4-H^{diastB}), 7.61 (2H, dd, J 8.4 and 4.2, quinolinyl 8-H), 7.56 (2H, dd, J 7.9 and 2.7, quinolinyl 5-H), 7.52-7.47 (2H, m, quinolinyl 7-H), 7.25-7.20 (2H, m, quinolinyl 6-H), 6.06 (1H, t, J 5.5, amide NH^{diastA}), 5.91 (1H, t, J 6.1, amide

NH^{diastB}), 5.19 (2H, br. s, NH_2^{diastA}), 5.17 (2H, br. s, NH_2^{diastB}), 3.85-3.75 (2H, m, 2-H_A), 3.77 (1H, d, J 11.8, 5-H_A^{diastA}), 3.65 (1H, d, J 11.8, 5-H_A^{diastB}), 3.62-3.52 (4H, m, 7-H_2), 3.33 (1H, dd, J 13.8 and 7.2, methylpropanamide 1-H_A^{diastA}), 3.25-3.06 (9H, m, methylpropanamide 1-H_B^{diastA}, methylpropanamide 1-H_2^{diastB}, 8a-H, 2-H_B and 5-H_B), 3.02-2.97 (2H, m, propanamide 3-H_A), 2.68-2.54 (4H, m, propanamide 3-H_B and propanamide 2-H), 2.01-1.93 (1H, m, 8-H_A^{diastA}), 1.80-1.70 (1H, m, 8-H_A^{diastB}), 1.59-1.45 (1H, m, 8-H_B^{diastA}), 1.44-1.39 (1H, m, 8-H_B^{diastB}), 1.30 (6H, d, J 6.3, methyl), 1.27-1.00 (8H, m, 3,4-H_4); δ_C (100 MHz, $CDCl_3$) 176.0 (propanamide C-1^{diastA}), 175.8 (propanamide C-1^{diastB}), 156.6 (quinolinyl C_2-2), 146.8 (quinolinyl C_2-8a), 137.8 (quinolinyl C-4^{diastA}), 137.7 (quinolinyl C-4^{diastB}), 129.3 (quinolinyl C_2-7), 127.0 (quinolinyl C_2-5), 125.6 (quinolinyl C_2-8), 124.3 (quinolinyl C_2-3), 122.8 (quinolinyl C_2-6), 121.9 (quinolinyl C-4a^{diastA}), 121.8 (quinolinyl C-4a^{diastB}), 74.7 (C-8a^{diastA}), 74.6 (C-8a^{diastB}), 68.0 (C_2-5), 67.5 (C_2-2), 63.3 (C-7^{diastA}), 63.2 (C-7^{diastB}), 45.2 (methylpropanamide C-1^{diastA}), 44.7 (methylpropanamide C-1^{diastB}), 42.6 (propanamide C_2-2), 42.2 (propanamide C_2-3), 36.1 (C_2-4a), 28.7 (C_2-4), 28.5 (C_2-8), 22.0 (C-3^{diastA}), 21.9 (C-3^{diastB}), 19.0 (methyl^{diastA}), 18.8 (methyl^{diastB}); HRMS found MH^+, 384.2280. $C_{22}H_{29}N_3O_3$ requires MH, 384.2287.

N- {[(4aR*,8aR*)- Octahydropyrano[4,3- b]pyran- 4a- yl]methyl}- 3- [2- amino- 6- (2- methylphenyl)quinolin- 3- yl]propanamide

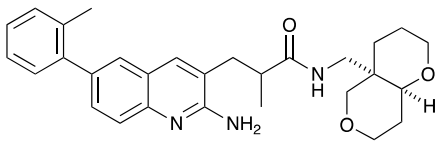


23

According to General Procedure J, the carbamate derivative **6e** (20.0 mg, 73.0 μmol) and the ester derivative **20** (30.1 mg, 77.0 μmol) gave an intermediate crude material that was eluted with 70:30 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM−EtOH–NH_4OH⟶84.7:13.6:1.7 DCM−EtOH–NH_4OH to yield the amine derivative **23** (20.0 mg, 60%) as a colourless oil, R_f 0.39

(84.7:13.6:1.7 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3337, 3211, 3063, 2933 , 2863, 1643, 1558, 1485, 1468, 1450, 1415; δ_H (400 MHz, $CDCl_3$) 7.70-7.23 (8H, m, Ar), 6.03 (1H, t, J 6.5, amide NH), 5.29 (1H, br. s, aminoquinolinyl NH_A), 5.28 (1H, br. s, aminoquinolinyl NH_B), 3.89 (1H, app. dd, J 11.1 and 4.9, 2-H_A), 3.81 (1H, d, J 11.5, 5-H_A), 3.67-3.62 (2H, m, 7-H_2), 3.38 (1H, dd, J 13.9 and 6.5, methylpropanamide 1-H_A), 3.34-3.27 (2H, m, 2-H_B and methylpropanamide 1-H_B), 3.23-3.17 (1H, m, 8a-H), 3.22 (1H, d, J 11.5, 5-H_B), 3.01 (2H, t, J 6.9, propanamide 3-H_2), 2.60 (2H, t, J 6.9, propanamide 2-H_2), 2.29 (3H, s, methyl), 2.02-1.91 (1H, m, 8-H_A), 1.64-1.51 (1H, m, 3-H_A), 1.47 (1H, app. dd, J 14.5 and 2.8, 8-H_B), 1.30-1.16 (3H, m, 3-H_B and 4-H_2); δ_C (100 MHz, $CDCl_3$) 172.4 (propanamide C-1), 156.5 (Ar C_1), 145.8 (Ar C_1), 141.7 (Ar C_1), 136.7 (Ar C_1), 136.4 (Ar C_1), 135.6 (Ar C_1), 131.0 (Ar C_1), 130.4 (Ar C_1), 130.0 (Ar C_1), 127.3 (Ar C_1), 126.9 (Ar C_1), 125.9 (Ar C_1), 125.2 (Ar C_1), 124.0 (Ar C_1), 123.0 (Ar C_1), 74.7 (C-8a), 67.8 (C-5), 67.6 (C-2), 63.4 (C-7), 45.1 (methylpropanamide C-1), 36.3 (C-4a), 36.0 (propanamide C-2), 28.7 (C-4), 28.6 (C-8), 26.9 (propanamide C-3), 22.1 (C-3), 20.6 (methyl); HRMS found MH^+, 460.2599. $C_{28}H_{33}N_3O_3$ requires MH, 460.2600.

N- {[(4aR*,8aR*)- Octahydropyrano[4,3- b]pyran- 4a- yl]methyl}- 3- [2- amino- 6- (2- methylphenyl)quinolin- 3- yl]- 2- methylpropanamide

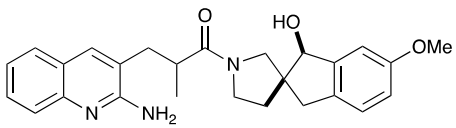


24

According to General Procedure J, the carbamate derivative **6e** (21.0 mg, 77.0 μmol) and the ester derivative **21** (32.8 mg, 81.0 μmol) gave an intermediate crude material that was eluted with 50:50 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM−EtOH–NH_4OH to yield the amine derivative **24** (14.0 mg, 37%, dr 50:50 by ^{1}H-NMR) as a colourless amorphous solid, R_f 0.28 (EtOAc); ν_{max}/cm^{-1} 3332, 2953, 2843, 1598, 1502, 1401, 1382, 1020, 1008; δ_H (400

MHz, $CDCl_3$) 7.67-7.13 (16H, m, Ar), 6.00 (1H, t, J 6.1, amide NH^{diastA}), 5.87 (1H, t, J 6.1, amide NH^{diastB}), 5.18 (4H, br. s, NH_2), 3.80-3.73 (2H, m, 2-H_A), 3.72 (1H, d, J 11.8, 5-H_A^{diastA}), 3.61 (1H, d, J 11.8, 5-H_A^{diasB}), 3.57-3.45 (4H, m, 7-H_2), 3.27 (1H, dd, J 13.8 and 7.3, N-methylpropanamide 1-H_A^{diastA}), 3.21-3.11 (4H, 8a-H^{diastA}, N-methylpropanamide 1-H_A^{diastB} and N-methylpropanamide 1-H_B), 3.10-3.01 (5H, m, 8a-H^{diastB}, 2-H_B and 5-H_B), 3.00-2.95 (2H, m, propanamide 3-H_A), 2.65-2.48 (4H, m, propanamide 2-H and propanamide 3-H_B), 2.22 (6H, s, methylphenyl), 2.09-1.95 (2H, m, 8-H_A), 1.89 (1H, dddd, J 14.5, 10.3, 6.7 and 3.3, 3-H_A^{diastA}), 1.68 (1H, dddd, J 14.5, 11.6, 6.7 and 3.3, 3-H_A^{diastB}), 1.55-1.40 (1H, m, 8-H_B^{diastA}), 1.41-1.33 (1H, m, 8-H_B^{diastB}), 1.33-0.90 (6H, m, 3-H_B and 4-H_2), 1.24 (6H, d, J 6.6, methylpropanamide); δ_C (100 MHz, $CDCl_3$) 176.0 (propanamide C-1^{diastA}), 175.7 (propanamide C-1^{diastB}), 156.8 (Ar C_1), 156.7 (Ar C_1), 145.8 (Ar C_1), 145.8 (Ar C_1), 141.6 (Ar C_2), 137.8 (Ar C_1), 137.7 (Ar C_1), 136.5 (Ar C_1), 135.6 (Ar C_1), 131.0 (Ar C_2), 131.0 (Ar C_2), 130.5 (Ar C_2), 130.0 (Ar C_2), 127.3 (Ar C_2), 126.9 (Ar C_2), 125.9 (Ar C_2), 125.1 (Ar C_2), 124.0 (Ar C_2), 122.3 (Ar C_1), 122.1 (Ar C_1), 74.8 (C-8a^{diastA}), 74.6 (C-8a^{diastB}), 68.0 (C_2-5), 67.6 (C_2-2), 63.3 (C-7^{diastA}), 63.2 (C-7^{diastB}), 45.2 (N-methylpropanamide C-1^{diastB}), 44.7 (N-methylpropanamide C-1^{diastA}), 42.8 (propanamide C-2^{diastB}), 42.2 (propanamide C-2^{diastA}), 36.1 (C_2-4a), 36.0 (propanamide C_2-3), 28.7 (C_2-4), 28.5 (C_2-8), 22.1 (C-3^{diastA}), 21.9 (C-3^{diastB}), 20.6 (methylpheniyl C_2), 19.0 (methylpropanamide C-1^{diasA}), 18.8 (methylpropanamide C-1^{diasB}); HRMS found MH^+, 474.2753. $C_{29}H_{35}N_3O_3$ requires MH, 474.2756.

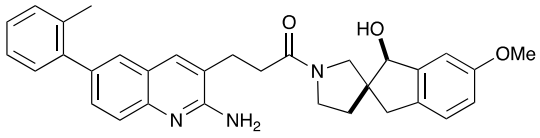
3- (2- Aminoquinolin- 3- yl)- 1- [(2R*,3R*)- 3- hydroxy- 5- methoxy- 1,3-dihydrospiro[indene- 2,3'- pyrrolidin]- 1'- yl]- 2- methylpropan- 1- one



25

According to General Procedure K, the acetate derivative **6d** (20.0 mg, 55.0 μmol) and the ester derivative **19** (18.3 mg, 57.0 μmol) gave an intermediate crude material that was eluted with 70:30 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM–EtOH–NH_4OH to yield the amine derivative **25** (5.90 mg, 29%, dr 50:50, rotamers minor:major by ^{1}H-NMR) as a colourless oil, R_f 0.32 and 0.40 (92.4:6.8:0.8 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3340, 3224, 2930, 1624, 1492, 1467, 1436; δ_H (600 MHz, $CDCl_3$) 7.81-6.57 (32H, m, Ar), 5.48 (2H, br. s, $NH^{diastA,minor}$), 5.36 (2H, br. s, $NH^{diastA,major}$), 5.29 (2H, br. s, $NH^{diastB,major}$), 5.23 (2H, br. s, $NH^{diastB,minor}$), 4.63 (2H, s, 3-H^{minor}), 4.55 (2H, s, 3-H^{major}), 3.79 (3H, s, methoxy^{diastA,major}), 3.78 (3H, s, methoxy^{diastA,minor}), 3.76 (3H, s, methoxy^{diastB,major}), 3.75 (3H, s, methoxy^{diastB,minor}), 3.75-3.47 (8H, m, 5'-H_2), 3.45-3.10 (8H, m, 2'-H_2), 3.10-2.90 (4H, m, propanone 3-H_A), 2.90-2.70 (8H, m, 1-H_A and propanone 3-H_B), 2.70-2.50 (8H, m, 1-H_B and propanone 2-H), 2.30-2.00 (4H, m, 4'-H_A), 1.90 (4H, m, 4'-H_B), 1.40-1.10 (12H, m, methyl); δ_C (150 MHz, $CDCl_3$) 175.1 (propanone C_2-1^{major}), 174.8 (propanone C_2-1^{minor}), 159.3 (Ar C_2), 159.0 (Ar C_2), 156.9 (Ar C_4), 146.7 (Ar C_2), 146.5 (Ar C_2), 145.6 (Ar C_2), 145.1 (Ar C_2), 138.0 (Ar C_2), 137.7 (Ar C_2), 132.9 (Ar C_2), 132.2 (Ar C_2), 129.7 (Ar C_2), 129.3 (Ar C_2), 127.1 (Ar C_4), 125.5 (Ar C_4), 124.4 (Ar C_4), 123.0 (Ar C_2), 122.8 (Ar C_2), 122.4 (Ar C_4), 115.1 (Ar C_4), 110.4 (Ar C_4), 109.8 (Ar C_4), 80.0 (C_2-3), 79.1 (C_2-3), 56.6 (C_4-2'), 55.6 (methoxy C_4), 53.8 (C_2-2), 51.8 (C_2-2), 46.3 (C-5'), 45.9 (C-5'), 45.3 (C_2-5'), 40.3 (C-1), 39.9 (C-1), 39.5 (C-1), 38.8 (C-1), 38.5 (C-4'), 36.5 (C-4'), 35.9 (C-4'), 34.2 (C-4'), 30.9 (propanone C_2-2), 30.0 (propanone C_2-2), 29.8 (propanone C_2-3), 29.0 (propanone C_2-3), 18.4 (methyl C_2), 18.3 (methyl C_2); HRMS found MH^+, 432.2277. $C_{26}H_{29}N_3O_3$ requires MH, 432.2287.

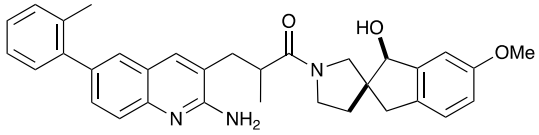
3- [2- Amino- 6- (2- methylphenyl)quinolin- 3- yl]- 1- [(2R*,3R*)- 3- hydroxy- 5- methoxy- 1,3- dihydrospiro[indene- 2,3'- pyrrolidin]- 1'- yl]propan- 1- one



26

According to General Procedure K, the acetate derivative **6d** (20.0 mg, 55.0 μmol) and the ester derivative **20** (22.5 mg, 57.0 μmol) gave an intermediate crude material that was eluted with 60:40 EtOAc–hexane→100:0 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 95.4:4.1:0.5 DCM−EtOH–NH_4OH to yield the amine derivative **26** (1.90 mg, 7%, rotamers 53:47 by ^{1}H-NMR) as a colourless oil, R_f 0.28 (92.4:6.8:0.8 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3311, 3189, 2954, 2911, 2851,1620, 1515, 1486, 1416; δ_H (600 MHz, $CDCl_3$) 7.80-6.77 (22H, m, Ar), 6.00 (4H, br. s, NH_2), 4.68 (1H, s, 3-H^{major}), 4.60 (1H, s, 3-H^{minor}), 3.79 (3H, s, methoxy^{major}), 3.78 (3H, s, methoxy^{minor}), 3.75-3.63 (2H, m, 5'-H_A), 3.61-3.43 (2H, m, 5'-H_B), 3.40-3.31 (2H, m, 2'-H_A), 3.25-3.19 (2H, m, 2'-H_B), 3.10-3.02 (4H, m, propanone 3-H_2), 2.98-2.86 (2H, m, 1-H_A), 2.74-2.66 (4H, m, propanone 2-H_2), 2.66-2.59 (2H, m, 1-H_B), 2.29 (3H, s, methyl^{major}), 2.27 (3H, s, methyl^{minor}), 1.62-1.54 (4H, m, 4'-H_2); δ_C (150 MHz, $CDCl_3$) 178.5 (propanone C_2-1), 159.7 (Ar C_2), 158.8 (Ar C_2), 146.1 (Ar C_2), 144.7 (Ar C_2), 141.9 (Ar C_2), 135.7 (Ar C_2), 135.6 (Ar C_2), 134.1 (Ar C_2), 133.1 (Ar C_2), 130.5 (Ar C_2), 130.4 (Ar C_2), 130.1 (Ar C_2), 127.4 (Ar C_2), 127.0 (Ar C_2), 126.5 (Ar C_2) 125.9 (Ar C_2), 125.8 (Ar C_2), 123.0 (Ar C_2), 115.5 (Ar C_2), 115.4 (Ar C_2), 109.7 (Ar C_2). 79.6 (C-3^{major}), 78.8 (C-3^{minor}), 55.6 (C_2-2' and methoxy C_2), 53.9 (C_2-2), 45.6 (C-5'^{minor}), 45.4 (C-5'^{major}), 40.7 (C-1^{minor}), 40.0 (C-1^{major}), 36.0 (C_2-4'), 34.5 (propanone C-2^{minor}), 34.3 (propanone C-2^{major}), 29.8 (propanone C_2-3), 22.8 (methyl^{minor}), 20.7 (methyl^{major}); HRMS found MH^+, 508.2595. $C_{32}H_{33}N_3O_3$ requires MH, 508.2600.

3- [2- Amino- 6- (2- methylphenyl)quinolin- 3- yl]- 1- [(2R*,3R*)- 3- hydroxy- 5- methoxy- 1,3- dihydrospiro[indene- 2,3'- pyrrolidin]- 1'- yl]- 2- methyl propan- 1- one

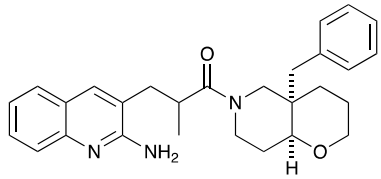


27

According to General Procedure K, the acetate derivative **6d** (24.0 mg, 66.0 μmol) and the ester derivative **21** (28.2 mg, 69.0 μmol) gave an intermediate crude material that was eluted with 70:30 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM−EtOH–NH_4OH to yield the amine derivative **27** (5.50 mg, 16%, dr 50:50, rotamers minor:major by ^{1}H-NMR) as a white amorphous solid, R_f 0.56 (92.4:6.8:0.8 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3380, 3214, 2933, 2875, 1620, 1489, 1444, 1415; δ_H (600 MHz, $CDCl_3$) 7.80-6.64 (44H, m, Ar), 5.47-5.18 (8H, m NH_2), 4.76 (1H, s, 3-$H^{diastA,minor}$), 4.73 (1H, s, 3-$H^{diastA,major}$), 4.65 (1H, s, 3-$H^{diastB,major}$), 4.61 (1H, s, 3-$H^{diastB,minor}$), 3.76-3.72 (12H, m, methoxy), 3.69-3.44 (8H, m, 5'-H_2), 3.32-3.18 (8H, m, 2'-H_2), 3.17-3.00 (4H, m, propanone 3-H_A), 3.00-2.80 (4H, m, 1-H_A), 2.80-2.40 (12H, m, 1-H_B, propanone 3-H_B and propanone 2-H), 2.30 (6H, s, methylphenyl^{diastA}), 2.29 (6H, s, methylphenyl^{diastB}), 1.75-1.58 (8H, m, 4'-H), 1.36-1.24 (12H, m, methylpropanone); δ_C (150 MHz, $CDCl_3$) 174.9 (propanone C_4-1), 159.3 (Ar C_4), 157.1 (Ar C_4), 145.8 (Ar C_4), 144.4 (Ar C_4), 141.7 (Ar C_4), 137.9 (Ar C_4), 137.7 (Ar C_4), 135.6 (Ar C_4), 132.7 (Ar C_4), 131.1 (Ar C_4), 130.5 (Ar C_4), 130.1 (Ar C_4), 127.4 (Ar C_4), 127.1 (Ar C_4), 126.0 (Ar C_4), 125.6 (Ar C_4), 125.2 (Ar C_4), 122.9 (Ar C_4), 115.2 (Ar C_4), 115.0 (Ar C_4), 109.7 (Ar C_4), 80.0 (C_2-$3^{diastA/minor}$), 79.2 (C_2-$3^{diastB/major}$), 56.7 (C_2-$2'^{diastB/major}$), 56.6 (C_2-$2'^{diastA/minor}$), 55.5 (methoxy C_4), 53.9 (C-$2^{diastA,minor}$), 53.6 (C-$2^{diastB,minor}$), 53.5 (C-$2^{diastA,major}$), 53.0 (C-$2^{diastB,major}$), 50.2 (C-$5'^{diastA,major}$), 46.4 (C-$5'^{diastA,minor}$), 45.4 (C-$5'^{diastB,major}$), 45.3 (C-$5'^{diastB,minor}$), 40.3 (C-$1^{diastA,major}$), 39.9 (C-$1^{diastA,minor}$), 38.9 (C-$1^{diastB,major}$), 38.6 (C-$1^{diastB,minor}$), 37.0 (C-$4'^{diastA,major}$), 36.3 (C-

4'^{diastA,minor}), 35.9 (C-4'^{diastB,major}), 35.6 (C-4'^{diastB,minor}), 34.2 (propanone C_2-2$^{diastB/major}$), 34.1 (propanone C_2-2$^{diastA/minor}$), 31.0 (propanone C-3^{diastA,major}), 30.6 (propanone C-3^{diastA,minor}), 29.8 (propanone C-3^{diastB,major}), 29.1 (propanone C-3^{diastB,minor}), 20.7 (phenylmethyl C_4), 18.8 (methylpropanone^{diastA,major}), 18.7 (methylpropanone^{diastA,minor}), 18.4 (methylpropanone^{diastB,minor}), 18.3 (methylpropanone^{diastB,major}); HRMS found MH^+, 522.2749. $C_{33}H_{35}N_3O_3$ requires MH, 522.2756.

1- [(4aR*,8aR*)- 4a- Benzyl- octahydro- 2H- pyrano[3,2- c]pyridin- 6- yl]- 3- (2- aminoquinolin- 3- yl)- 2- methylpropan- 1- one

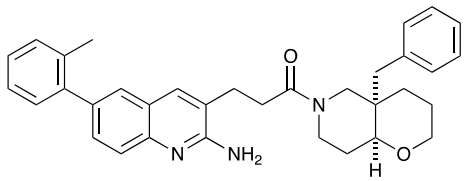


28

According to General Procedure L, the carbamate derivative **6i** (20.0 mg, 54.0 μmol) and the ester derivative **19** (18.0 mg, 57.0 μmol) gave an intermediate crude material that was eluted with 20:80 EtOAc–hexane→100:0 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM−EtOH–NH_4OH to yield the amine derivative **28** (4.90 mg, 18%, dr 50:50, rotamers minor:major by ^{1}H-NMR) as a colourless oil, R_f 0.56 (50:50 EtOAc); ν_{max}/cm^{-1} 3391, 2984, 2842, 1627,1427, 1077; δ_H (600 MHz, $CDCl_3$) 7.77-6.60 (40H, m, Ar), 5.36 (4H, br. s, NH_2^{diastA}), 5.18 (4H, br. s, NH_2^{diastB}), 4.34 (1H, app. d, J 11.3, 7-$H_A^{minor,diastA}$), 4.14 (2H, d, J 13.2, 5-H_A^{major}), 4.02-3.90 (2H, m, 2-H_A^{diastA}), 3.89-3.81 (2H, m, 2-H_A^{diastB}), 3.76-3.65 (1H, m, 7-$H_A^{major,diastA}$), 3.62 (2H, d, J 13.2, 5-H_A^{minor}), 3.56 (2H, app. d J 13.2, 7-H_A^{diastB}), 3.43-2.95 (20H, m, 5-H_B, 2-H_B, 8a-H, 7-H_B and propananone 2-H), 2.71-2.63 (8H, m, propananone 3-H_2), 2.46 (2H, d, J 13.4, methylphenyl 1-H_A^{minor}), 2.36 (2H, d, J 13.4, methylphenyl 1-H_A^{major}), 2.23 (2H, d, J 13.4, methylphenyl 1-H_B^{minor}), 2.08 (2H, d, J 13.4, methylphenyl 1-H_B^{major}), 2.00-1.85 (4H, m, 8-H_A), 1.70-1.57 (8H, m, 8-H_B and 3-H_A), 1.55-1.19 (8H, m, 3-H_B and 4-H_A), 1.36 (3H, s, methyl^{diastA,minor}), 1.35 (3H, s,

methyl^{diastB,minor}), 1.33, (3H, s, methyl^{diastA,major}), 1.32 (3H, s, methyl^{diastB,major}), 1.08-0.95 (4H, m, 4-H_B); δ_C (150 MHz, $CDCl_3$) 175.0 (propanone C_2-1^{diastA}), 174.8 (propanone C_2-1^{diastB}), 157.0 (Ar C_2), 156.6 (Ar C_2), 146.9 (Ar C_4) 137.8 (Ar C_4), 136.9 (Ar C_2), 136.8 (Ar C_2), 130.9 (Ar C_2), 130.7 (Ar C_2), 130.4 (Ar C_4), 129.3 (Ar C_2), 129.1 (Ar C_2), 128.1 (Ar C_4), 127.9 (Ar C_4), 127.0 (Ar C_2), 126.9 (Ar C_2), 126.4 (Ar C_2), 126.1 (Ar C_4), 125.5 (Ar C_4), 124.3 (Ar C_4), 122.7 (Ar C_4), 122.3 (Ar C_2), 74.9 (C_4-8a), 67.9 (C_2-2^{major}), 67.1 (C_2-2^{minor}), 43.9 (C_2-5^{minor}), 41.3 (C_2-5^{major}), 41.0 (phenylmethyl C_4-1), 40.7 (C_2-7^{major}), 37.1 (C_2-7^{minor}), 36.8 (C_2-4a^{diastA}), 36.3 (C_2-4a^{diastB}), 36.2 (propanona C_2-2^{diastA}), 35.7 (propanone C_2-2^{diastB}), 30.6 (C_2-4^{diastA}), 29.8 (C_2-4^{diastB}), 28.1 (C_2-8^{diastA}), 28.0 (C_2-8^{diastB}), 22.3 (propanone C_4-3), 22.1 (C_4-3), 19.7 (methyl C_2-1^{diasA}), 19.2 (methyl C_2-1^{diastB}); HRMS found MH^+, 444.2642. $C_{28}H_{33}N_3O_2$ requires MH, 444.2651.

1- [(4aR*,8aR*)- 4a- Benzyl- octahydro- 2H- pyrano[3,2- c]pyridin- 6- yl]- 3- [2- amino- 6- (2- methylphenyl)quinolin- 3- yl]propan- 1- one

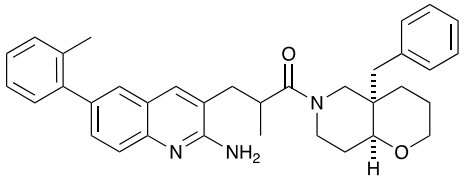


29

According to General Procedure L, the carbamate derivative **6i** (20.0 mg, 54.0 μmol) and the ester derivative **20** (22.5 mg, 57.0 μmol) gave an intermediate crude material that was eluted with 30:70 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 50:50 92.4:6.8:0.8 DCM−EtOH–NH_4OH to yield the amine derivative **29** (8.50 mg, 39%, rotamers 69:31 by ^{1}H-NMR) as a colourless oil, R_f 0.30 (92.4:6.8:0.8 DCM−EtOH–NH_4OH); ν_{max}/cm^{-1} 3336, 3193, 3060, 3026, 2933, 2853, 1629, 1452, 1416, 1094; δ_H (400 MHz, $CDCl_3$) 7.77-7.00 (26H, m, Ar), 5.43 (4H, br. s, NH_2), 4.39 (1H, app. d, J 13.1, 7-H_A^{minor}), 4.18 (1H, d, J 13.2, 5-H_A^{major}), 4.03-3.83 (2H, m, 2-H_A), 3.72-3.61 (1H, m, 7-H_A^{major}), 3.55 (1H, d, J 13.2, 5-H_A^{minor}), 3.45-3.19 (5H, m, 2-H_B, 7-H_B^{major} and 8a-H), 3.18-2.96 (7H, m, 5-H_B,

7-H_B^{minor} and propanone 3-H_2), 2.94-2.71 (5H, m, phenylmethyl 1-H_A^{minor} and propanone 2-H_2), 2.64 (1H, d, J 13.5, phenylmethyl 1-H_A^{major}), 2.47 (1H, d, J 13.5, phenylmethyl 1-H_B^{minor}), 2.32-2.22 (1H, m, phenylmethyl 1-H_B^{major}), 2.29 (6H, s, methyl^{minor}), 2.28 (6H, s, methyl^{major}), 2,17-2.05 (1H, m, 8-H_A^{minor}), 2.01-1.83 (1H, m, 8-H_A^{major}), 1.80-1.55 (4H, m, 3-H_A and 8-H_B), 1.50-1.30 (4H, m, 3-H_B and 4-H_A), 1.17-1.07 (2H, m, 4-H_B); δ_C (100 MHz, $CDCl_3$) 171.8 (propanone C-1^{minor}), 171.2 (propanone C-1^{major}), 156.7 (Ar C_2), 146.2 (Ar C_1), 145.7 (Ar C_1), 141.8 (Ar C_2), 136.7 (Ar C_1), 136.6 (Ar C_1), 136.5 (Ar C_1), 136.3 (Ar C_1), 135.6 (Ar C_1), 130.9 (Ar C_2), 130.7 (Ar C_1), 130.4 (Ar C_2), 130.1 (Ar C_2), 128.3 (Ar C_1), 128.1 (Ar C_2), 127.9 (Ar C_1), 127.8 (Ar C_1), 127.8 (Ar C_1), 127.8 (Ar C_2), 127.3 (Ar C_2), 126.9 (Ar C_2), 126.9 (Ar C_1), 126.8 (Ar C_1), 126.4 (Ar C_2), 126.2 (Ar C_1), 126.0 (Ar C_1), 126.0 (Ar C_1), 125.9 (Ar C_2), 125.1 (Ar C_2), 124.0 (Ar C_1), 123.8 (Ar C_1), 75.4 (C_2-8a), 67.9 (C_2-2), 48.7 (C-5^{minor}), 43.5 (C-5^{minor}), 41.4 (methylenephenyl C_2-1), 40.9 (C-7^{major}), 37.5 (C-7^{minor}), 36.6 (C_2-4a), 32.7 (propanone C_2-2), 30.7 (C_2-4), 28.0 (C_2-8), 26.7 (propanone C_2-3), 22.3 (C_2-3), 20.7 (methylphenyl C_2-1); HRMS found MH^+, 520.2959. $C_{34}H_{37}N_3O_2$ requires MH, 520.2964.

1- [(4aR*,8aR*)- 4a- Benzyl- octahydro- 2H- pyrano[3,2- c]pyridin- 6- yl]- 3- [2- amino- 6- (2- methylphenyl)quinolin- 3- yl]- 2- methylpropan- 1- one

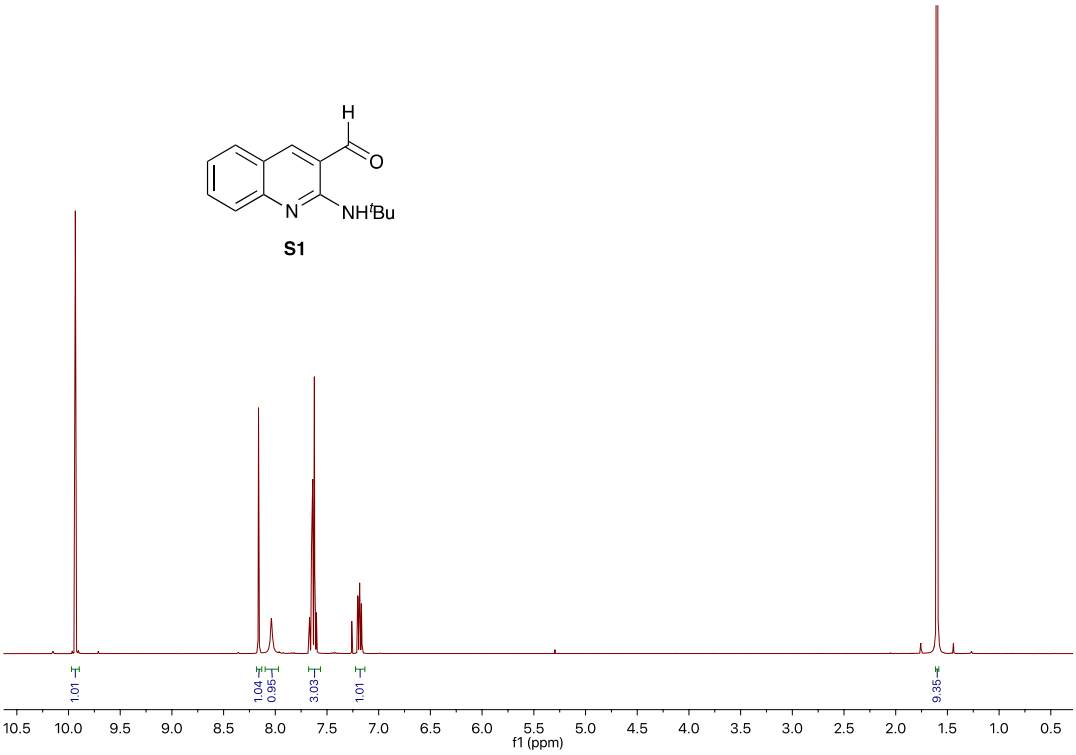


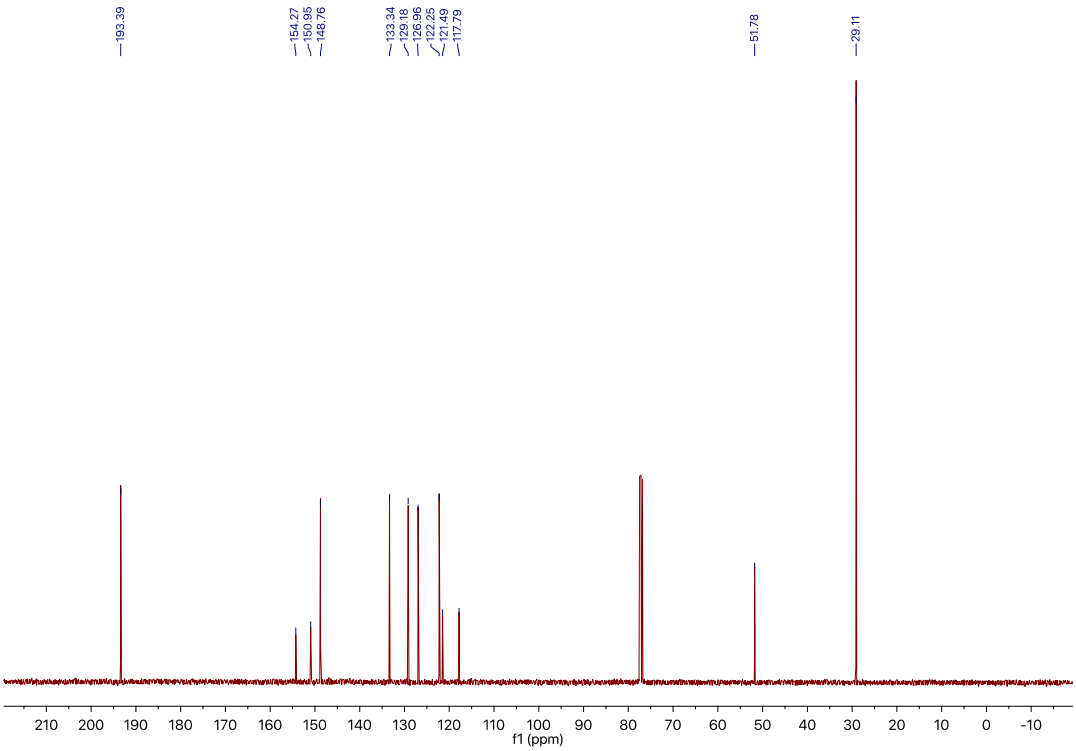
30

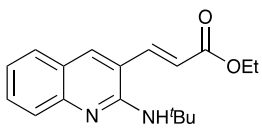
According to General Procedure L, the carbamate derivative **6i** (20.0 mg, 54.0 μmol) and the ester derivative **21** (23.2 mg, 57.0 μmol) gave an intermediate crude material that was eluted with 0:100 EtOAc–hexane→100:0 EtOAc–hexane. The final crude material was purified by flash column chromatography eluting with 92.4:6.8:0.8 DCM−EtOH–NH_4OH to yield the

amine derivative **30** (4.20 mg, 15%, dr 50:50, rotamers minor:major by ^{1}H-NMR) as a colourless oil, R_f 0.56 (50:50 EtOAc); ν_{max}/cm^{-1} 3254, 2981, 2846, 1617, 1427, 1413, 1075; δ_H (600 MHz, $CDCl_3$) 7.80-6.62 (52H, m, Ar), 5.46 (4H, br. s, NH_2^{diastA}), 5.22 (4H, br. s, NH_2^{diastB}), 4.40 (1H, app. d, J 12.7, 7-$H_A^{minor,diastA}$), 4.15 (2H, d, J 12.8, 5-H_A^{major}), 4.03-3.92 (2H, m, 2-H_A^{diastA}), 3.90-3.82 (2H, m, 2-H_A^{diastB}), 3.77-3.69 (1H, m, 7-$H_A^{major,diastA}$), 3.65 (2H, d, J 13.2, 5-H_A^{minor}), 3.58 (2H, app. d, J 12.4, 7-H_A^{diastB}), 3.46-3.02 (20H, m, 5-H_B, 2-H_B, 8a-H, 7-H_B and propanone 2-H), 2.75-2.64 (8H, m, propanone 3-H_2), 2.37 (4H, d, J 13.6, methylenephenyl 1-H_A), 2.30 (3H, s, methylphenyl 1-$H_3^{diastA,major}$), 2.22 (3H, s, methylphenyl 1-$H_3^{diastA,minor}$), 2.20 (3H, s, methylphenyl 1-$H_3^{diastB,major}$), 2.17 (3H, s, methylphenyl 1-$H_3^{diastB,minor}$), 2.13 (4H, d, J 13.6, methylenephenyl 1-H_B), 2.08-1.88 (4H, m, 8-H_A), 1.77-1.60 (8H, m, 8-H_B and 3-H_A), 1.55-1.20 (8H, m, 3-H_B and 4-H_A), 1.37 (3H, s, methylpropanone 1-$H_3^{diastA,minor}$), 1.36 (3H, s, methylpropanone 1-$H_3^{diastB,minor}$), 1.34 (3H, s, methylpropanone 1-$H_3^{diastA,major}$), 1.33 (3H, s, methylpropanone 1-$H_3^{diastB,major}$), 1.05-0.95 (4H, m, 4-H_B); δ_C (150 MHz, $CDCl_3$) 174.9 (propanone C_2-1^{minor}), 174.6 (propanone C_2-1^{major}), 156.6 (Ar C_4), 148.1 (Ar C_2), 147.5 (Ar C_2), 141.7 (Ar C_2), 141.5 (Ar C_2), 137.8 (Ar C_4), 135.6 (Ar C_2), 135.4 (Ar C_2), 130.8 (Ar C_2), 130.6 (Ar C_4), 130.4 (Ar C_4), 130.3 (Ar C_4), 130.1 (Ar C_4), 128.1 (Ar C_4), 127.9 (Ar C_2), 127.8 (Ar C_4), 127.3 (Ar C_2), 127.1 (Ar C_4), 126.9 (Ar C_8), 126.4 (Ar C_2), 126.1 (Ar C_2), 125.8 (Ar C_2), 125.7 (Ar C_4), 125.0 (Ar C_4), 123.9 (Ar C_2), 123.1 (Ar C_2), 122.5 (Ar C_2), 74.8 (C_4-8a), 67.8 (C_4-2), 43.7 (C_2-5^{minor}), 41.2 (C_2-5^{major}), 40.9 (methylenephenyl C_4-1), 40.7 (C_2-7^{major}), 37.1 (C_2-7^{minor}), 36.8 (C_2-4a^{diastA}), 36.2 (C_2-4a^{diastB}), 36.0 (propanona C_2-2^{diastA}), 35.6 (propanona C_2-2^{diastB}), 31.9 (C_1-4$^{diastA.minor}$), 30.6 (C_1-4^{diastA,major}), 29.7 (C_2-4^{diastB}), 28.1 (C_2-8^{diastA}), 27.2 (C_2-8^{diastB}), 25.6 (propanone C_2-3^{diastB}), 22.2 (propanone C_2-3^{diastA}), 22.0 (C_2-3^{diastA}), 20.6 (C_2-3^{diastB}), 19.7 (methylphenyl C_2-1^{diasA}), 19.1 (methylphenyl C_2-1^{diasB}), 14.1 (methylpropanona C_2-1^{diasA}), 13.4 (methylpropanona C_2-1^{dias}); HRMS found MH$^+$, 534.3113. $C_{35}H_{39}N_3O_2$ requires MH, 534.3120.

1.4. ^{1}H and ^{13}C NMR spectra



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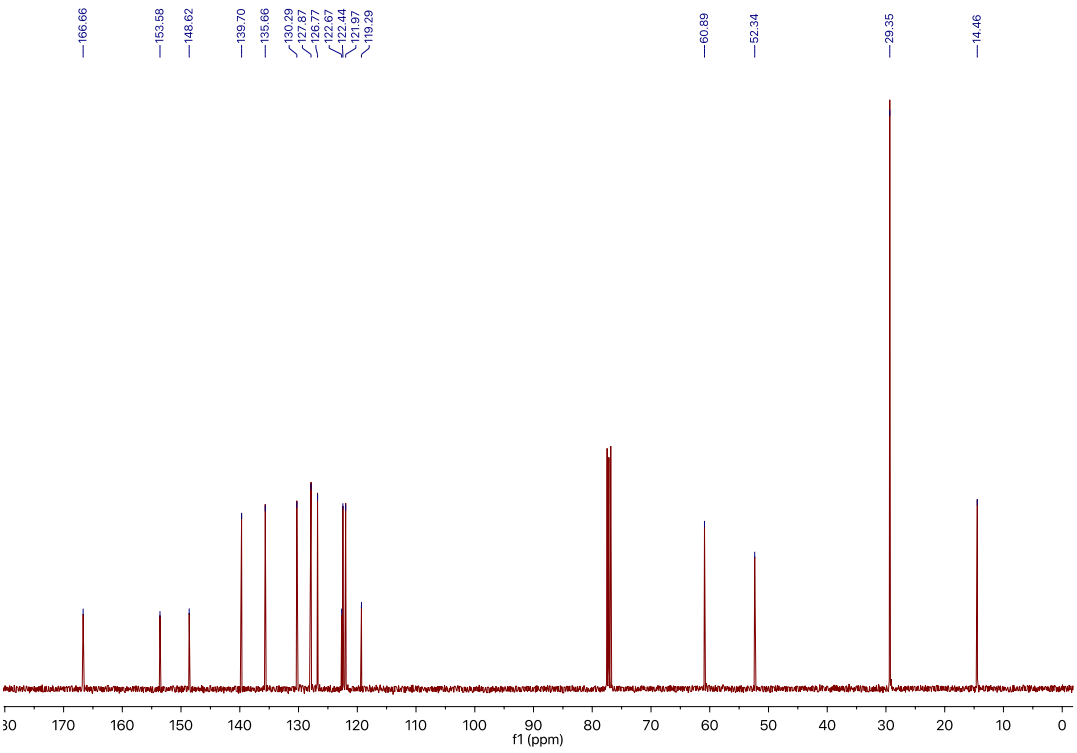
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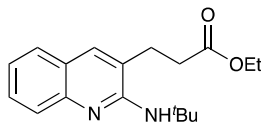
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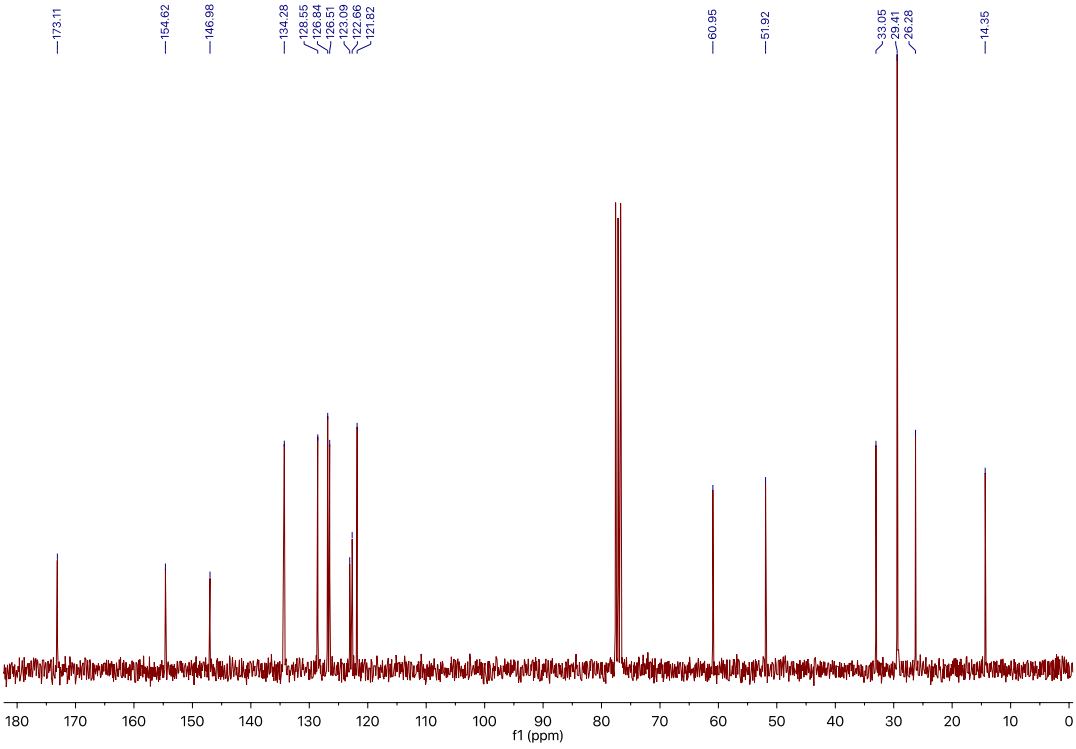
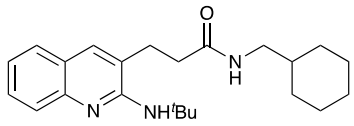
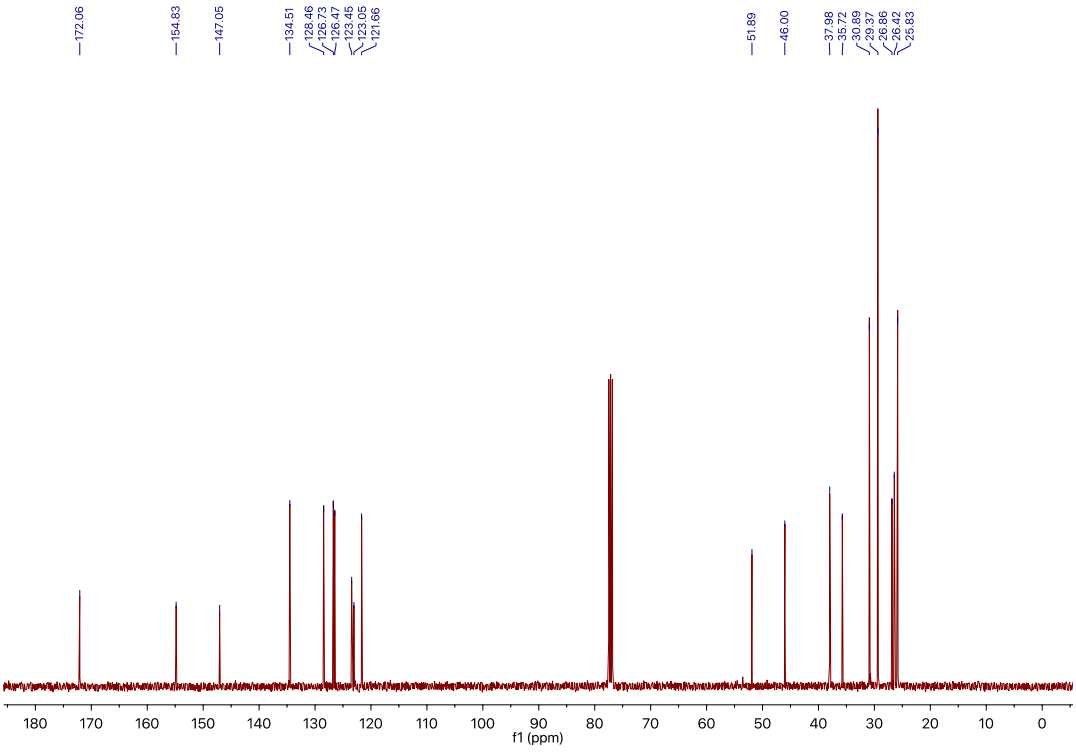
9.04
3.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

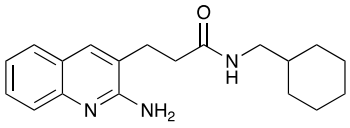

173.11
154.62
146.98
134.28
128.55
126.84
126.51
123.09
122.66
121.82
60.95
51.92
33.05
29.41
26.28
14.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
H
N
NH^{t}Bu

S3

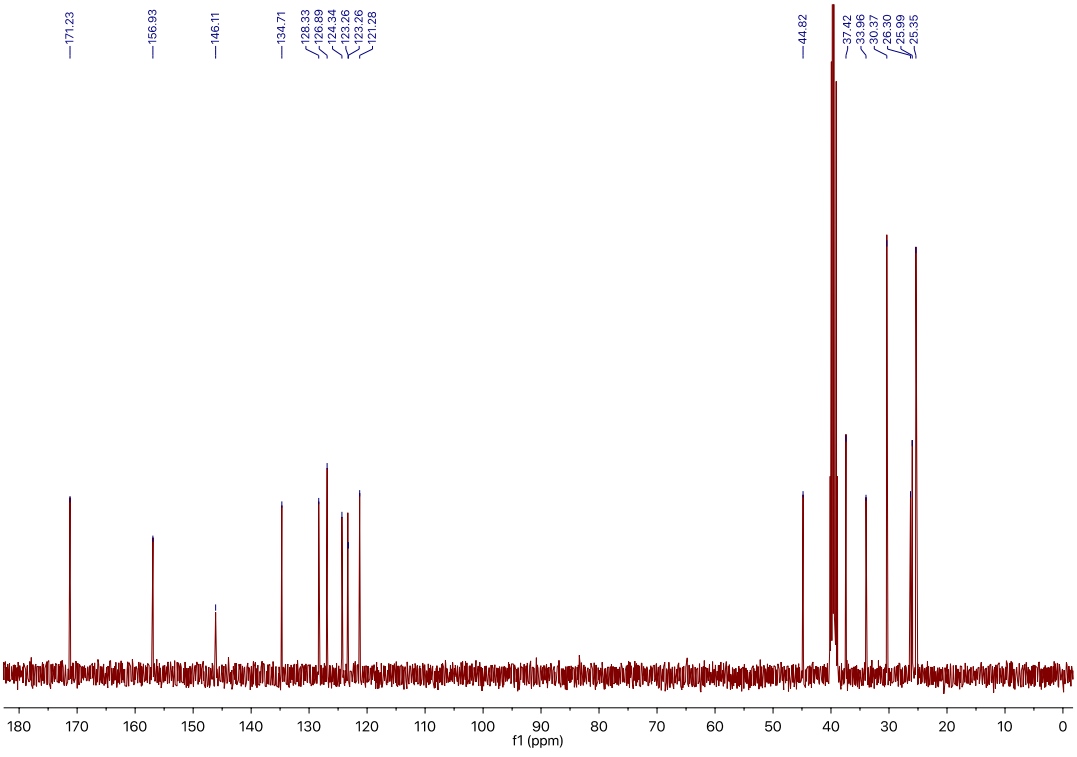
1.00
3.03
1.00
0.99
0.97
2.01
2.04
2.00
14.05
1.01
3.07
2.04
f1 (ppm)

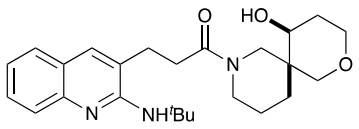

172.06
154.83
147.05
134.51
128.46
126.73
126.47
123.45
123.05
121.66
51.89
46.00
37.98
35.72
30.89
29.37
26.86
26.42
25.83
f1 (ppm)


O
N
H
N
NH2

2

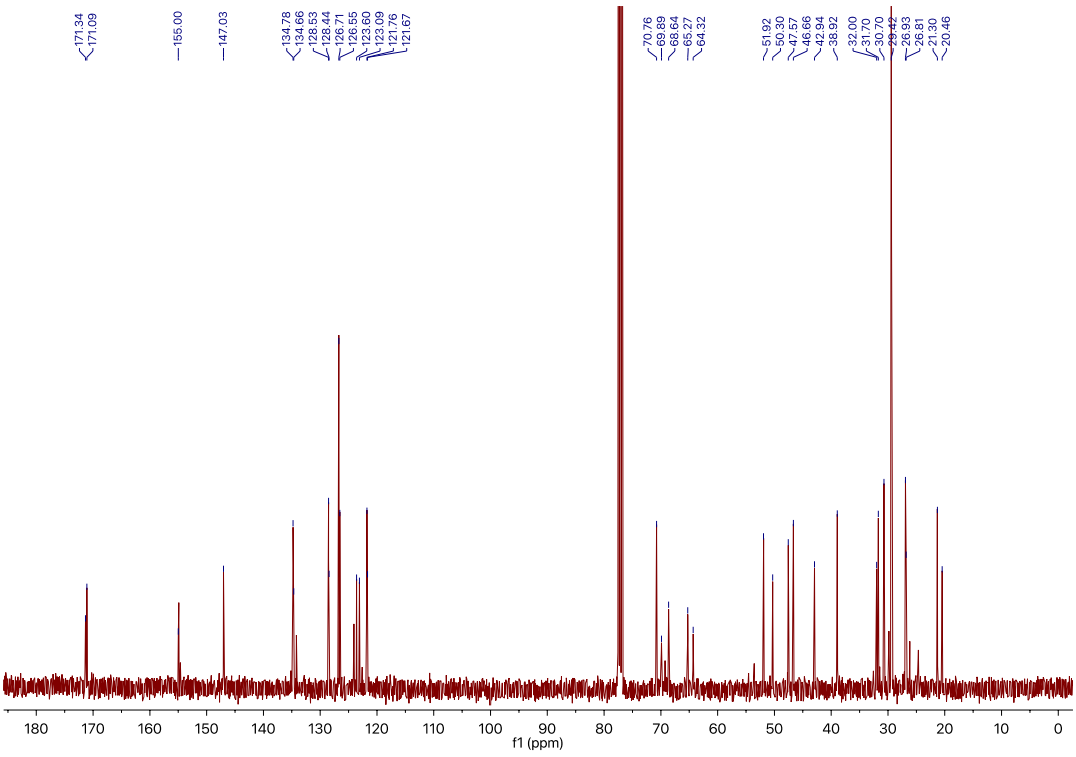
1.00
1.05
1.05
2.08
1.06
2.07
2.09
2.06
2.06
5.07
1.10
3.06
2.06
f1 (ppm)

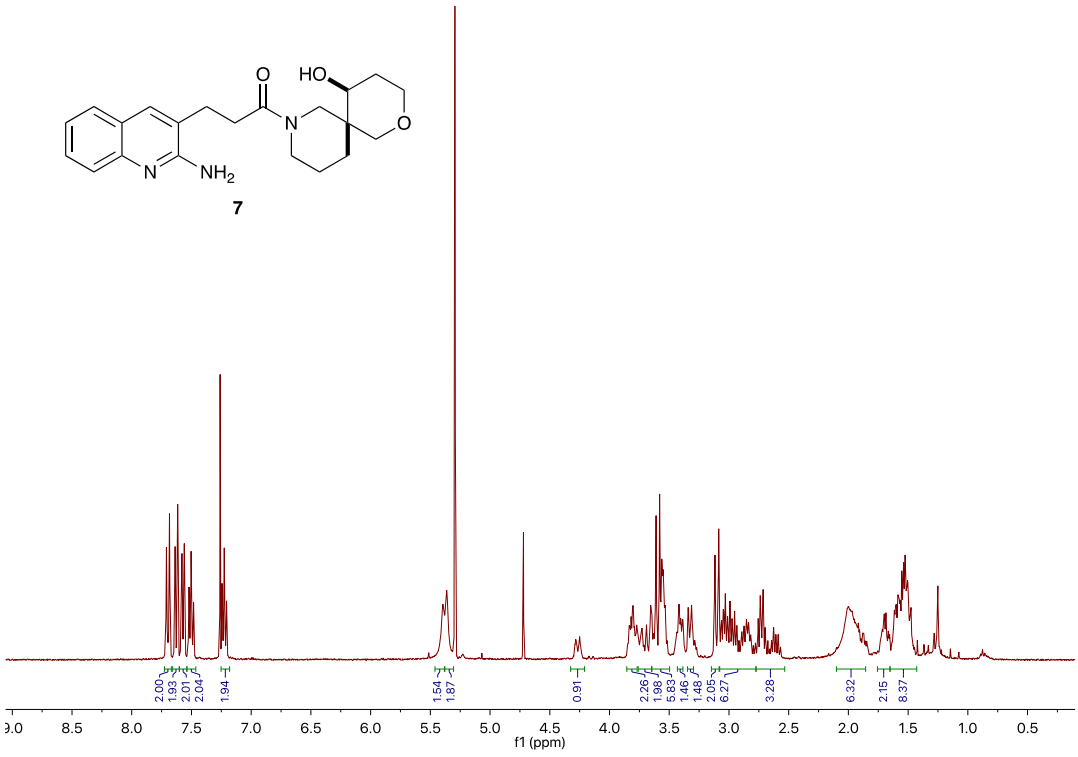

171.23
156.93
146.11
134.71
128.33
126.89
124.34
123.26
123.26
121.28
44.82
37.42
33.96
30.37
26.30
25.99
25.35
f1 (ppm)


O
HO
N
O
N
NH^{t}Bu

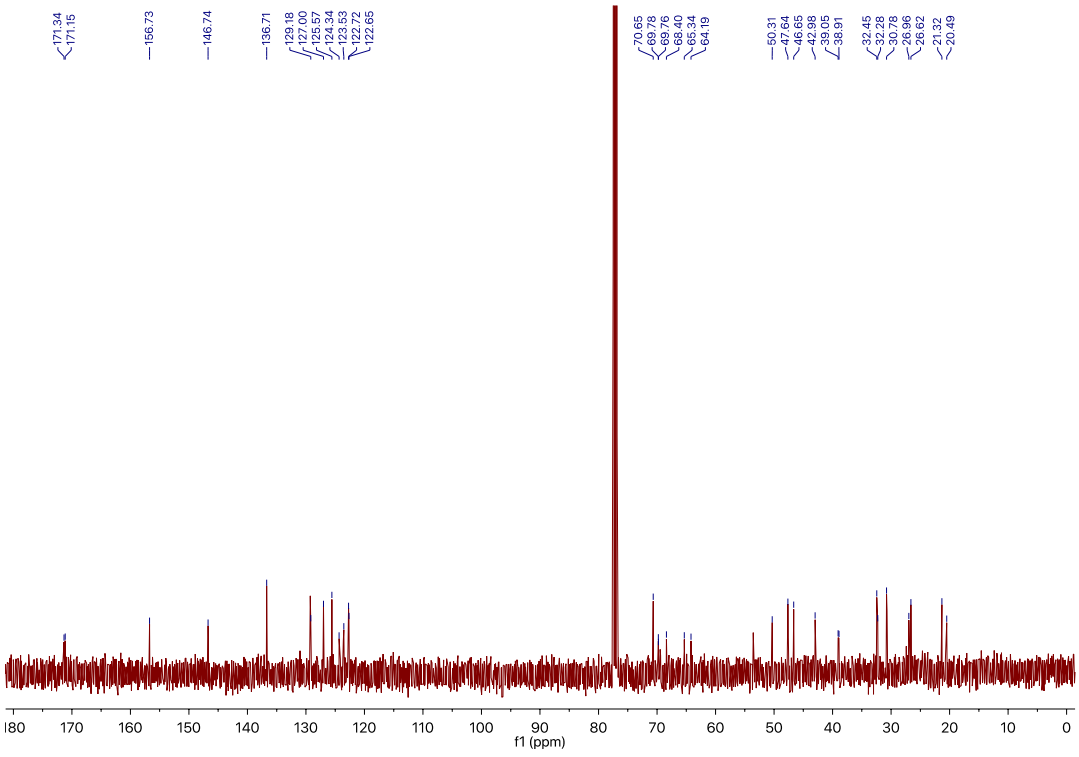
S4

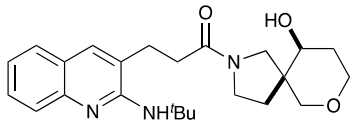
2.00
2.02
2.04
2.06
2.06
1.80
0.82
2.20
6.25
2.61
0.83
0.95
5.16
4.59
1.63
1.04
2.25
24.68
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


171.34
171.09
155.00
147.03
134.78
134.66
128.53
128.44
126.71
126.55
123.60
123.09
121.76
121.67
70.76
69.89
68.64
65.27
64.32
51.92
50.30
47.57
46.66
42.94
38.92
32.00
31.70
30.70
30.42
26.93
26.81
21.30
20.46
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
HO
N
O
N
NH2
2.00
1.93
2.01
2.04
1.94
1.54
1.87
0.91
2.26
1.98
5.83
1.48
2.05
6.27
3.28
6.32
2.15
8.37
f1 (ppm)

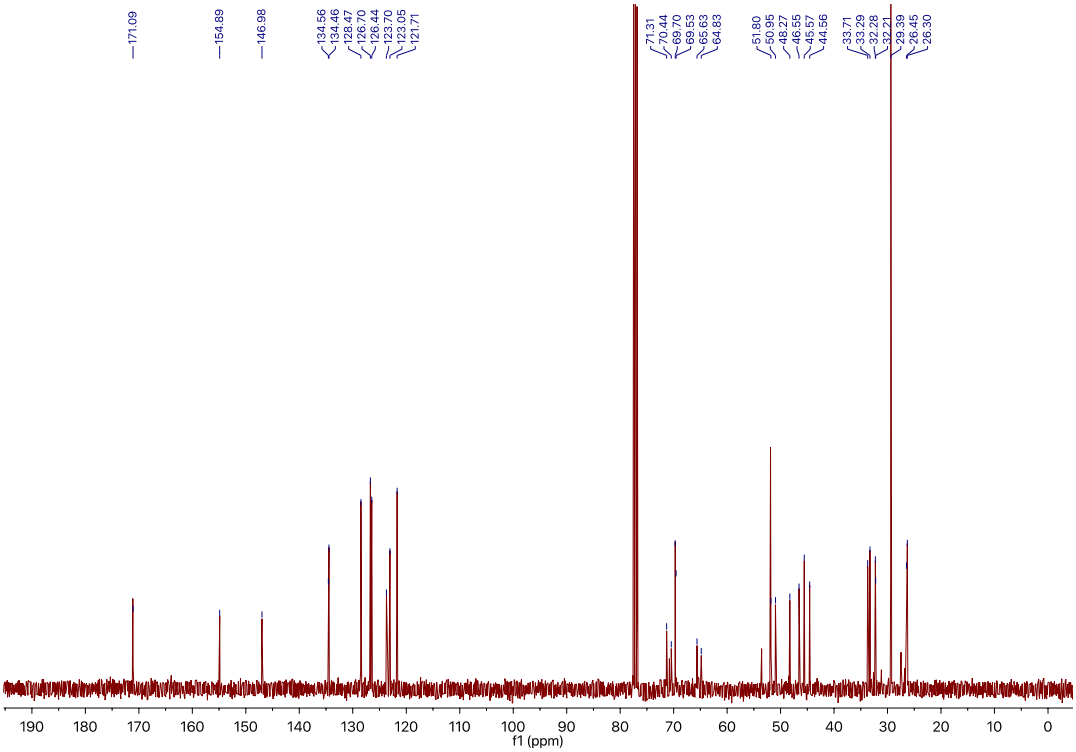
7

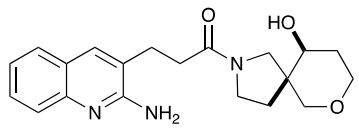

171.34
171.15
156.73
146.74
136.71
129.18
127.00
125.57
124.34
123.53
122.72
122.65
70.65
69.78
69.76
68.40
65.34
64.19
50.31
47.64
46.65
42.98
39.05
38.91
32.45
32.28
30.78
26.96
26.62
21.32
20.49
f1 (ppm)


O
HO
N
N
NH^{t}Bu
O

S5

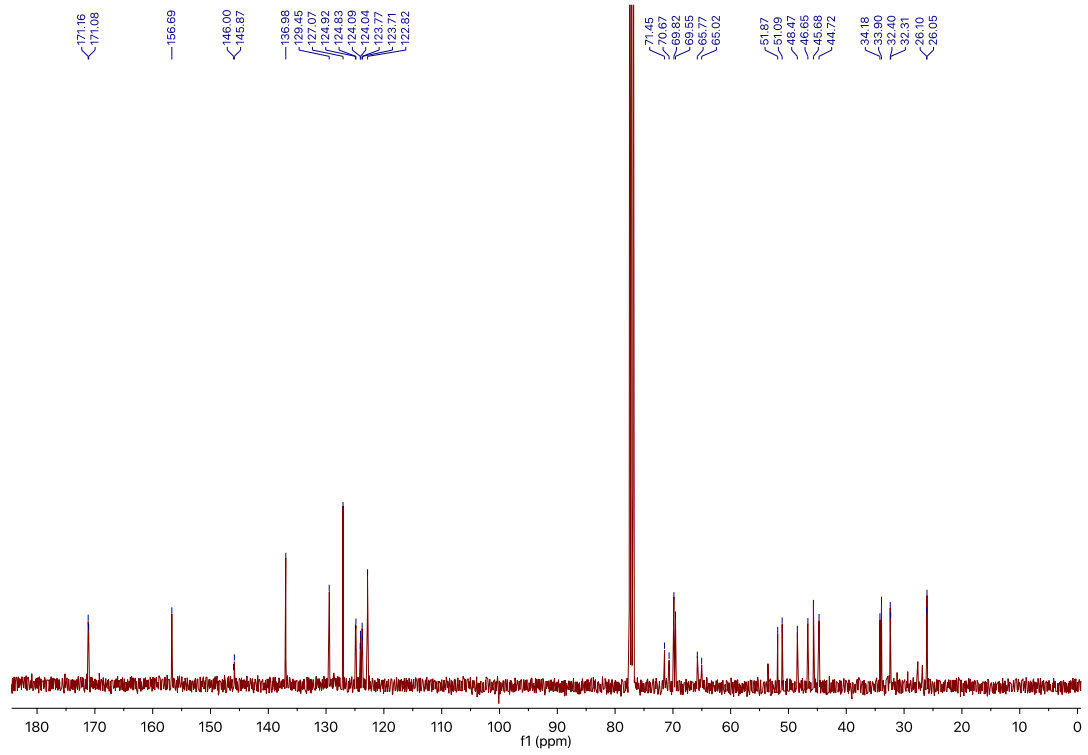
2.00
6.09
2.03
1.86
2.05
4.41
5.79
3.56
1.92
4.01
4.01
1.43
2.14
2.12
20.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

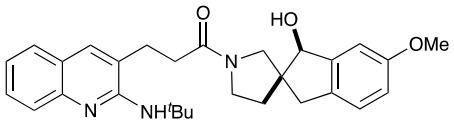

171.09
154.89
146.98
134.56
134.46
128.47
128.20
126.44
123.70
123.05
121.71
71.31
70.44
69.70
69.53
65.63
64.83
51.80
50.95
48.27
46.55
45.57
44.56
33.71
33.29
32.28
32.21
29.39
26.45
26.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
HO
N
N
NH2
O

8

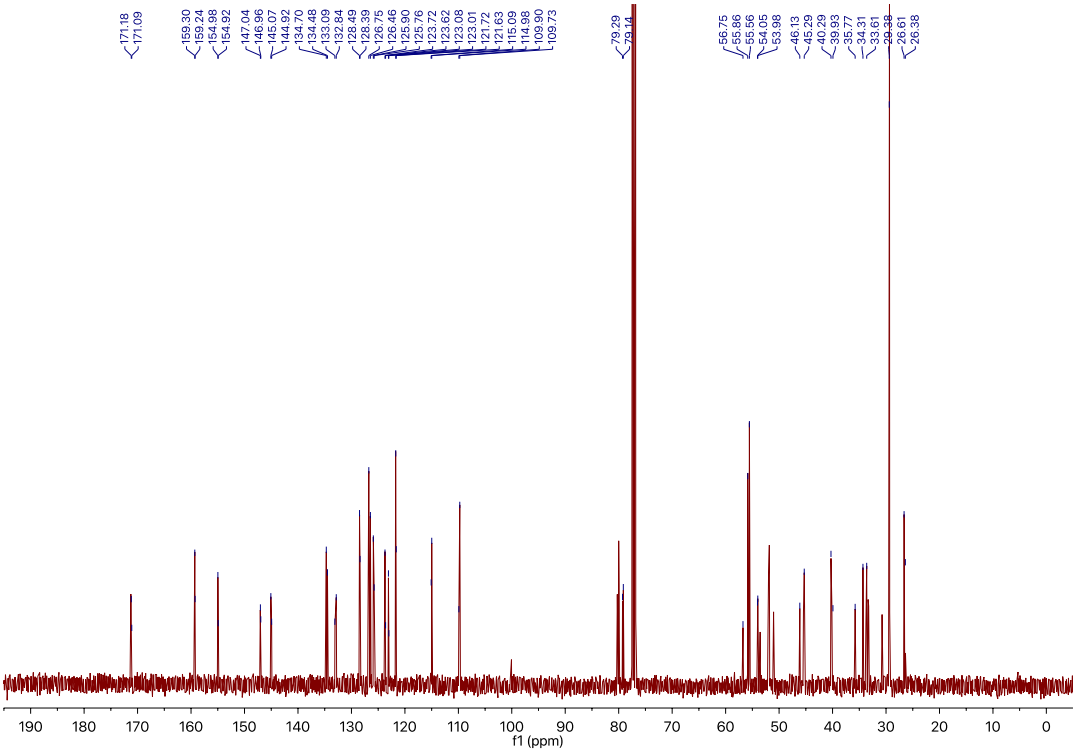
1.95
1.97
1.96
1.98
2.03
1.80
1.77
2.06
4.33
3.44
3.11
1.84
2.68
4.06
4.19
1.09
2.04
2.22
2.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

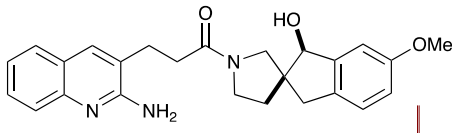

171.16
171.08
156.69
146.00
145.87
136.98
129.45
127.07
124.92
124.83
124.09
124.04
123.77
123.71
122.82
71.45
70.67
69.82
69.55
65.77
65.02
51.87
51.09
48.47
46.65
45.68
44.72
34.18
33.90
32.40
32.31
26.10
26.05
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
HO
N
OMe
N
NH^{t}Bu

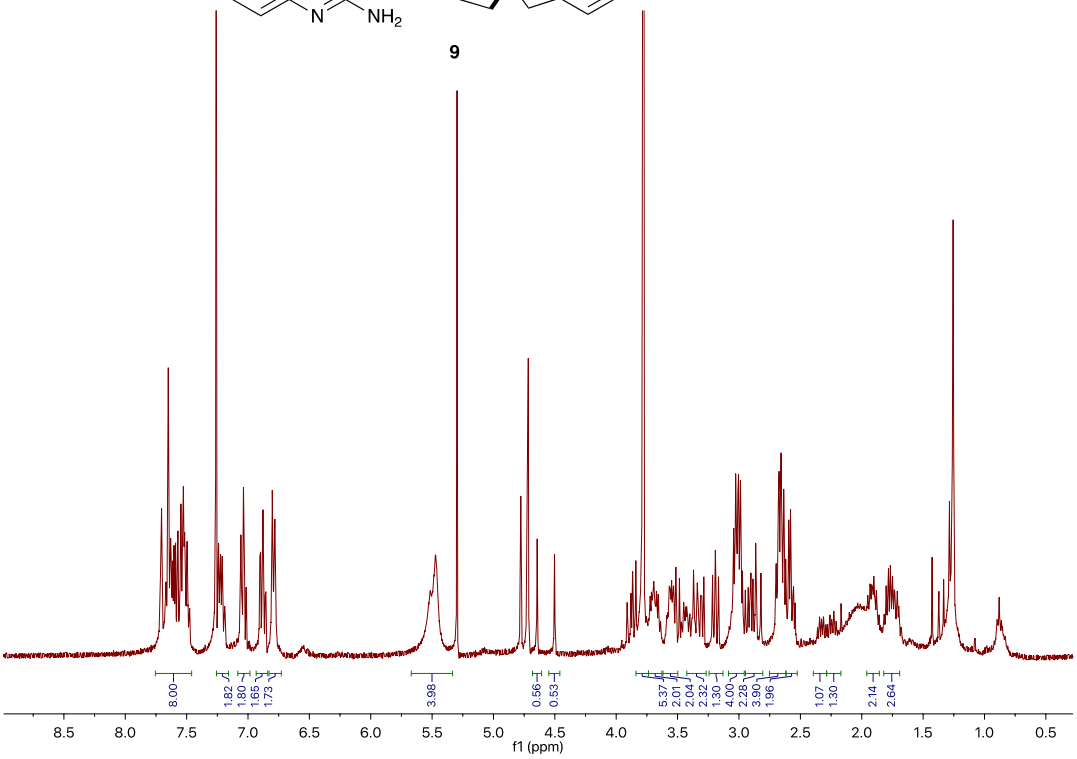
S6

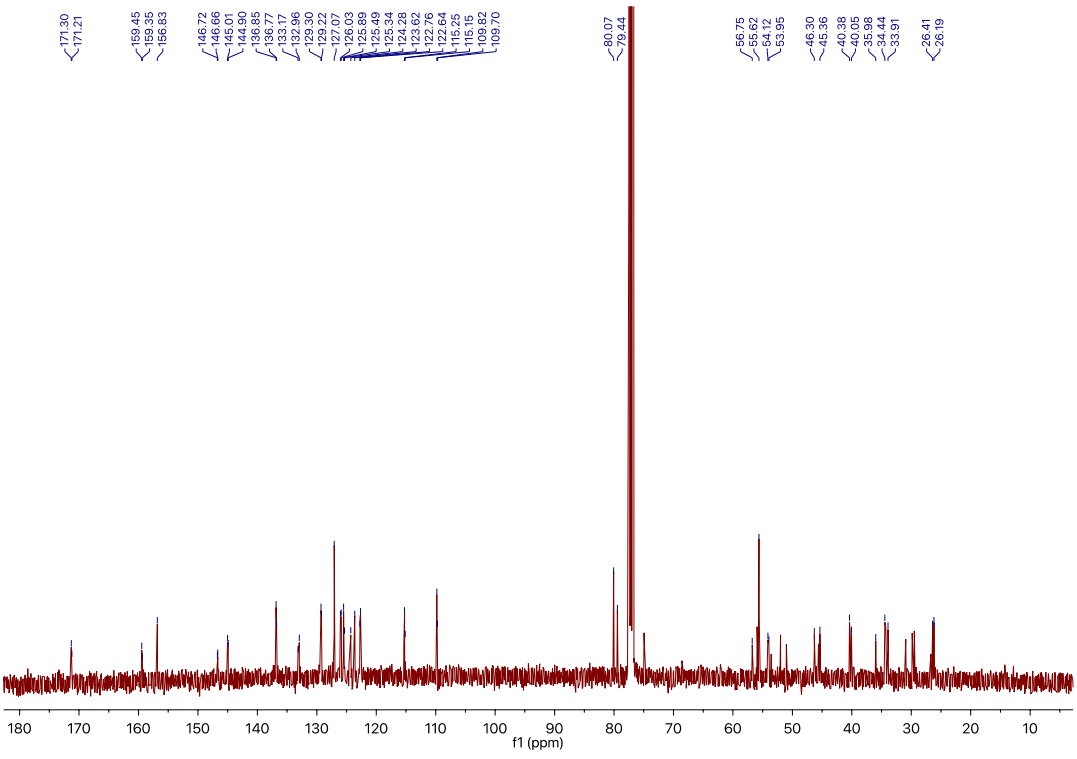
2.00
6.03
2.06
1.97
1.96
1.96
1.90
1.30
6.11
1.16
2.52
1.63
1.13
4.39
2.56
6.56
1.20
1.53
1.14
18.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

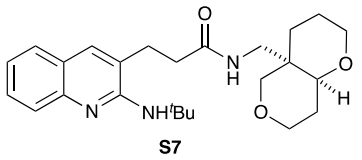

171.18
171.09
159.30
159.24
154.98
154.92
147.04
146.96
145.07
144.92
134.70
134.48
133.09
132.84
128.49
128.39
126.75
126.46
125.90
125.76
123.72
123.62
123.08
123.01
121.72
121.63
115.09
114.98
109.90
109.73
79.29
79.14
56.75
55.86
55.56
54.05
53.98
46.13
45.29
40.29
39.93
35.77
34.31
33.61
29.38
26.61
26.38
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
HO
N
OMe
N
NH2

9

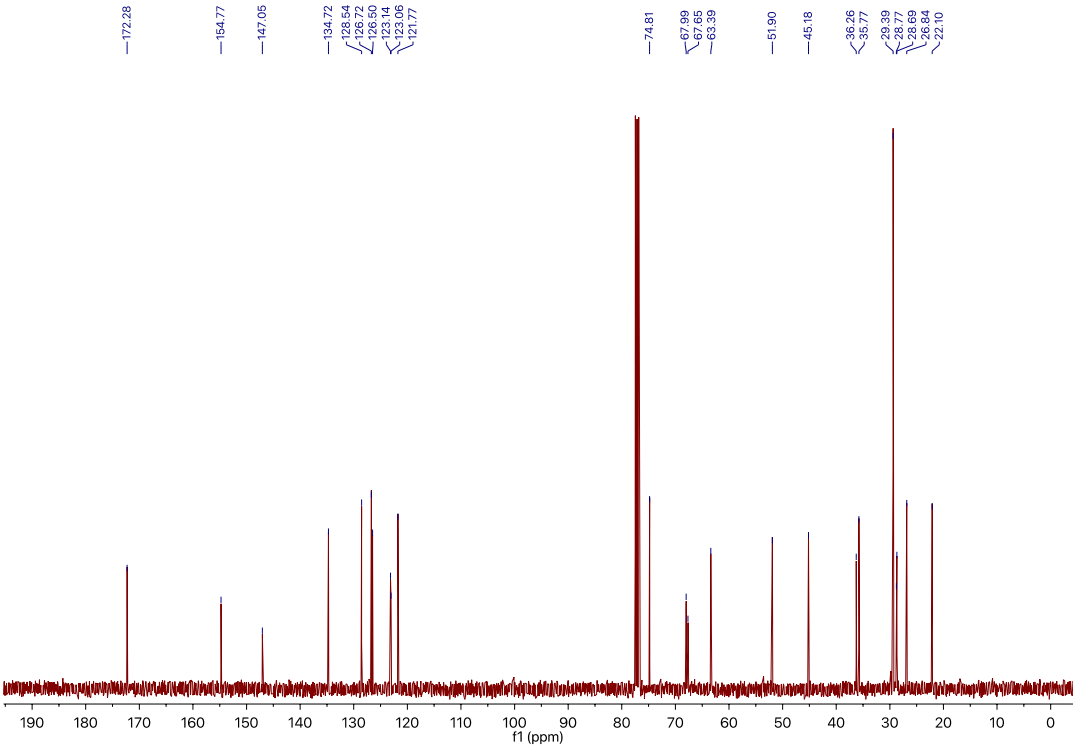

8.00
1.82
1.80
1.65
1.73
3.98
0.56
0.53
5.37
2.01
2.04
2.32
1.30
4.00
2.28
3.90
1.96
1.07
1.30
2.14
2.64
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

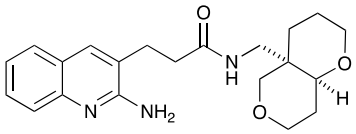

171.30
171.21
159.45
159.35
156.83
146.72
146.66
145.01
144.90
136.85
136.77
133.17
132.96
129.30
129.22
127.07
126.03
125.89
125.49
125.34
124.28
123.62
122.76
122.64
115.25
115.15
109.82
109.70
80.07
79.44
56.75
55.62
54.12
53.95
46.30
45.36
40.38
40.05
35.98
34.44
33.91
26.41
26.19
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
N
H
O
O
H
N
NH^{t}Bu

S7

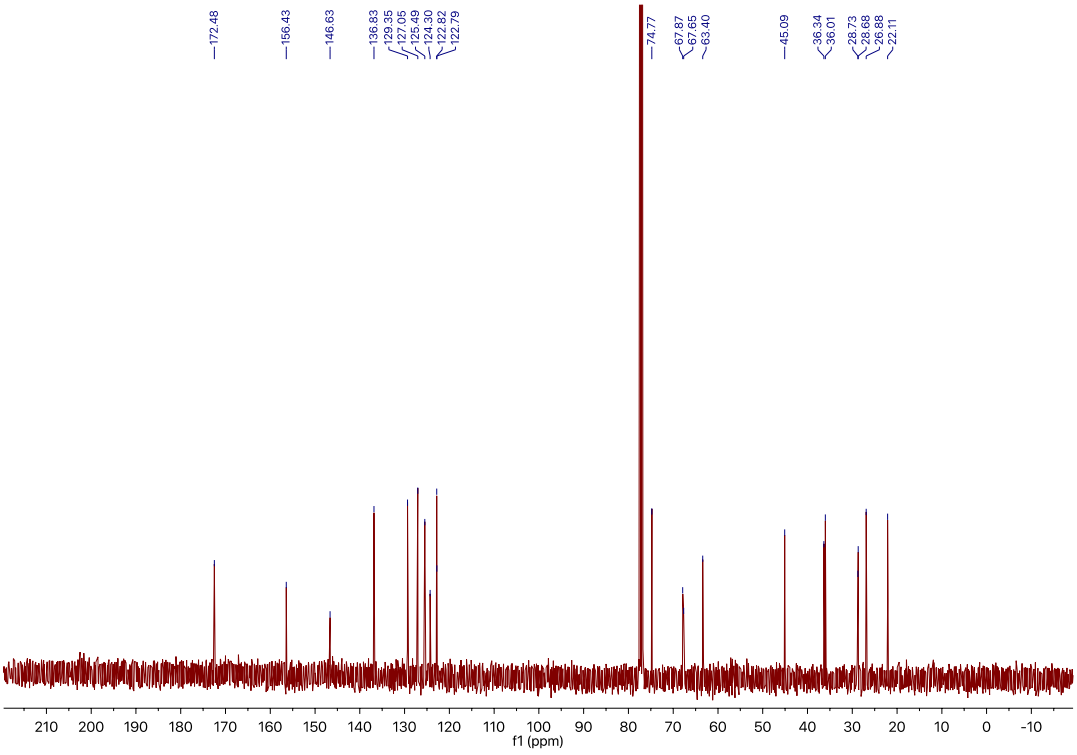
1.00
0.97
1.98
0.99
0.98
0.98
0.98
1.01
2.01
1.04
3.97
2.01
2.00
1.09
10.06
1.18
3.20
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

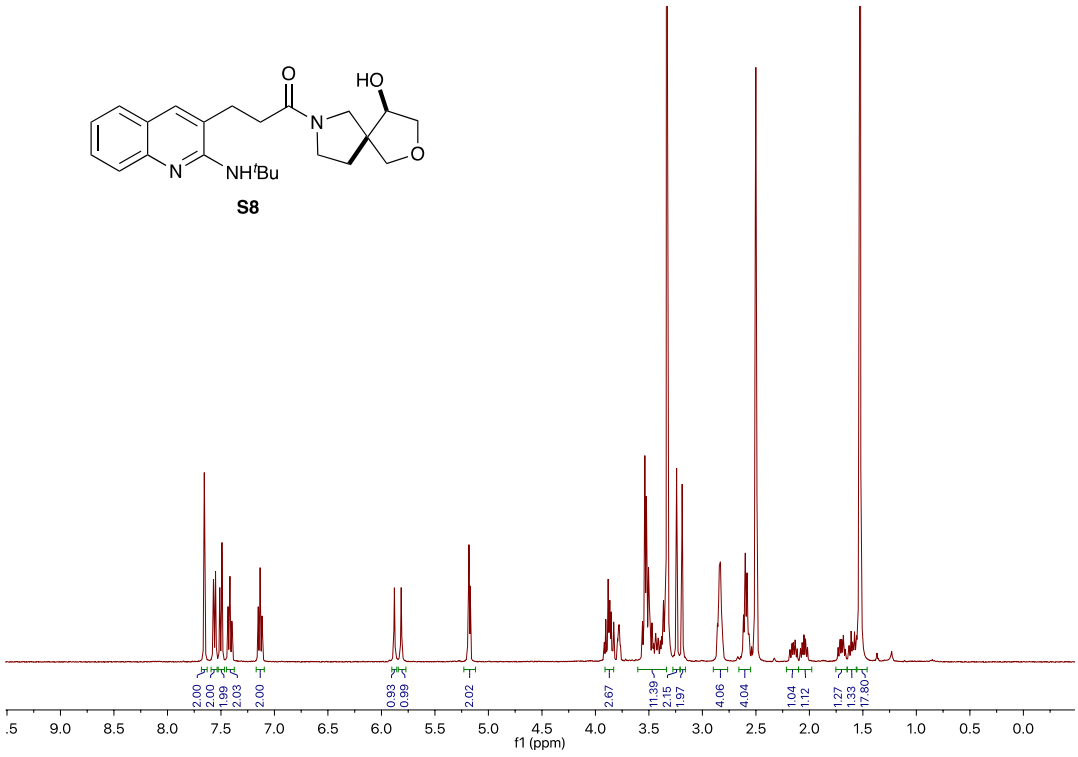

172.28
154.77
147.05
134.72
128.54
126.72
126.50
123.14
123.06
121.77
74.81
67.99
67.65
63.39
51.90
45.18
36.26
35.77
29.39
28.77
28.69
26.84
22.10
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
H
O
O
H
N
NH2

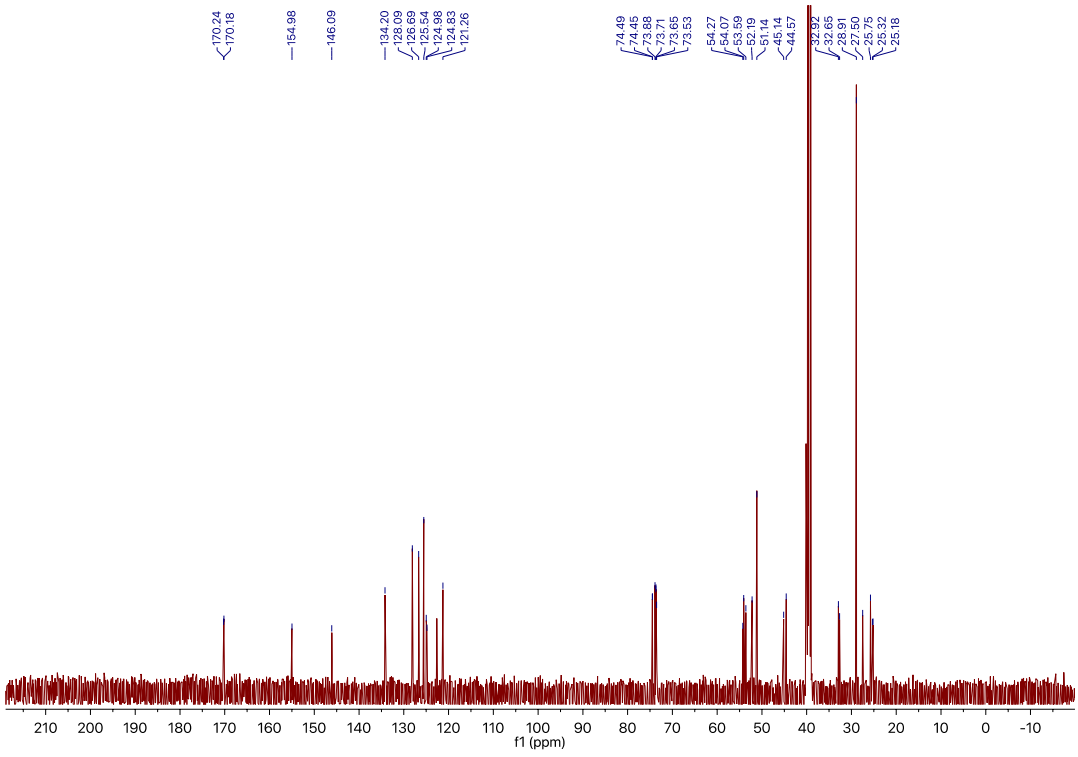
10

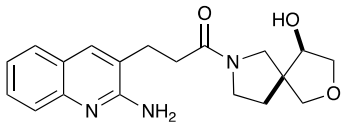
1.00
1.01
1.02
1.05
1.02
1.00
2.09
1.03
1.07
2.08
1.10
2.03
1.96
2.04
2.05
1.08
1.08
1.05
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


172.48
156.43
146.63
136.83
129.35
127.05
125.49
124.30
122.82
122.79
74.77
67.87
67.65
63.40
45.09
36.34
36.01
28.73
28.68
26.88
22.11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
HO
N
N
NH^{t}Bu
O
2.00
2.00
1.99
2.03
2.00
0.93
0.99
2.02
2.67
11.39
2.15
1.97
4.06
4.04
1.04
1.12
1.27
1.33
17.80
f1 (ppm)

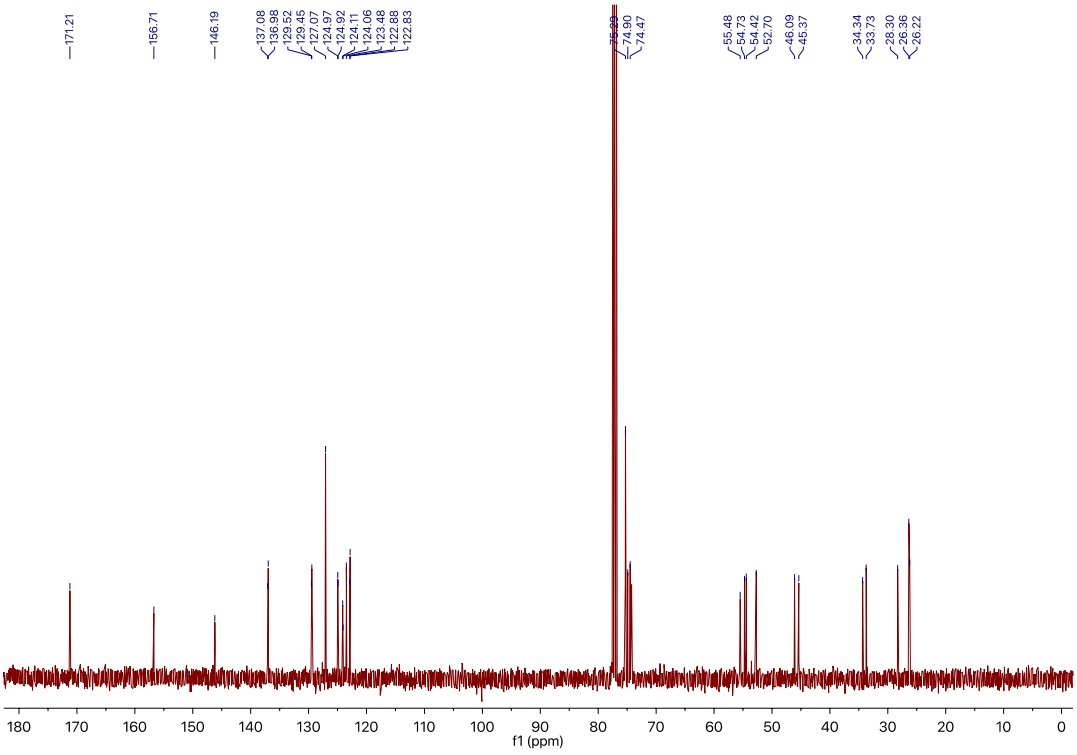
S8

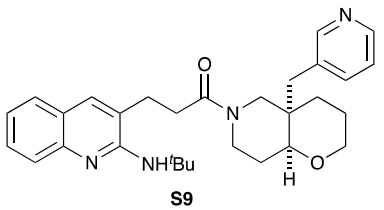

170.24
170.18
154.98
146.09
134.20
128.09
126.69
125.54
124.98
124.83
121.26
74.49
74.45
73.88
73.71
73.65
73.53
54.27
54.07
53.59
52.19
51.14
45.14
44.57
32.92
32.65
28.91
27.50
25.75
25.32
25.18
f1 (ppm)


O
HO
N
O
N
NH2

11

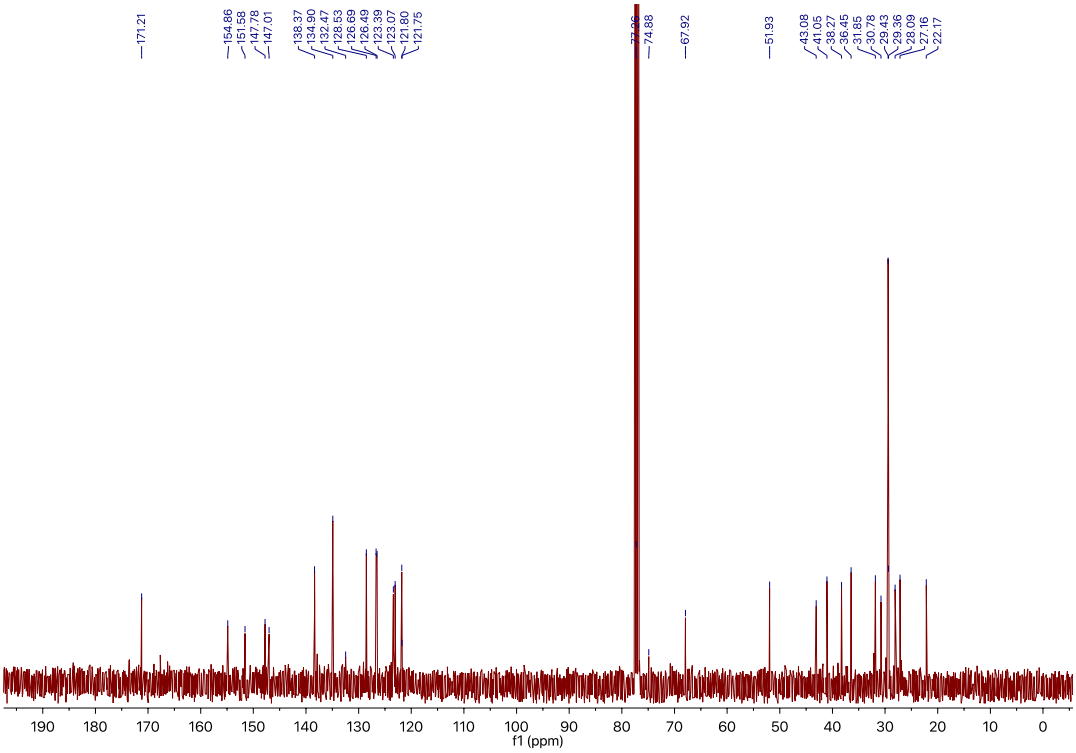
1.86
1.83
1.87
1.88
1.84
3.32
2.11
4.90
3.03
2.08
2.35
1.41
1.60
3.89
3.85
1.06
0.93
1.02
0.96
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

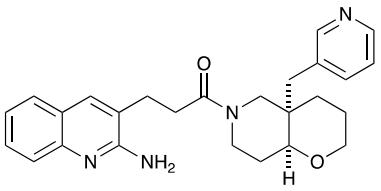

171.21
156.71
146.19
137.08
136.98
129.52
129.45
127.07
124.97
124.92
124.11
124.06
123.48
122.88
122.83
77.00
74.90
74.47
55.48
54.73
54.42
52.70
46.09
45.37
34.34
33.73
28.30
26.36
26.22
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N
O
N
N
NH^{t}Bu
H
O

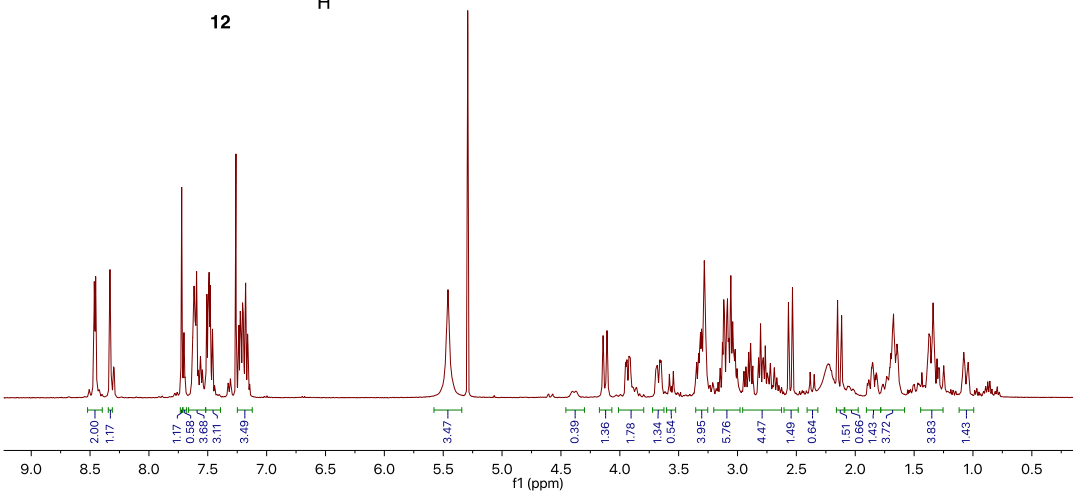
S9

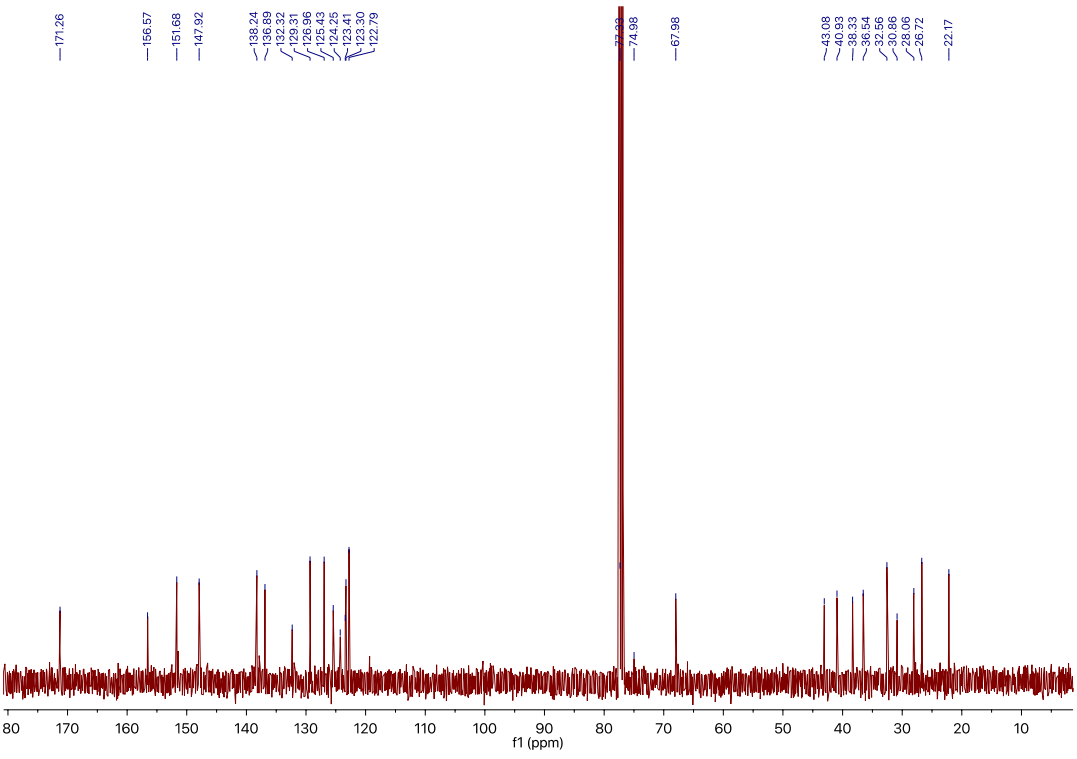
2.00
1.00
0.47
2.86
6.25
2.19
2.15
0.47
1.30
0.38
1.34
1.81
1.40
0.30
4.46
2.01
4.93
3.65
1.06
0.61
1.94
1.03
3.03
17.93
6.04
2.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

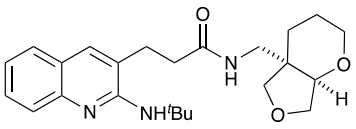

171.21
154.86
151.58
147.78
147.01
138.37
134.90
132.47
128.53
126.69
126.49
123.39
123.07
121.80
121.75
77.26
74.88
67.92
51.93
43.08
41.05
38.27
36.45
31.85
30.78
29.43
29.36
28.09
27.16
22.17
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


N
O
N
N
NH2
H
O

12

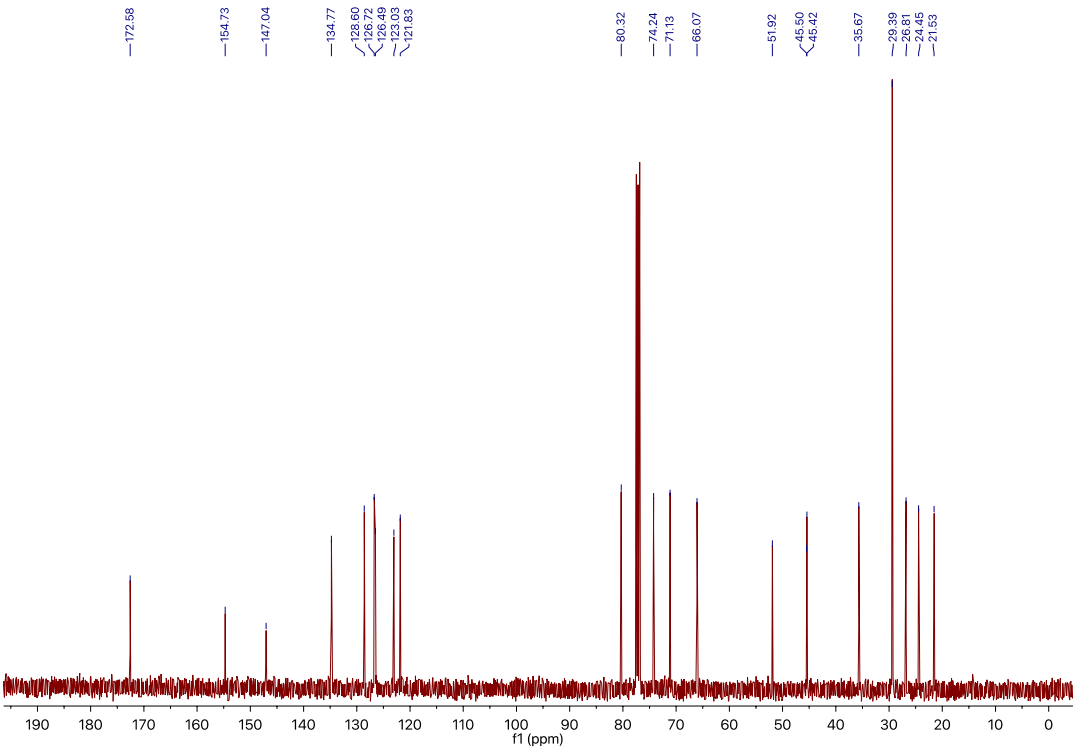

2.00
1.17
1.17
0.58
3.68
3.11
3.49
3.47
0.39
1.36
1.78
1.34
0.64
3.95
5.76
4.47
1.49
0.64
1.51
0.66
1.43
3.72
3.83
1.43
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

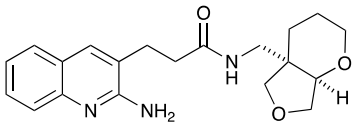

171.26
166.57
151.68
147.92
138.24
136.89
132.32
129.31
126.96
125.43
124.25
123.41
123.00
122.79
77.39
74.98
67.98
43.08
40.93
38.33
36.64
31.86
30.55
28.06
26.72
22.17
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
N
H
O
H
N
O
NH^{t}Bu

S10

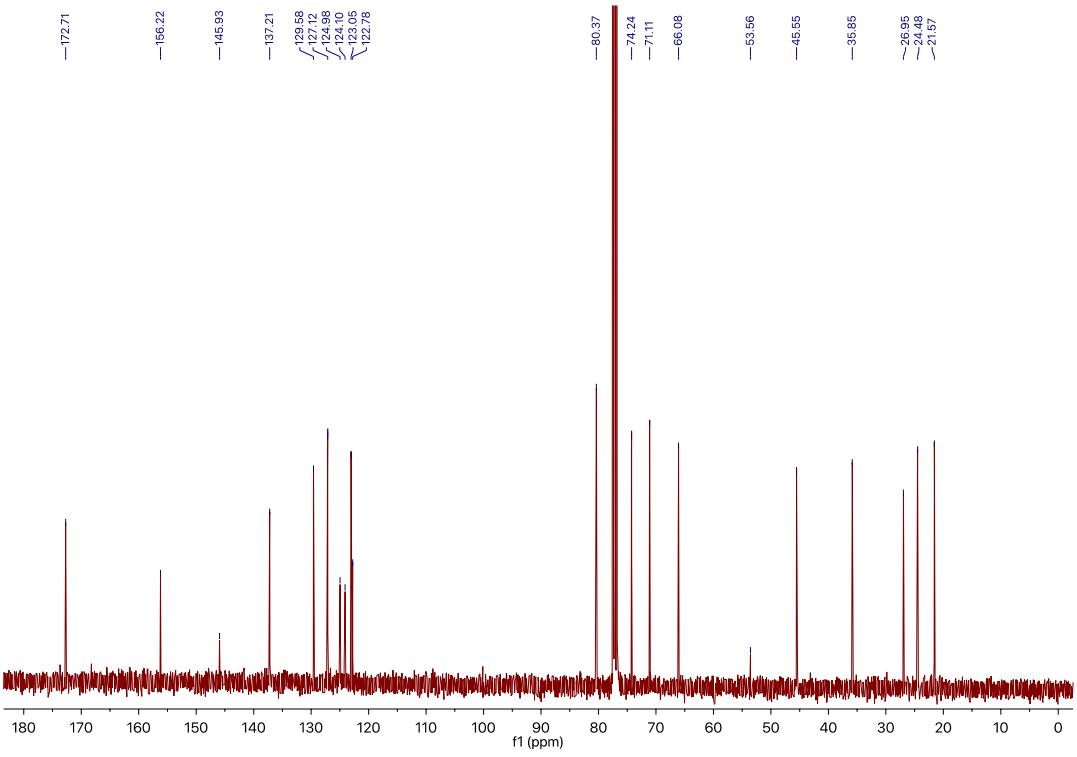
1.00
0.94
1.92
0.97
0.95
1.04
1.02
1.91
1.01
0.99
1.00
1.03
1.98
1.99
1.98
9.26
1.96
1.10
0.82
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

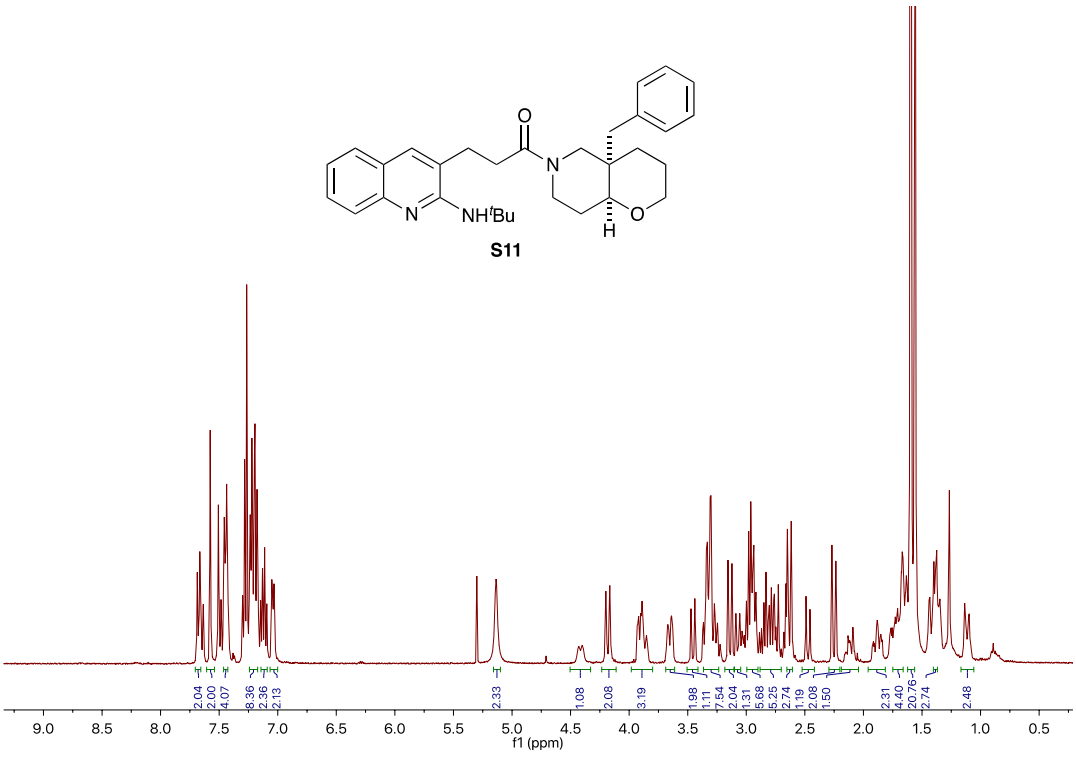

172.58
154.73
147.04
134.77
128.60
126.72
126.49
123.03
121.83
80.32
74.24
71.13
66.07
51.92
45.50
45.42
35.67
29.39
26.81
24.45
21.53
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
H
O
H
N
NH2
O

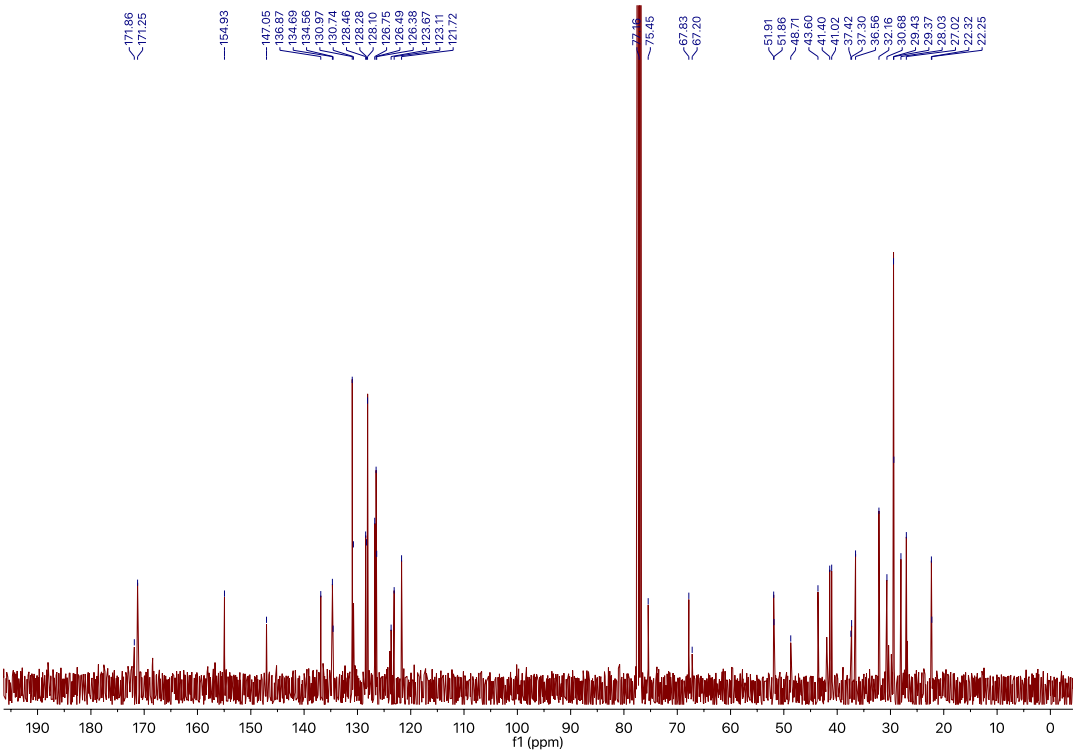
13

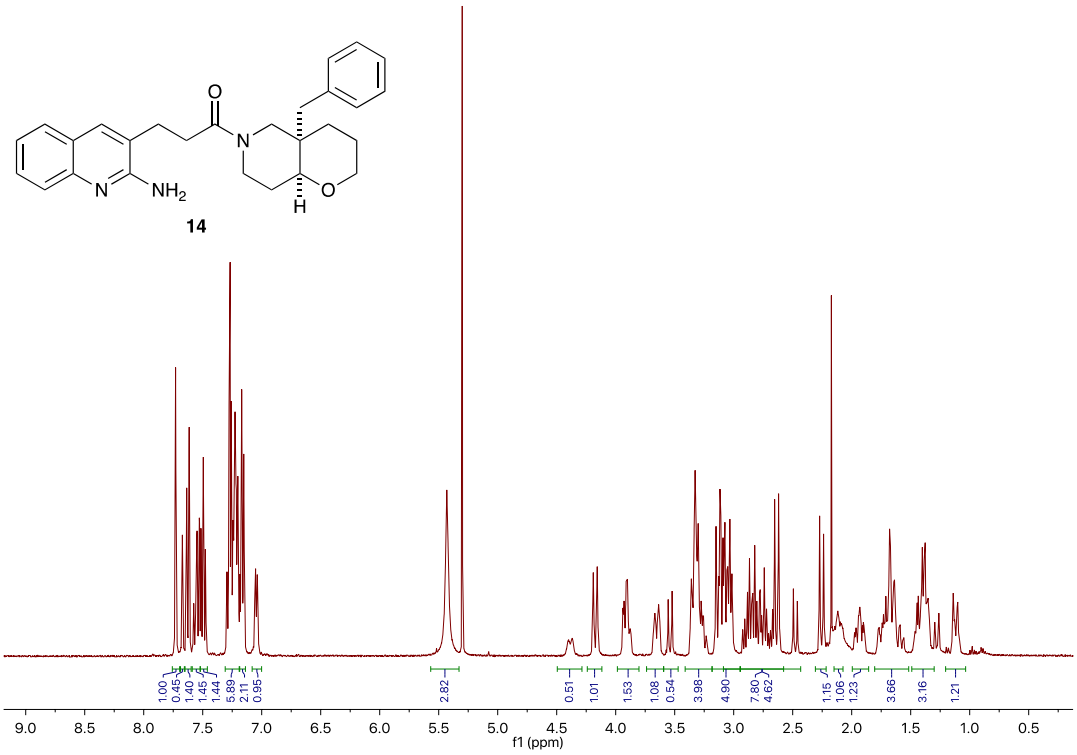
0.97
1.02
0.99
1.00
0.98
0.94
1.85
1.02
2.05
1.01
0.99
1.01
1.10
2.06
2.02
2.13
1.09
1.91
1.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

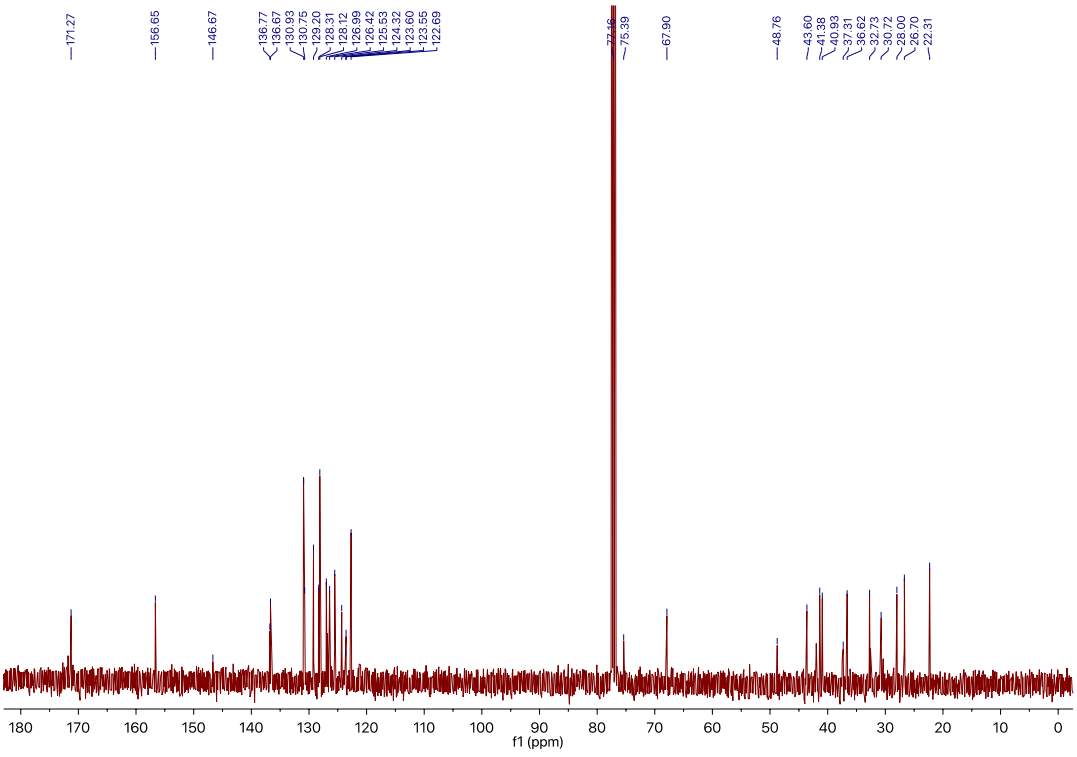

172.71
156.22
145.93
137.21
129.58
127.12
124.98
124.10
123.05
122.78
80.37
74.24
71.11
66.08
53.56
45.55
35.85
26.95
24.48
21.57
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

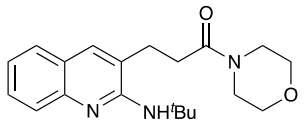

O
N
N
NH^{t}Bu
H
O
2.04
2.00
4.07
8.36
2.36
2.13
2.33
1.08
2.08
3.19
1.98
1.11
7.54
2.04
1.31
5.68
5.25
2.74
1.19
2.08
1.50
2.31
4.40
20.76
2.74
2.48
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

S11


171.86
171.25
154.93
147.05
136.87
134.69
134.56
130.97
130.74
128.46
128.28
128.10
126.75
126.49
126.38
123.67
123.11
121.72
77.16
75.45
67.83
67.20
51.91
51.66
48.71
43.60
41.40
41.02
37.42
37.30
36.56
32.16
30.68
29.43
29.37
28.03
27.02
22.32
22.25
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

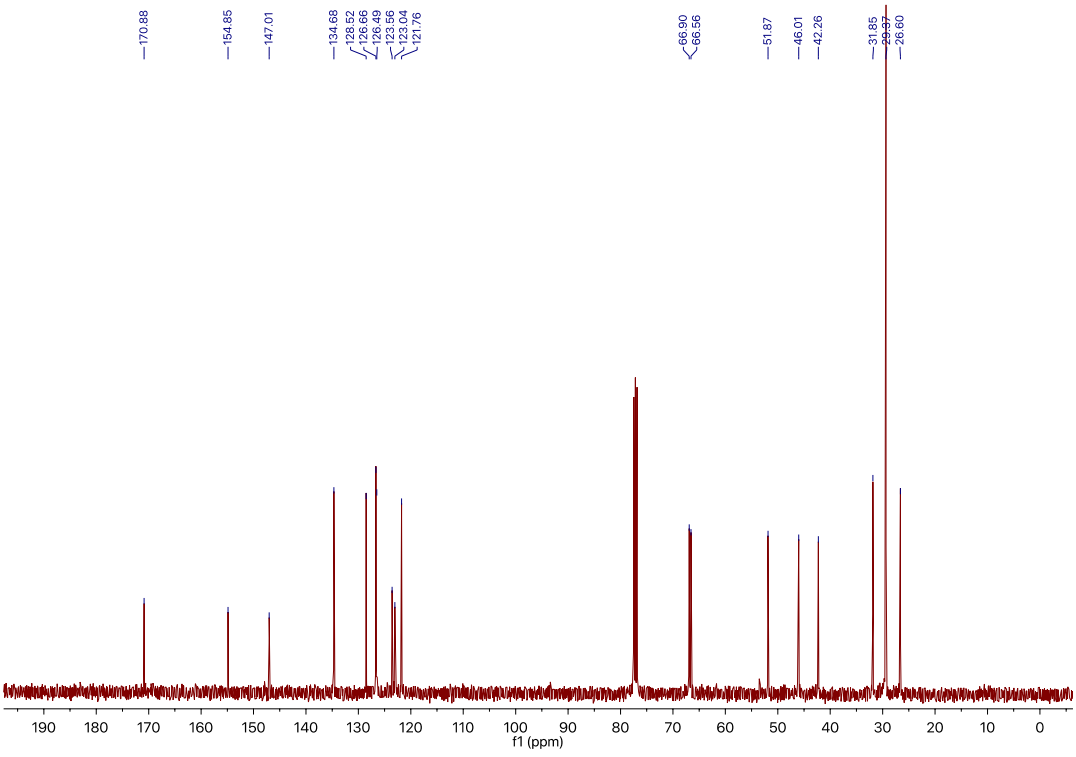

O
N
NH2
N
O
H
14
1.00
0.45
1.40
1.45
1.44
5.89
2.11
0.95
2.82
0.51
1.01
1.53
1.08
0.54
3.98
4.90
7.80
4.62
1.15
1.06
1.23
3.66
3.16
1.21
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

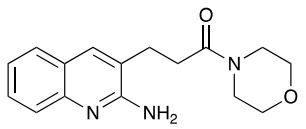

171.27
166.65
146.67
136.77
136.67
130.93
130.75
129.20
128.31
128.12
126.99
126.42
125.53
124.32
123.60
123.55
122.69
77.16
75.39
67.90
48.76
43.60
41.38
40.93
37.31
36.62
32.73
30.72
28.00
26.70
22.31
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
O
N
NH^{t}Bu

S12

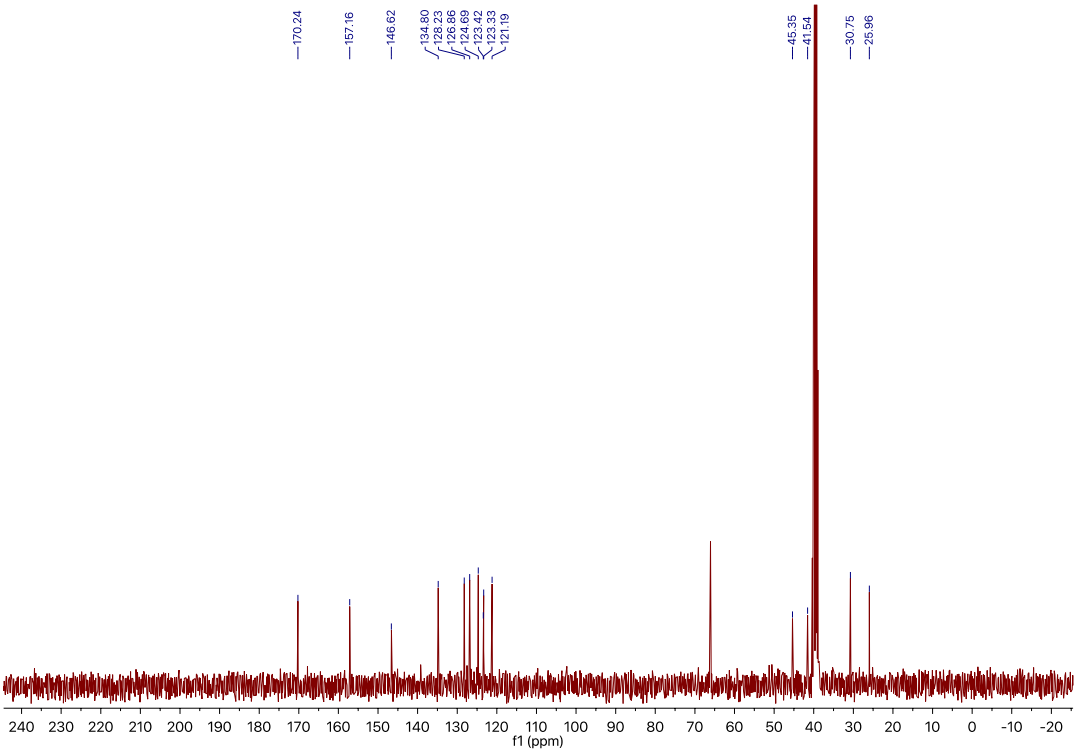
0.98
0.99
1.01
1.06
0.98
1.06
3.98
1.98
1.96
2.02
1.98
9.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

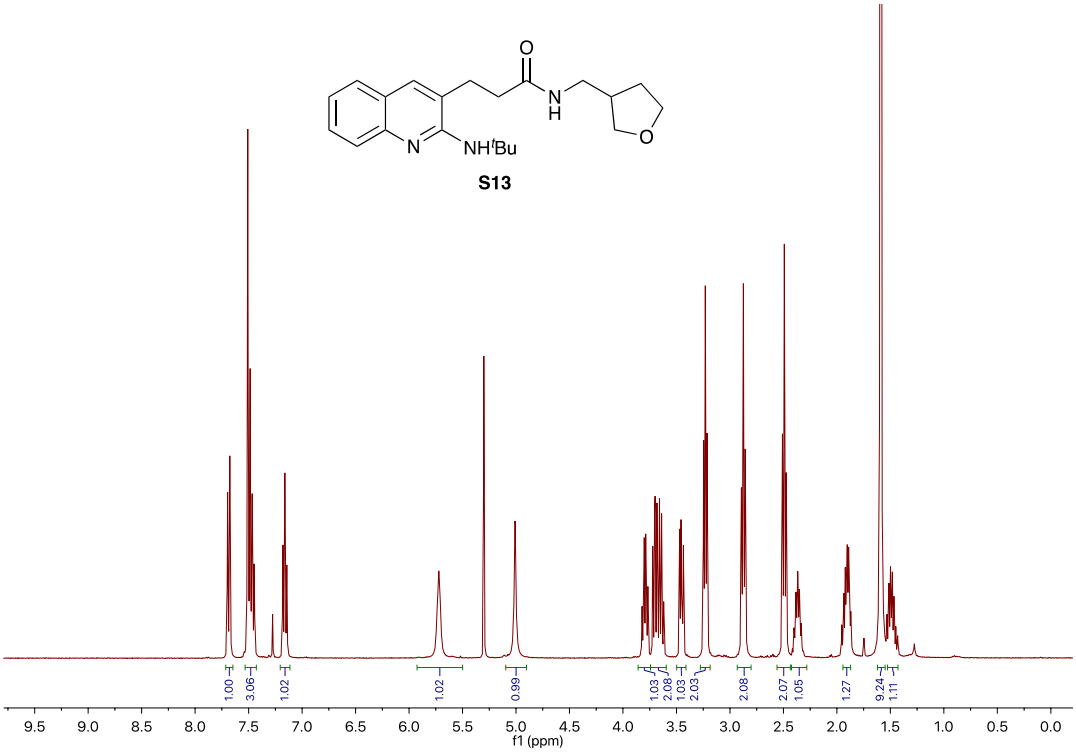

170.88
154.85
147.01
134.68
128.52
126.66
126.49
123.56
123.04
121.76
66.90
66.56
51.87
46.01
42.26
31.85
29.37
26.60
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
O
N
NH2

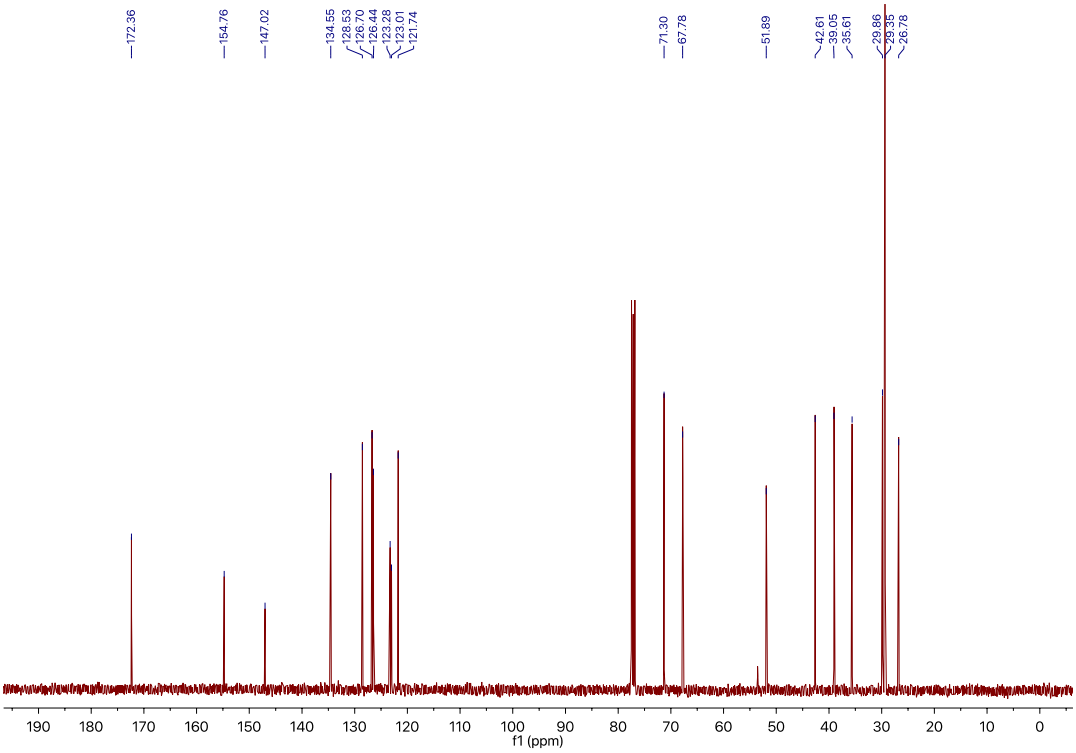
15

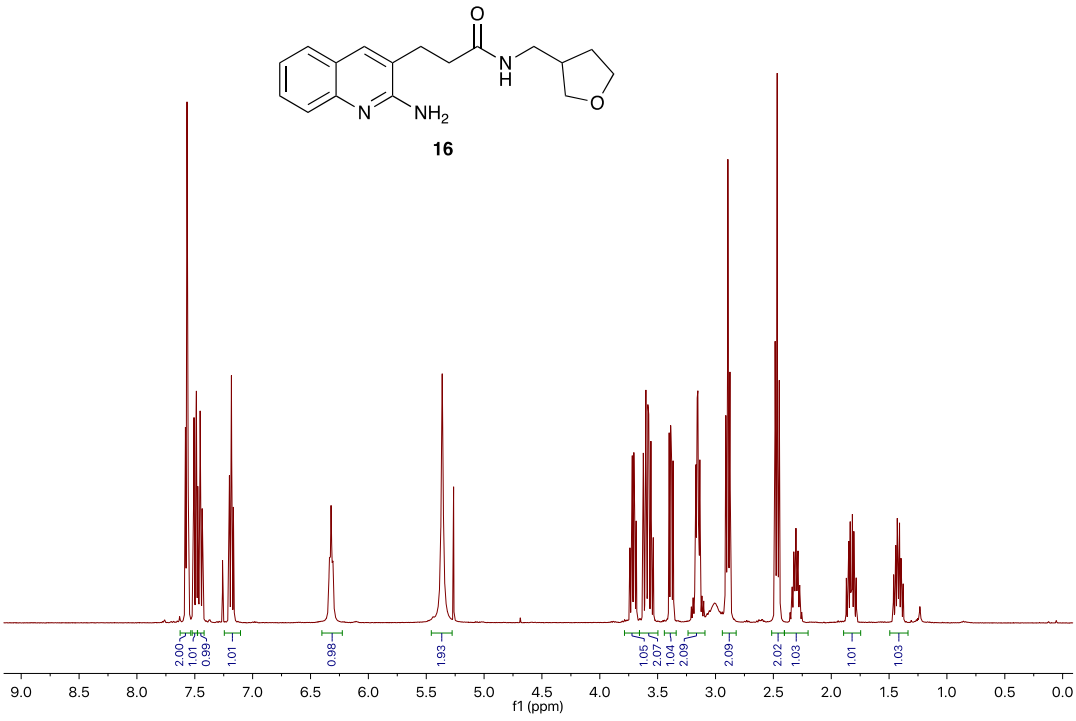
1.00
1.00
1.98
0.99
1.95
3.97
3.92
2.01
2.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

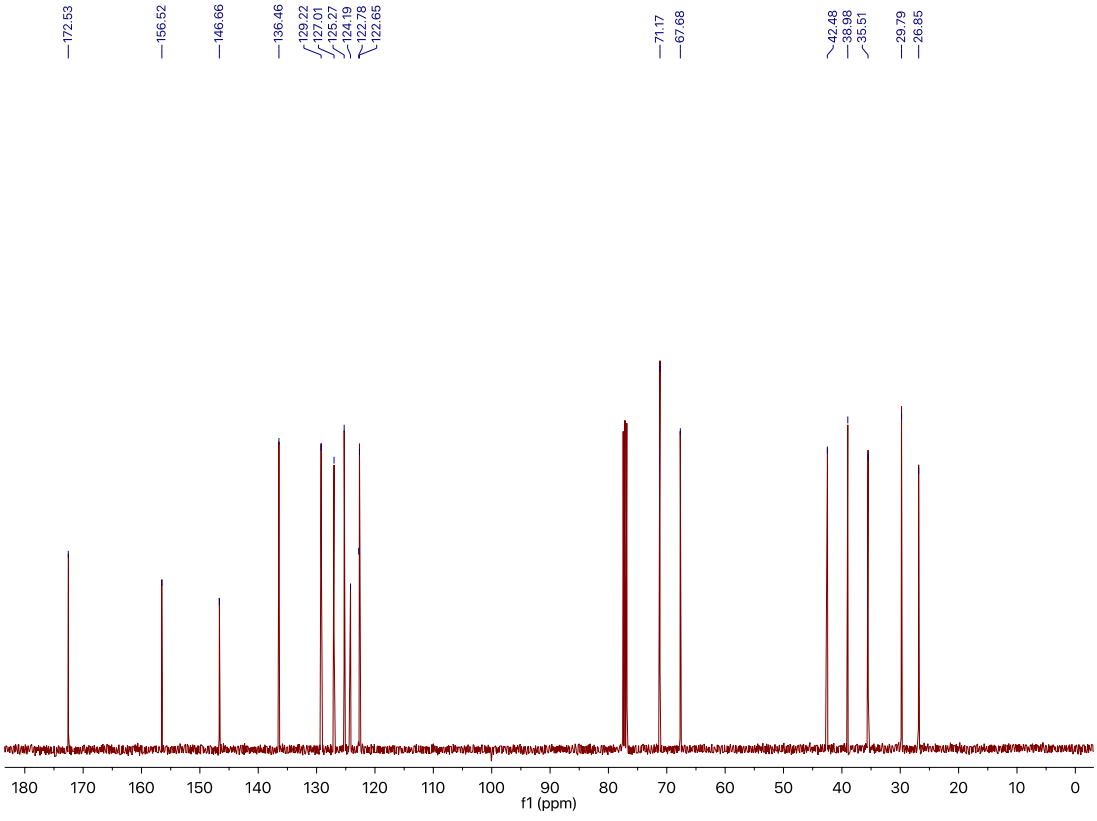

170.24
157.16
146.62
134.80
128.23
126.86
124.69
123.42
123.33
121.19
45.35
41.54
30.75
25.96
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

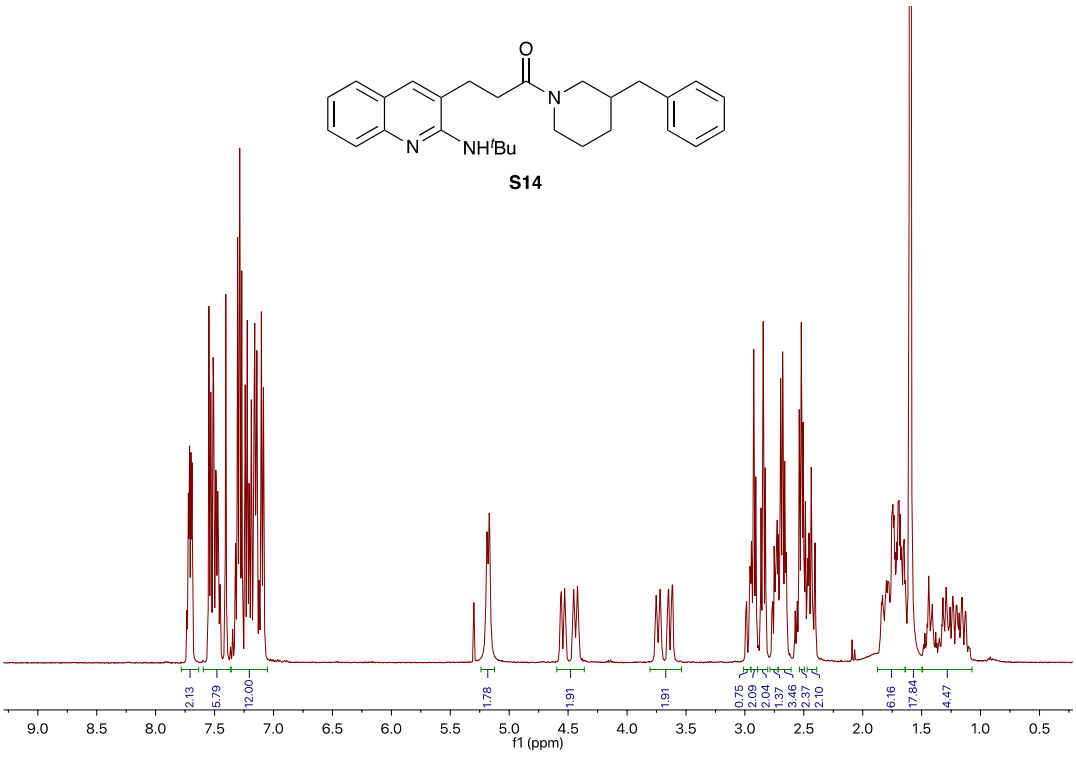

O
N
H
N
NH^{t}Bu
O
1.00
3.06
1.02
1.02
0.99
1.03
2.08
1.03
2.03
2.08
2.07
1.05
1.27
9.24
1.11
f1 (ppm)

S13

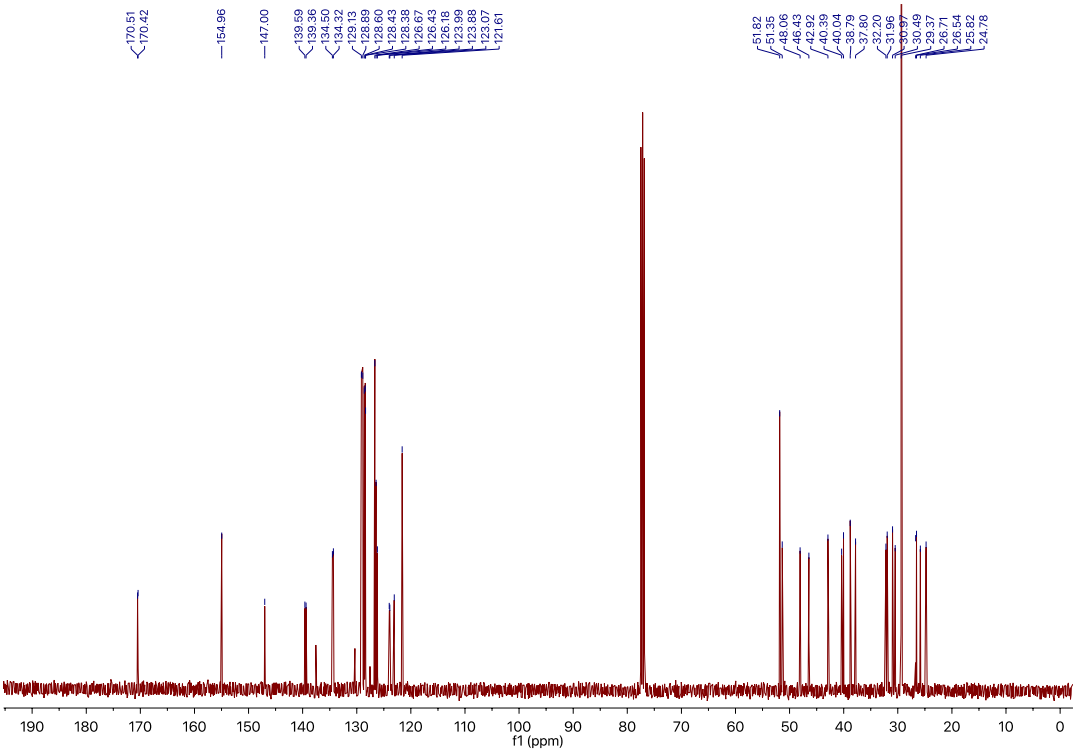

172.36
154.76
147.02
134.55
128.53
126.70
126.44
123.28
123.01
121.74
71.30
67.78
51.89
42.61
39.05
35.61
29.86
29.35
26.78
f1 (ppm)

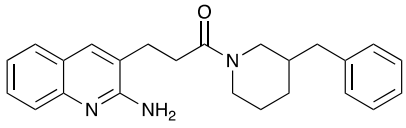

O
N
H
N
NH2
O
16
2.00
1.01
0.99
1.01
0.98
1.93
1.05
2.07
1.04
2.09
2.09
2.02
1.03
1.01
1.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


172.53
156.52
146.66
136.46
129.22
127.01
125.27
124.19
122.78
122.65
71.17
67.68
42.48
38.98
35.51
29.79
26.85
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

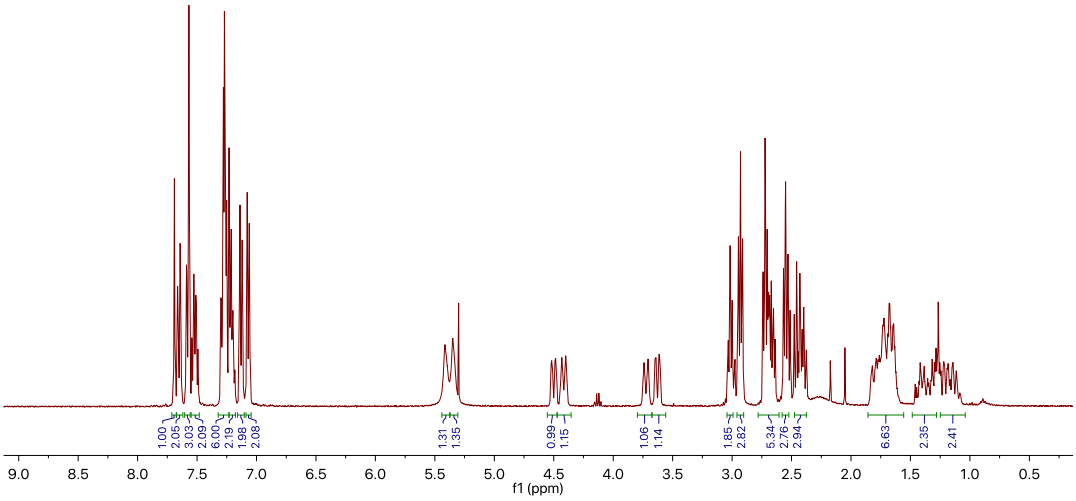

O
N
N
NH^{t}Bu
2.13
5.79
12.00
1.78
1.91
1.91
0.75
2.09
2.04
1.37
3.46
2.37
2.10
6.16
17.84
4.47
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

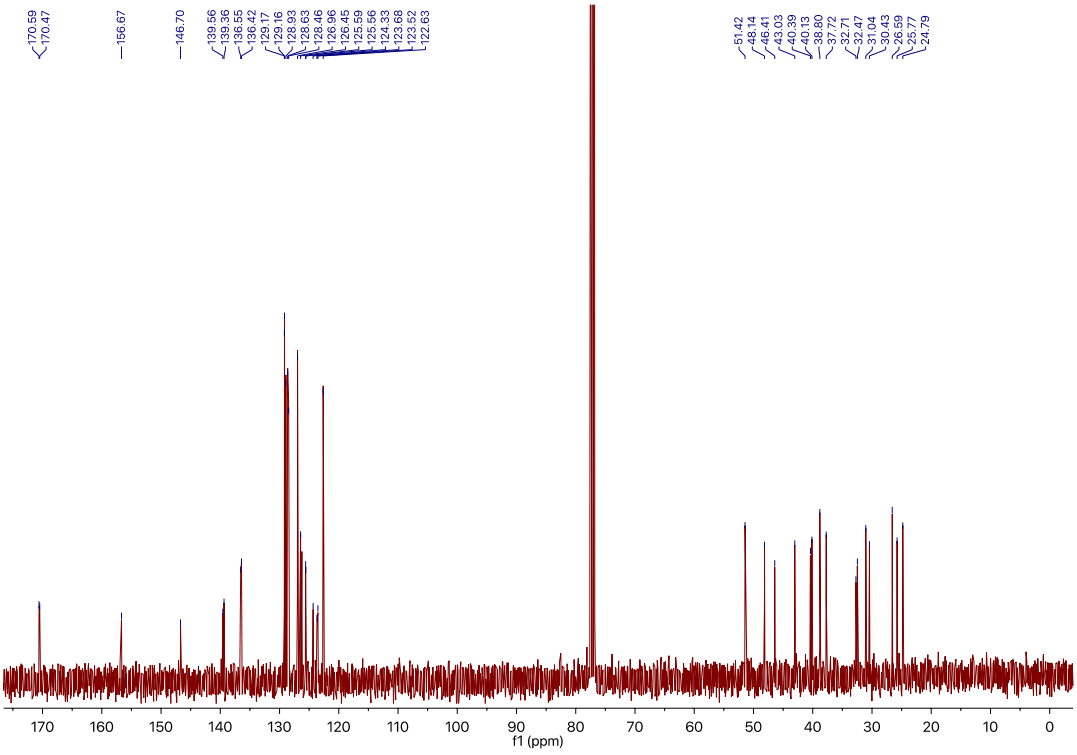
S14

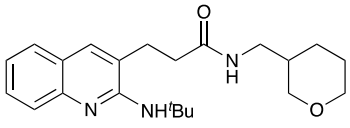

170.51
170.42
154.96
147.00
139.59
139.36
134.50
134.32
129.13
128.89
128.60
128.43
128.38
126.67
126.43
126.18
123.98
123.88
123.07
121.61
51.82
51.35
48.06
46.43
42.92
40.39
40.04
38.79
37.80
32.20
31.96
30.97
30.49
29.37
26.71
26.54
25.82
24.78
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
N
NH2

17

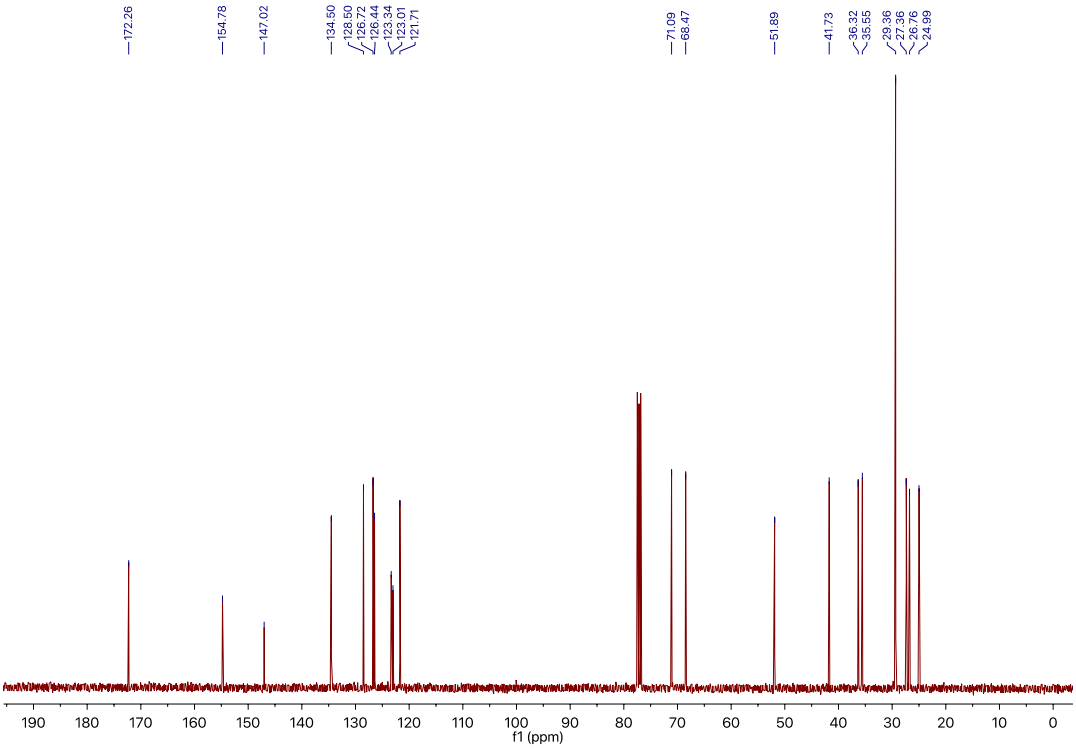

1.00
2.05
3.03
2.09
6.00
2.19
1.98
2.08
1.31
1.35
0.99
1.15
1.06
1.14
1.85
2.82
5.34
2.76
2.94
6.63
2.35
2.41
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

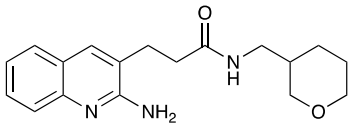

170.59
170.47
156.67
146.70
139.56
139.36
136.55
136.42
129.17
129.16
128.93
128.63
128.46
126.96
126.45
125.59
125.56
124.33
123.68
123.52
122.63
51.42
48.14
46.41
43.03
40.39
40.13
38.80
37.72
32.71
32.47
31.04
30.43
26.59
25.77
24.79
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
H
N
NH^{t}Bu
O

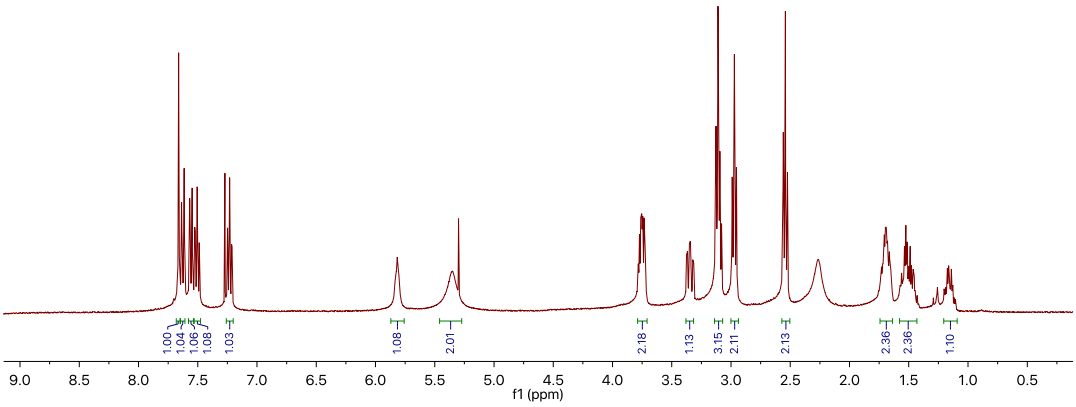
S15

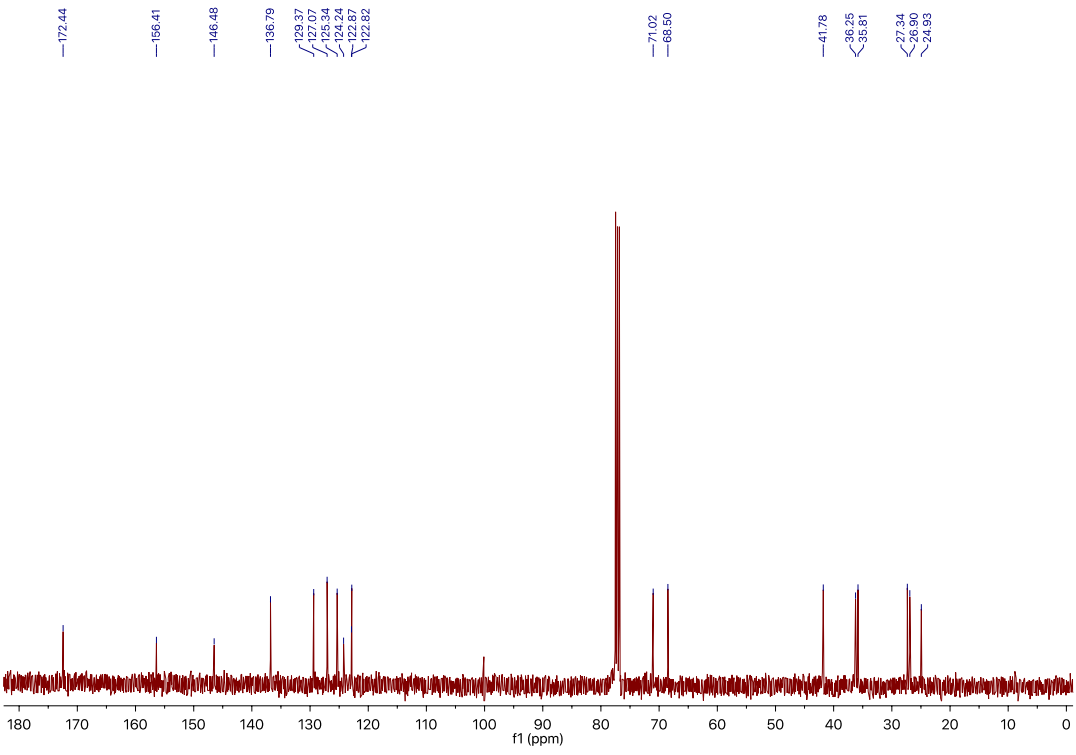
1.00
3.06
1.01
0.98
0.97
2.08
1.05
3.09
2.09
2.06
2.08
9.09
1.99
1.08
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

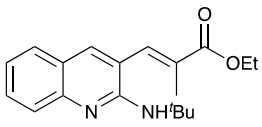

172.26
154.78
147.02
134.50
128.50
128.72
126.44
123.34
123.01
121.71
71.09
68.47
51.89
41.73
36.32
35.55
29.36
27.36
26.76
24.99
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
H
N
NH2
O

18

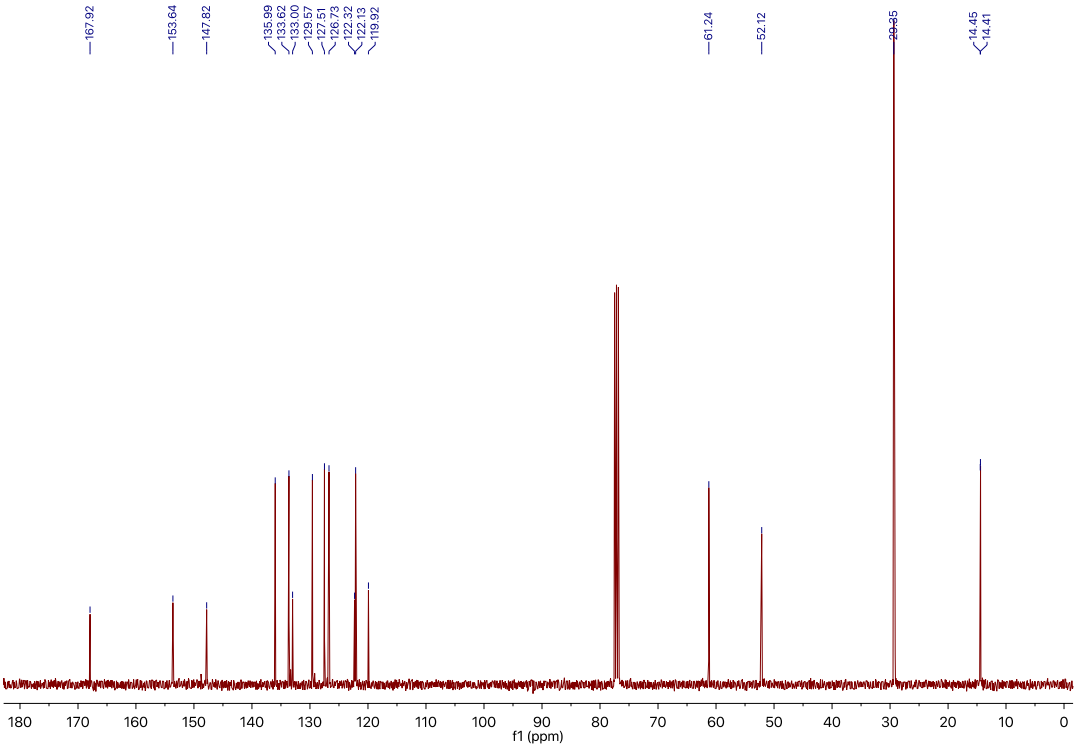

1.00
1.04
1.06
1.08
1.03
1.08
2.01
2.18
1.13
3.15
2.11
2.13
2.36
2.36
1.10
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

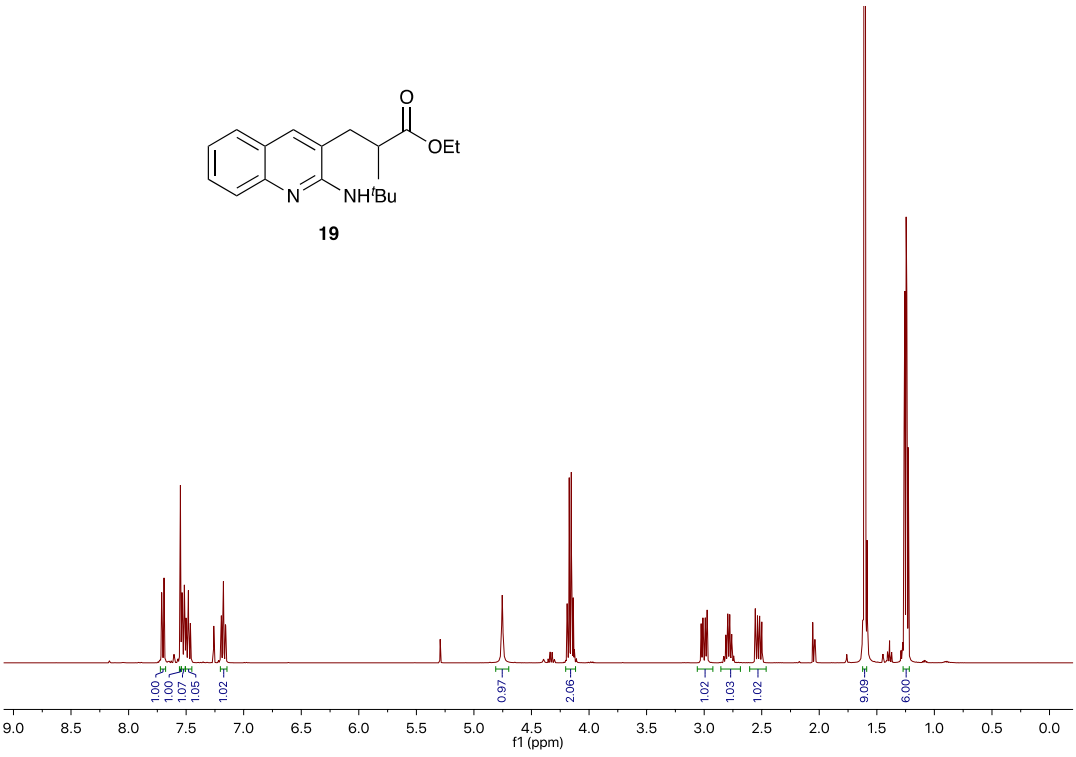

172.44
156.41
146.48
136.79
129.37
127.07
125.34
124.24
122.87
122.82
71.02
68.50
41.78
36.25
35.81
27.34
26.90
24.93
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OEt
N
NHtBu

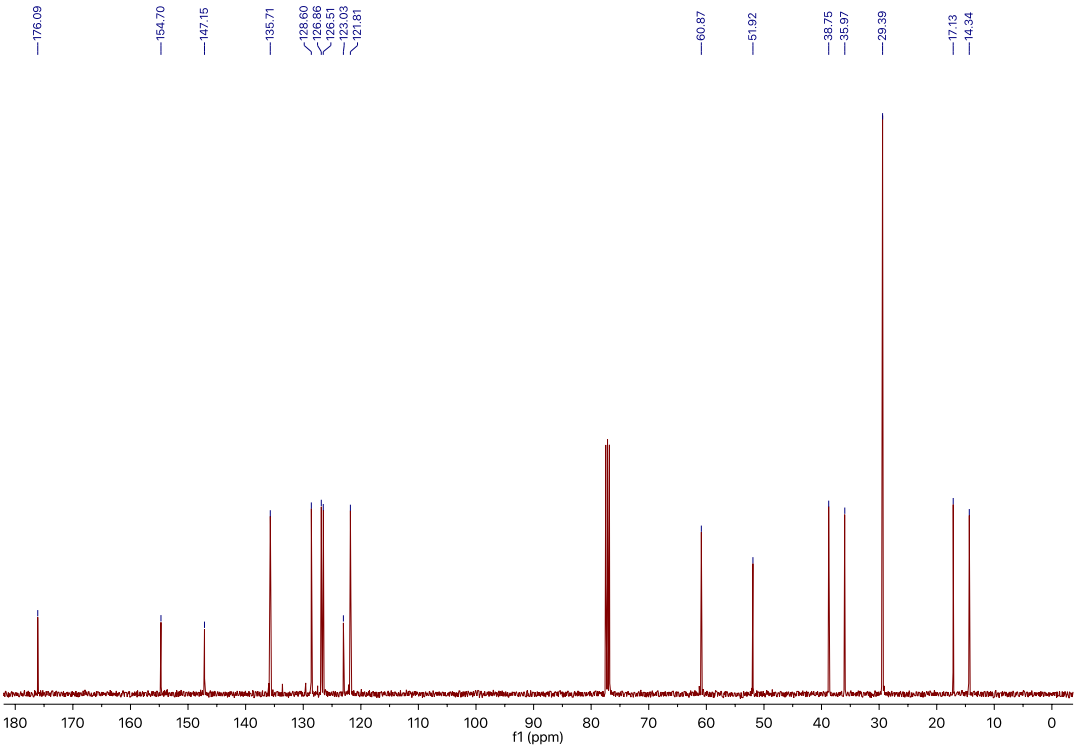
S16

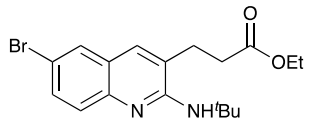
1.00
0.99
1.09
0.99
1.07
1.06
0.94
2.10
3.06
9.01
3.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


167.92
153.64
147.82
135.99
133.62
133.00
129.57
127.51
126.73
122.32
122.13
119.92
61.24
52.12
29.95
14.45
14.41
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OEt
N
NHᵗBu
1.00
1.00
1.07
1.05
1.02
0.97
2.06
1.02
1.03
1.02
9.09
6.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

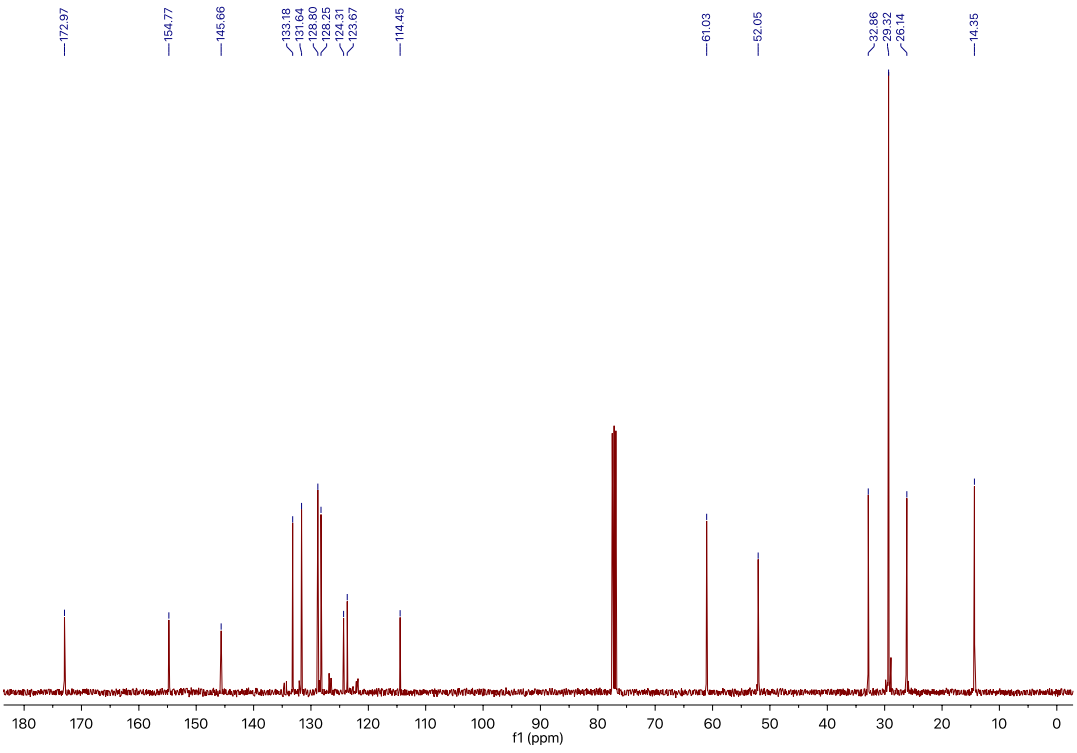
19

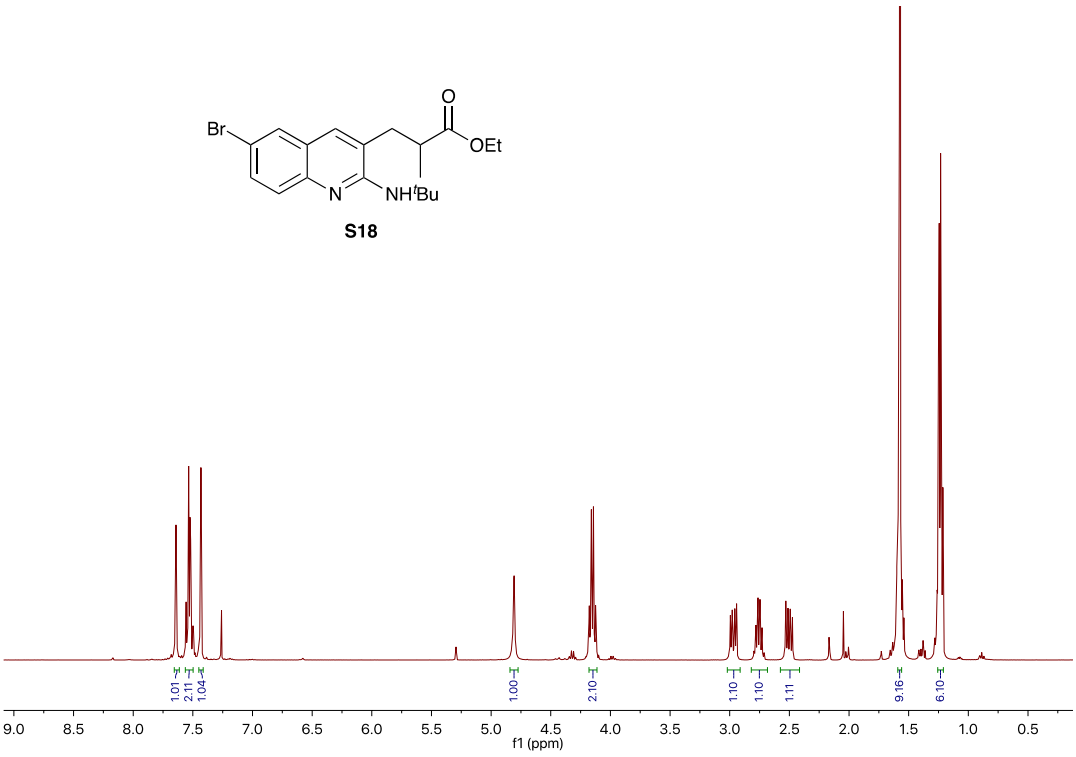

176.09
154.70
147.15
135.71
128.60
126.86
126.51
123.03
121.81
60.87
51.92
38.75
35.97
29.39
17.13
14.34
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
O
OEt
N
NH^{t}Bu

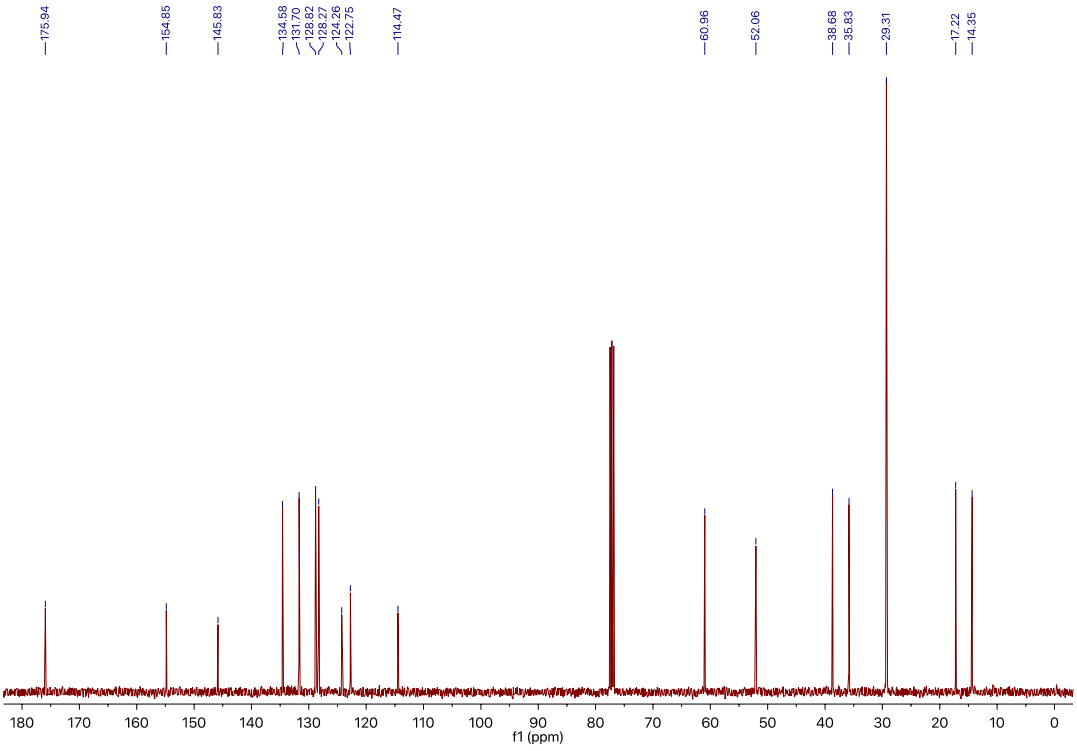
S17

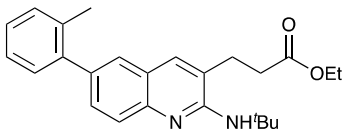
1.00
2.04
1.01
1.01
2.23
2.23
2.36
9.07
3.17
f1 (ppm)


172.97
154.77
145.66
133.18
131.64
128.80
128.25
124.31
123.67
114.45
61.03
52.05
32.86
29.32
26.14
14.35
f1 (ppm)


Br
O
OEt
N
NH^{t}Bu
1.01
2.11
1.04
1.00
2.10
1.10
1.10
1.11
9.16
6.10
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

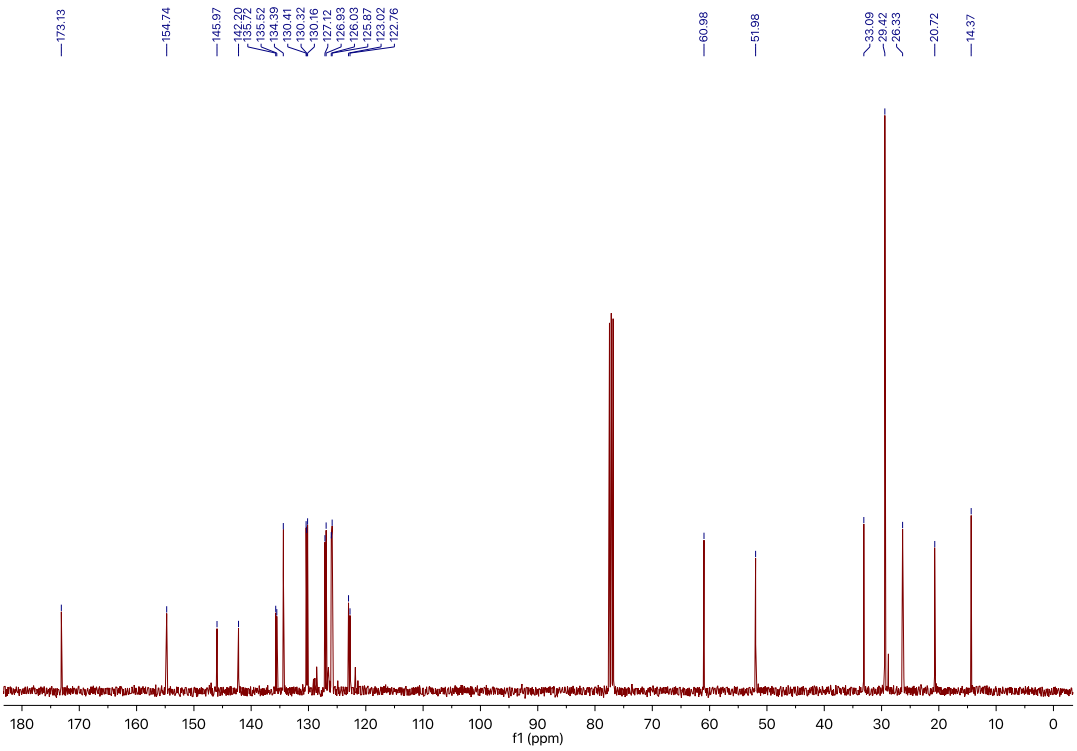
S18

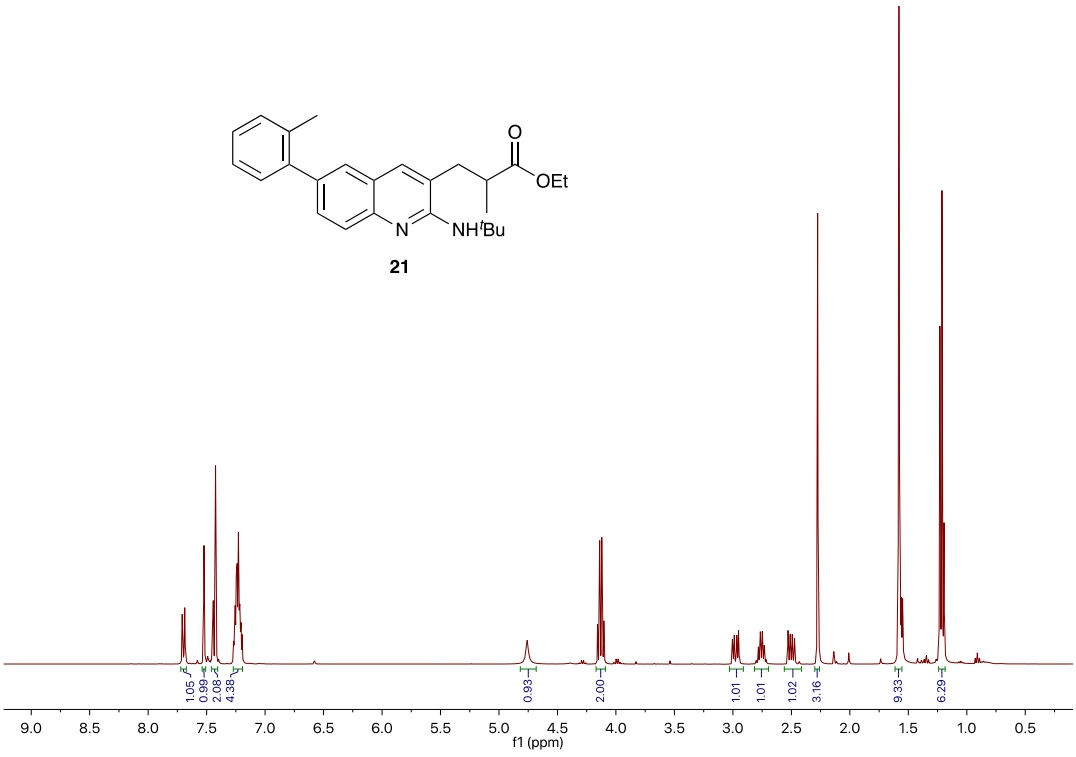

175.94
154.85
145.83
134.58
131.70
128.82
128.27
124.26
122.75
114.47
60.96
52.06
38.68
35.83
29.31
17.22
14.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OEt
N
NH^{t}Bu

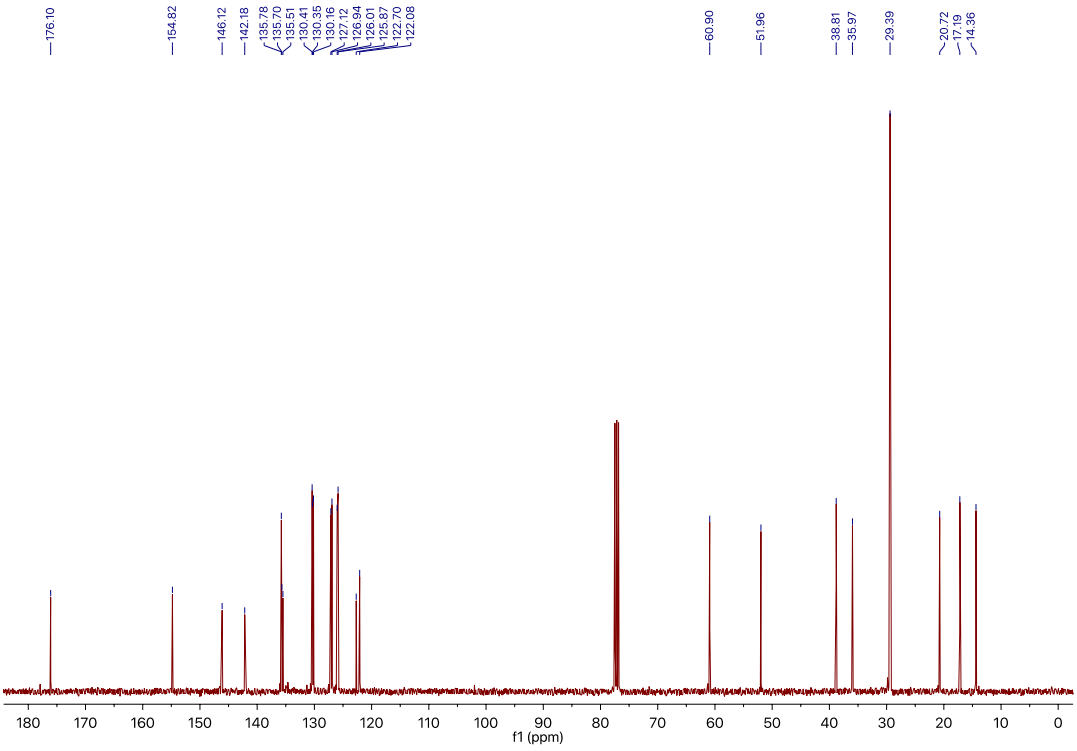
20

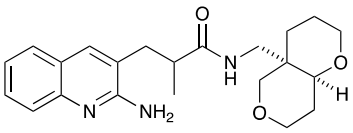
8.00
0.98
2.07
2.06
2.08
2.67
9.01
3.14
f1 (ppm)


173.13
154.74
145.97
142.20
135.72
135.52
134.39
130.41
130.32
130.16
127.12
126.93
126.03
125.87
123.02
122.76
60.98
51.98
33.09
29.42
26.33
20.72
14.37
f1 (ppm)

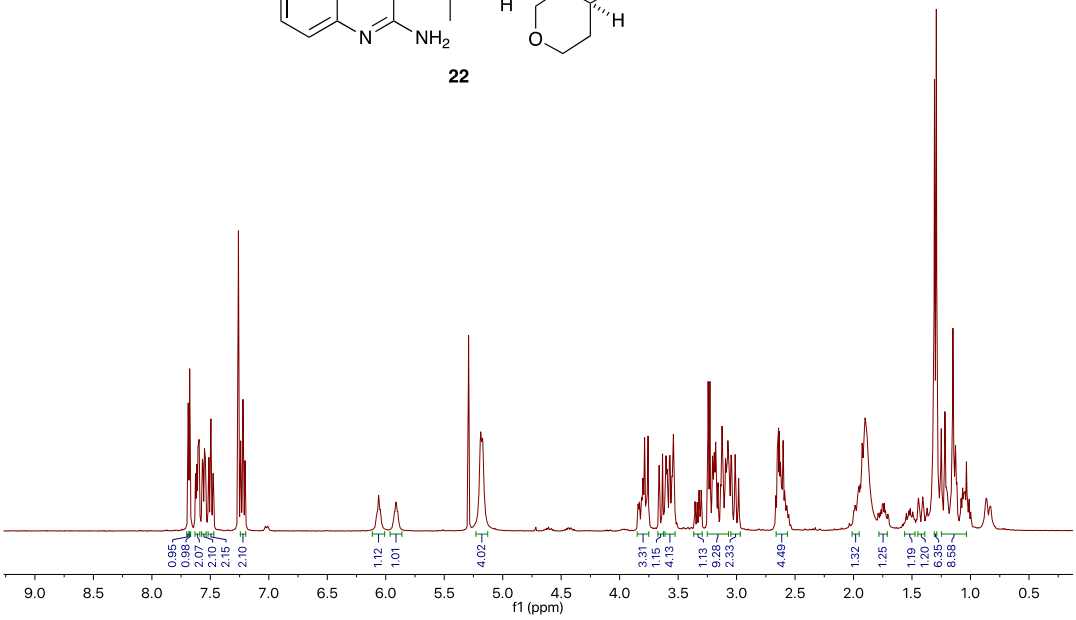

O
OEt
N
NH^{t}Bu
1.05
0.99
2.08
4.38
0.93
2.00
1.01
1.01
1.02
3.16
9.33
6.29
f1 (ppm)

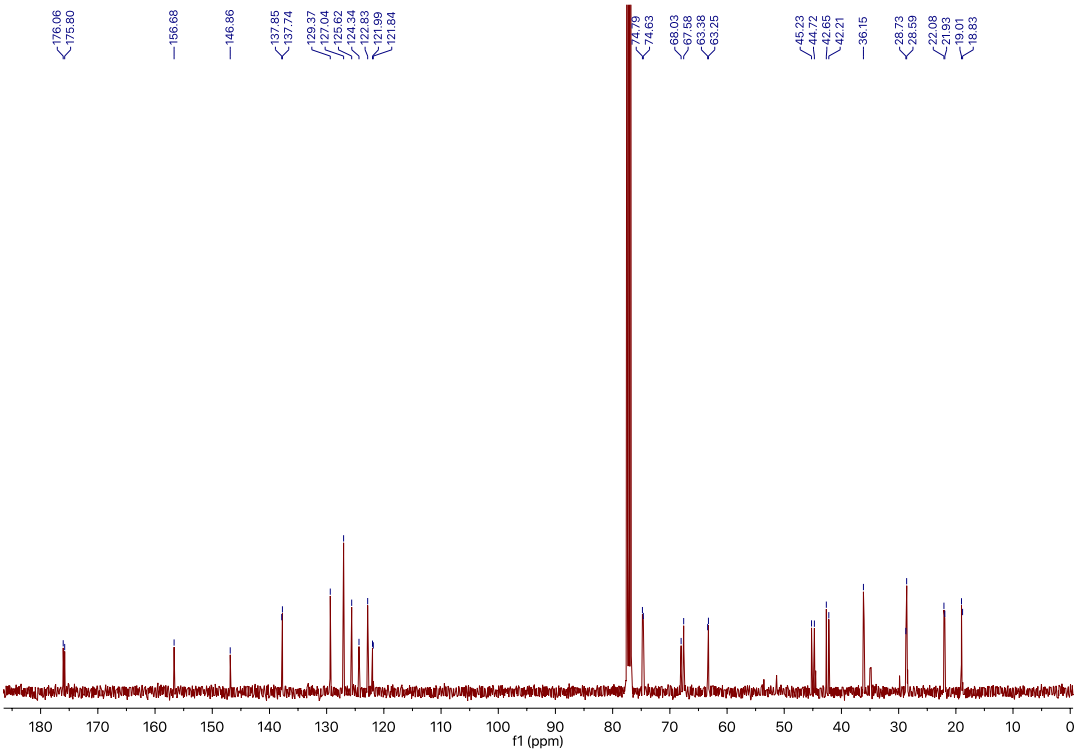
21

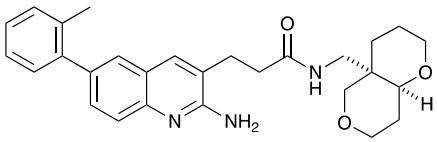

176.10
154.82
146.12
142.18
135.78
135.70
135.51
130.41
130.35
130.16
127.12
126.94
126.01
125.87
122.70
122.08
60.90
51.96
38.81
35.97
29.39
20.72
17.19
14.36
f1 (ppm)



22

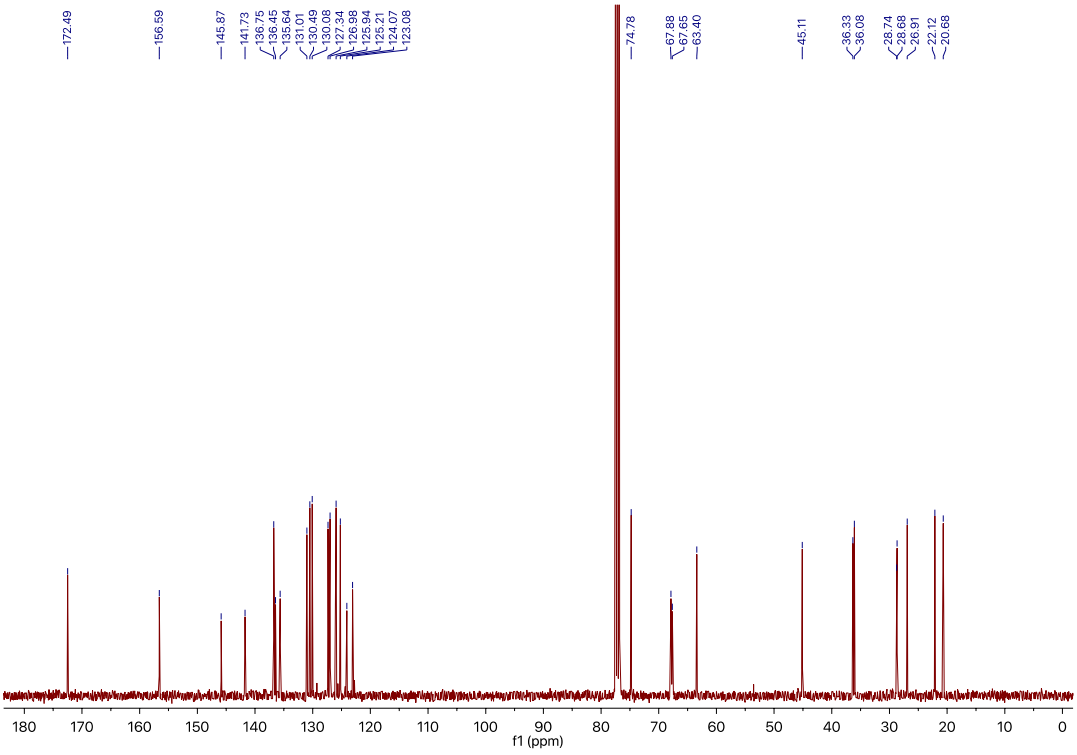

0.95
0.98
2.07
2.10
2.15
2.10
1.12
1.01
4.02
3.31
1.15
4.13
1.13
9.28
2.33
4.49
1.32
1.25
1.19
1.20
6.35
8.58
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

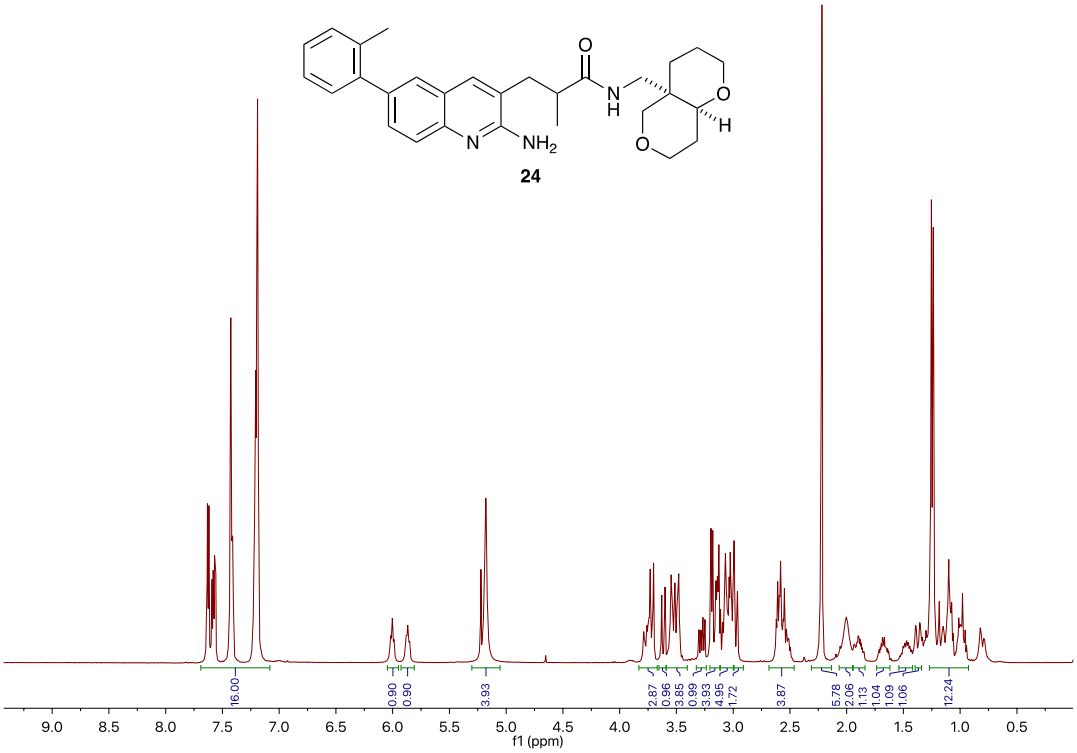

176.06
175.80
156.68
146.86
137.85
137.74
129.37
127.04
125.62
124.34
122.83
121.99
121.84
74.79
74.63
68.03
67.58
63.38
63.25
45.23
44.72
42.65
42.21
36.15
28.73
28.59
22.08
21.93
19.01
18.83
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

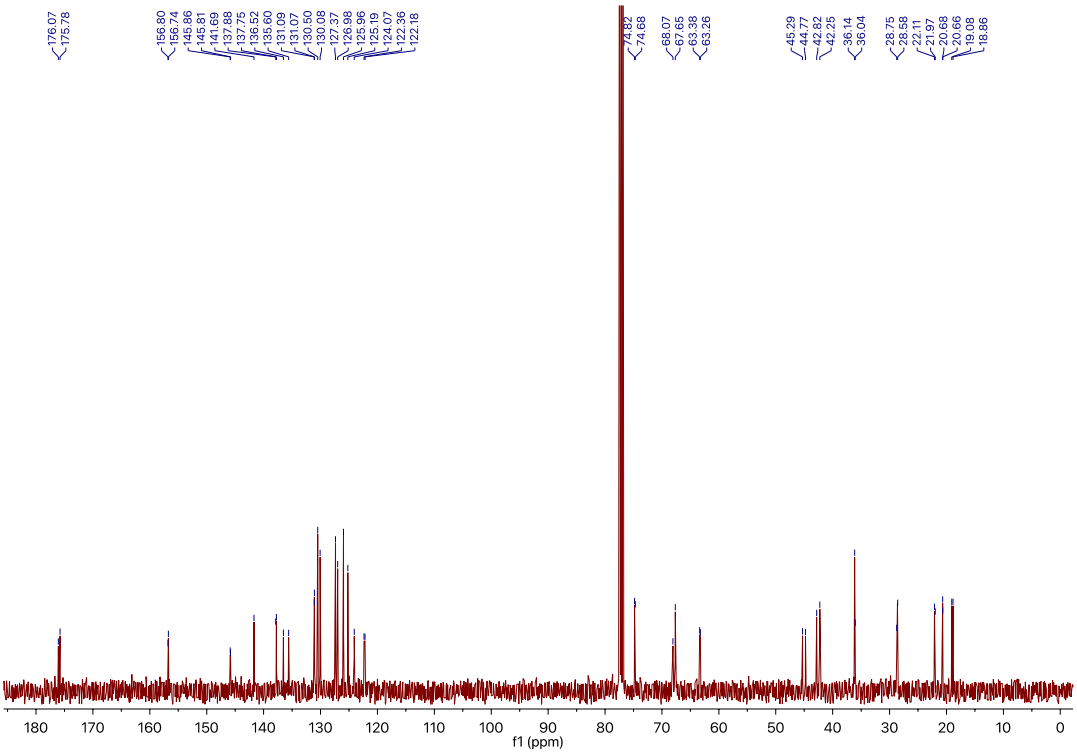


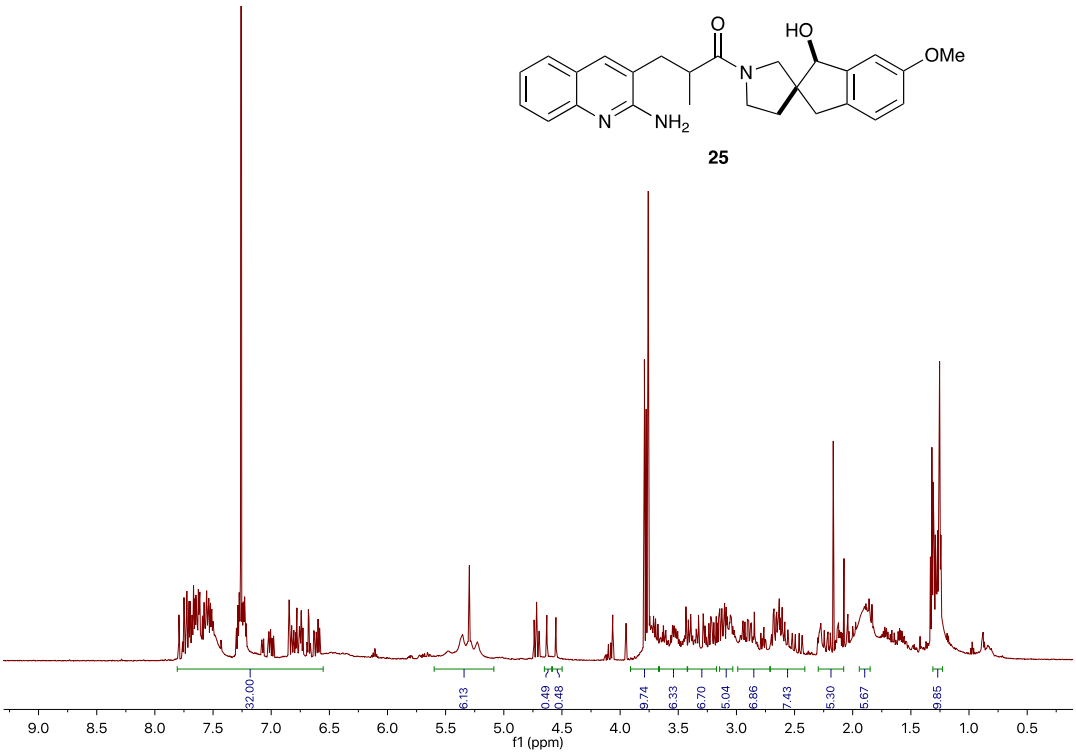
23

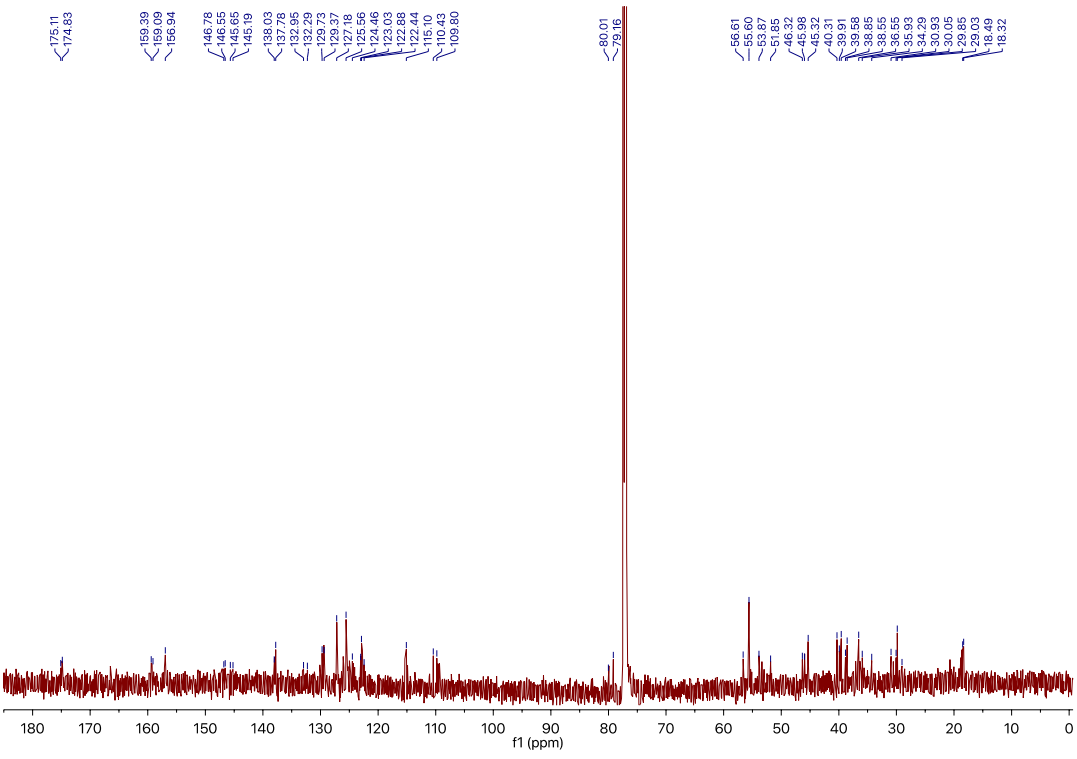
8.17
0.96
2.10
0.98
1.02
2.01
1.00
2.01
1.95
2.00
2.00
2.84
1.10
1.08
1.00
3.15
f1 (ppm)

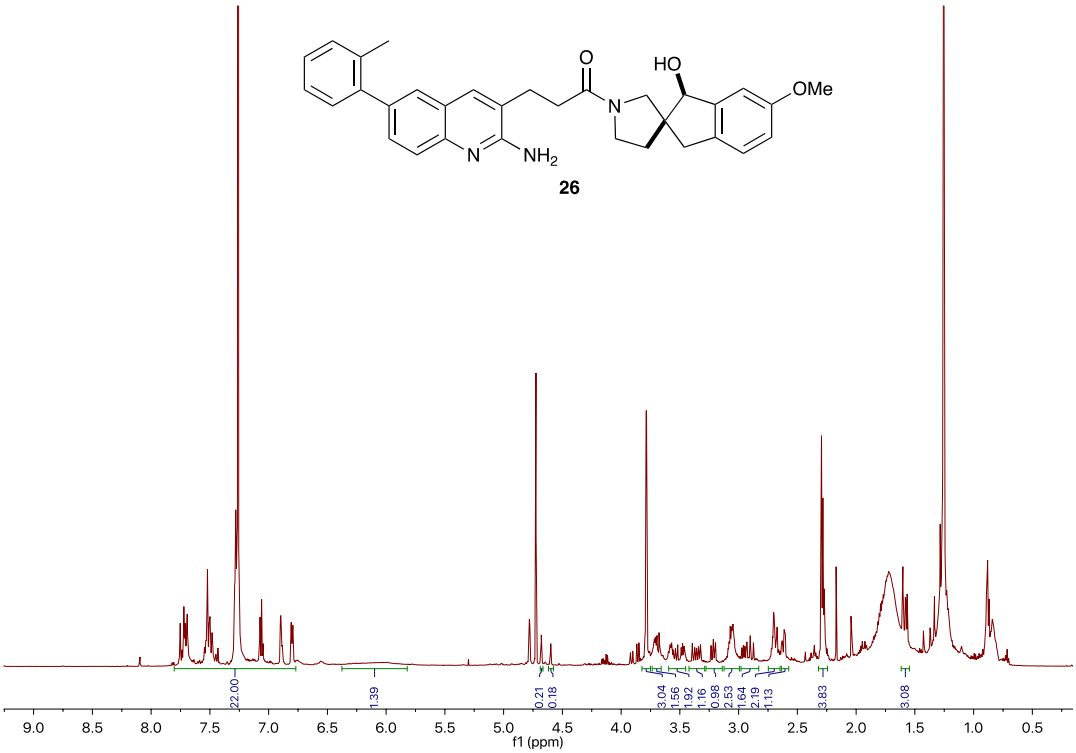

172.49
156.59
145.87
141.73
136.75
136.45
135.64
131.01
130.49
130.08
127.34
126.98
125.94
125.21
124.07
123.08
74.78
67.88
67.65
63.40
45.11
36.33
36.08
28.74
28.68
26.91
22.12
20.68
f1 (ppm)


O
N
H
O
H
N
NH2
O
24
16.00
0.90
0.90
3.93
2.87
0.96
3.85
0.99
3.93
4.95
1.72
3.87
5.78
2.06
1.13
1.04
1.09
1.06
12.24
f1 (ppm)

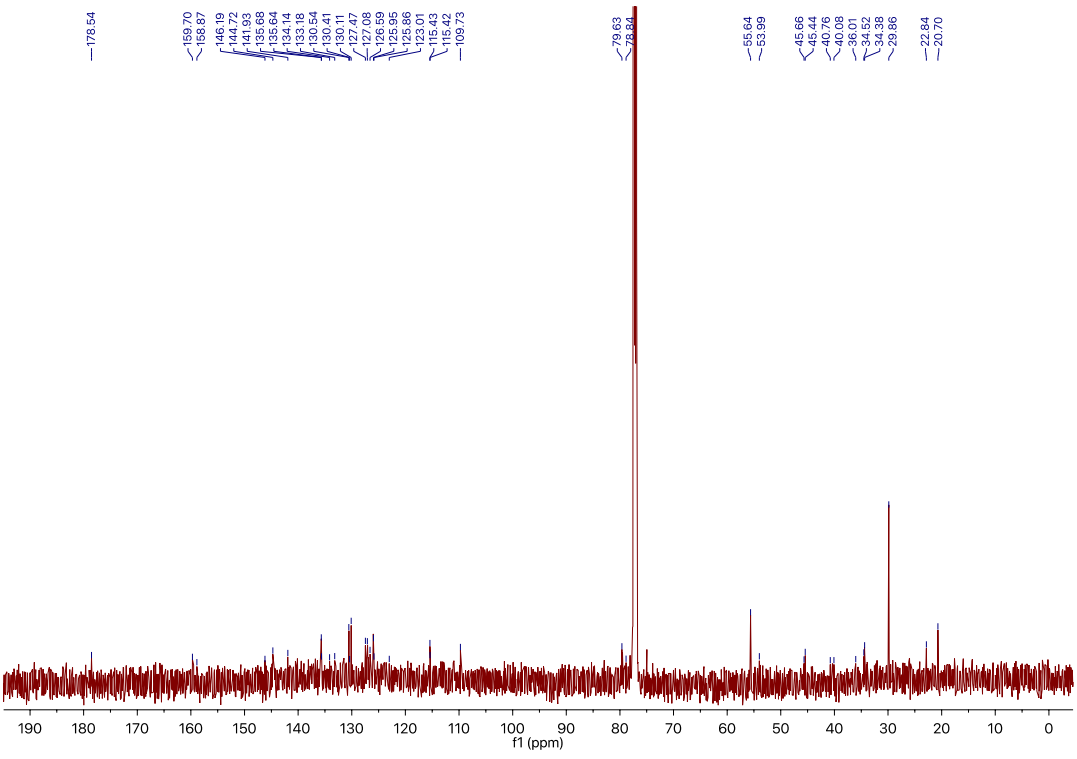

176.07
175.78
156.80
156.74
145.86
145.81
141.69
137.88
137.75
136.52
135.60
131.09
131.07
130.50
130.08
127.37
126.98
125.96
125.19
124.07
122.36
122.18
74.82
74.68
68.07
67.65
63.38
63.26
45.29
44.77
42.82
42.25
36.14
36.04
28.75
28.58
22.11
21.97
20.68
20.66
19.08
18.86
f1 (ppm)

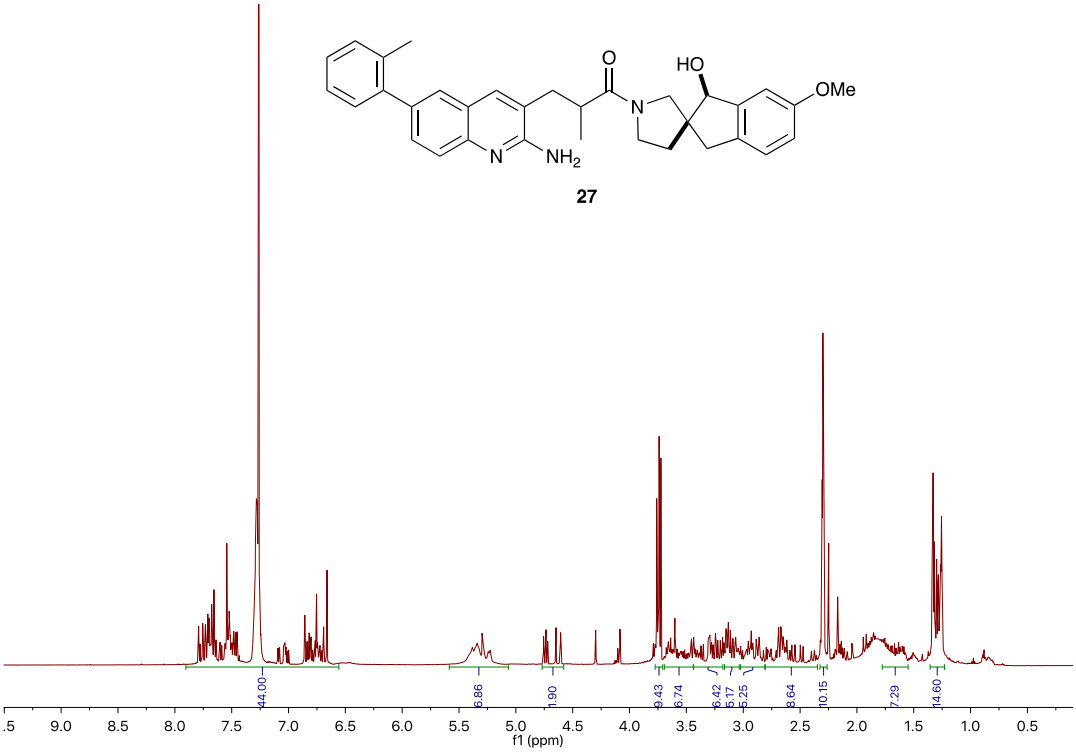

O
HO
N
OMe
N
NH2
25
32.00
6.13
0.49
0.48
9.74
6.33
6.70
5.04
6.86
7.43
5.30
5.67
9.85
f1 (ppm)


175.11
174.83
159.39
159.09
156.94
146.78
146.65
145.65
145.19
138.03
137.78
132.95
132.29
129.73
129.37
127.18
125.56
124.46
123.03
122.88
122.44
115.10
110.43
109.80
80.01
79.16
56.61
55.60
53.87
51.85
46.32
45.98
45.32
40.31
39.91
39.58
38.85
38.85
38.55
35.93
34.29
30.93
30.05
29.85
29.03
18.49
18.32
f1 (ppm)

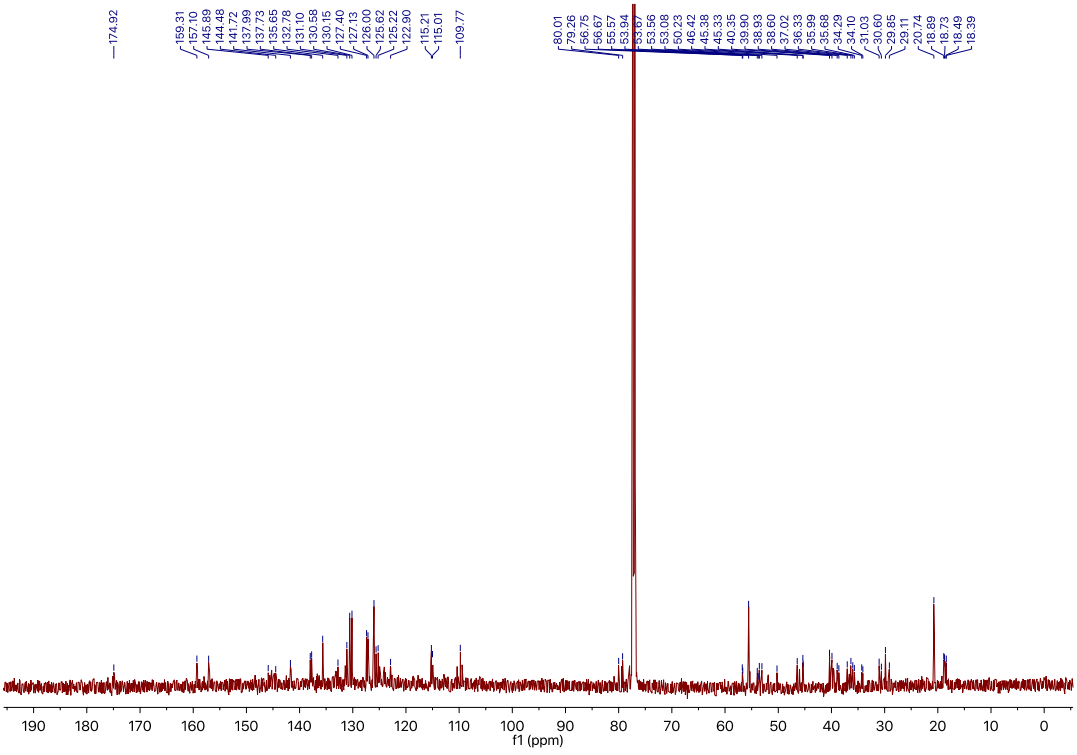

O
HO
N
OMe
N
NH2
22.00
1.39
0.21
0.18
3.04
1.56
1.92
1.16
0.98
2.53
1.64
2.19
1.13
3.83
3.08
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

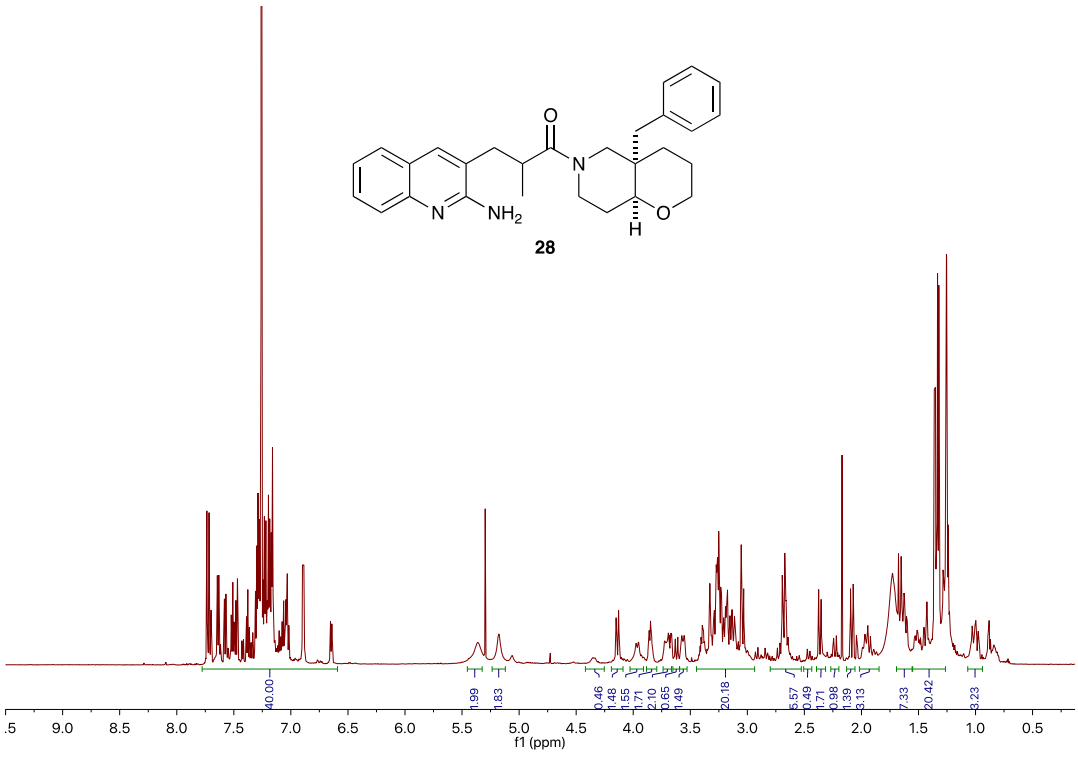
26

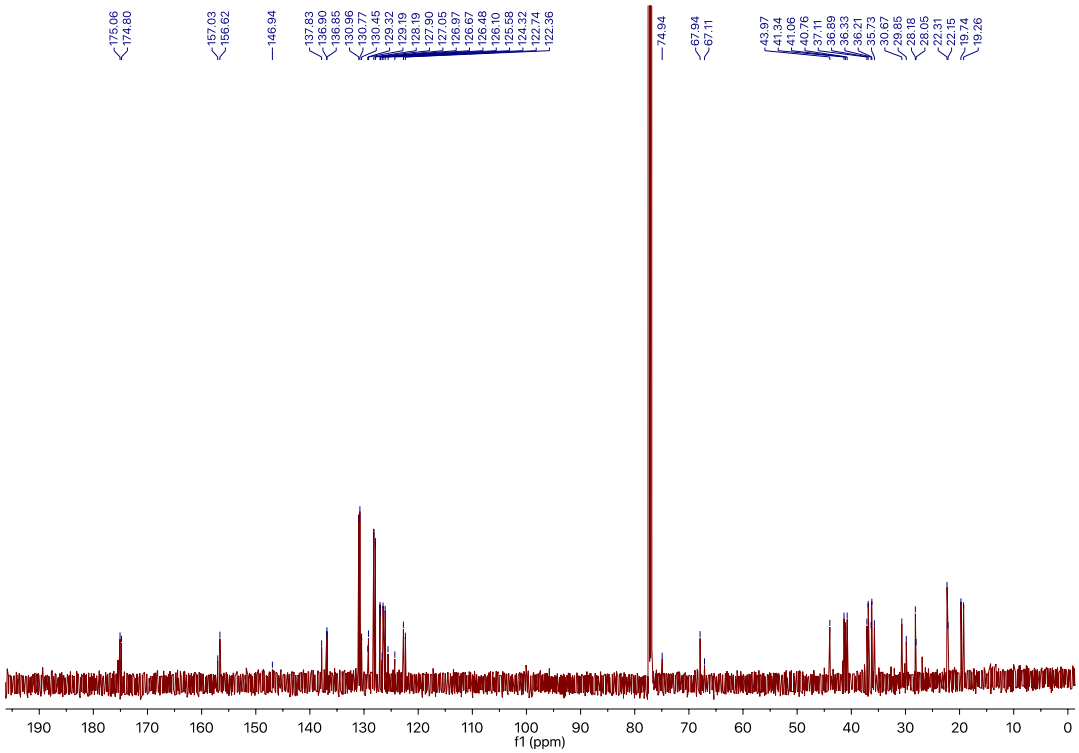

178.54
159.70
158.87
146.19
144.72
141.93
135.68
135.64
134.14
133.18
130.54
130.41
130.11
127.47
127.08
126.59
125.95
125.86
123.01
115.43
115.42
109.73
79.63
78.84
55.64
53.99
45.66
45.44
40.76
40.08
36.01
34.52
34.38
29.86
22.84
20.70
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

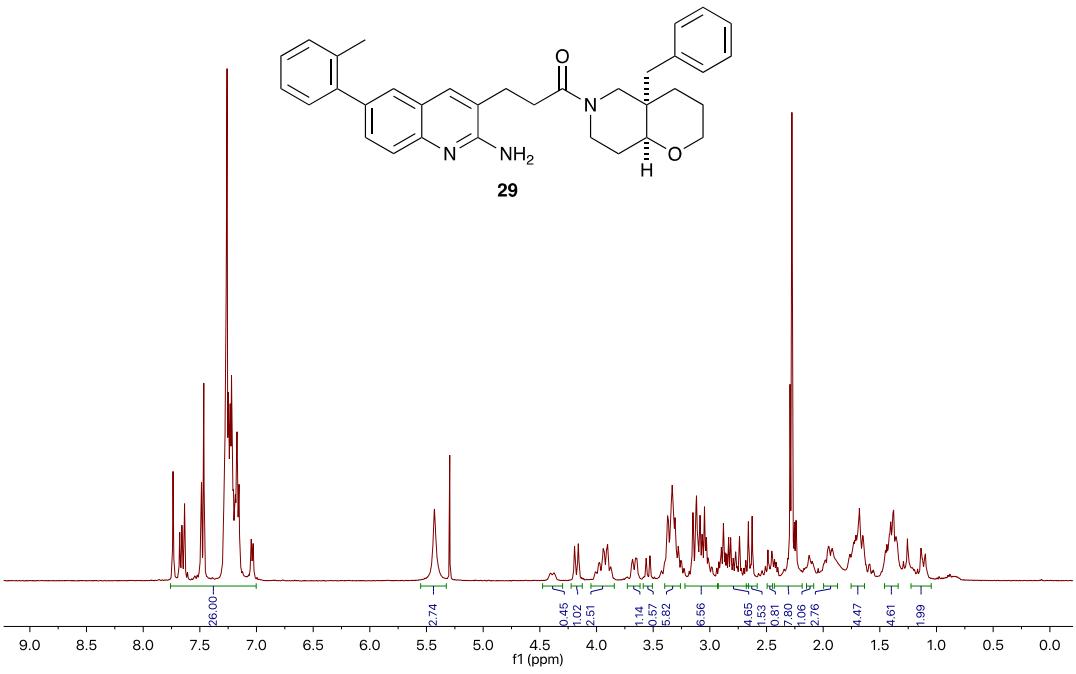

O
HO
OMe
N
N
NH2
44.00
6.86
1.90
9.43
6.74
6.42
5.17
5.25
8.64
10.15
7.29
14.60
f1 (ppm)

27

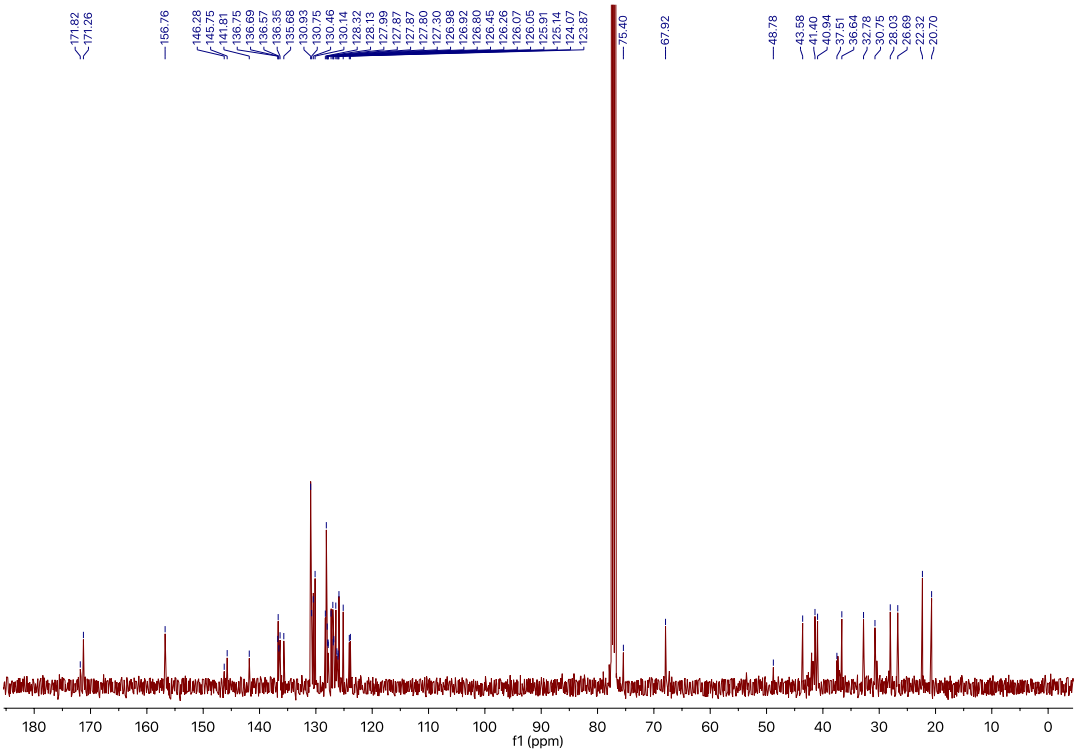

174.92
159.31
157.10
145.99
144.48
141.72
137.99
137.73
135.65
132.78
131.10
130.58
130.15
127.40
127.13
126.00
125.62
125.22
122.90
115.21
115.01
109.77
80.01
79.26
78.75
56.67
55.57
53.94
53.67
53.56
53.08
50.23
46.42
45.38
45.33
40.35
39.90
38.93
38.60
37.02
36.33
35.99
35.68
34.29
34.10
31.03
30.60
29.85
29.11
20.74
18.89
18.73
18.49
18.39
f1 (ppm)


O
N
N
NH2
H
O
28
40.00
1.99
1.83
0.46
1.48
1.55
1.71
2.10
0.65
1.49
20.18
5.57
0.49
1.71
0.98
1.39
3.13
7.33
20.42
3.23
f1 (ppm)


175.06
174.80
157.03
156.62
146.94
137.83
136.90
136.85
130.96
130.77
130.45
129.32
129.19
128.19
127.90
127.05
126.97
126.67
126.48
126.10
125.58
124.32
122.74
122.36
74.94
67.94
67.11
43.97
41.34
41.06
40.76
37.11
36.89
36.33
36.21
35.73
30.67
29.85
28.18
28.05
22.31
21.15
19.74
19.26
f1 (ppm)


O
N
N
NH2
O
H
26.00
2.74
0.45
1.02
2.51
1.14
0.57
5.82
6.56
4.65
1.53
0.81
7.80
1.06
2.76
4.47
4.61
1.99
f1 (ppm)

29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156.76
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141.81
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136.69
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135.35
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130.75
130.46
130.14
128.32
128.13
127.99
127.87
127.87
127.80
127.30
126.98
126.92
126.80
126.45
126.26
126.07
126.05
125.91
125.14
124.07
123.87
75.40
67.92
48.78
43.58
41.40
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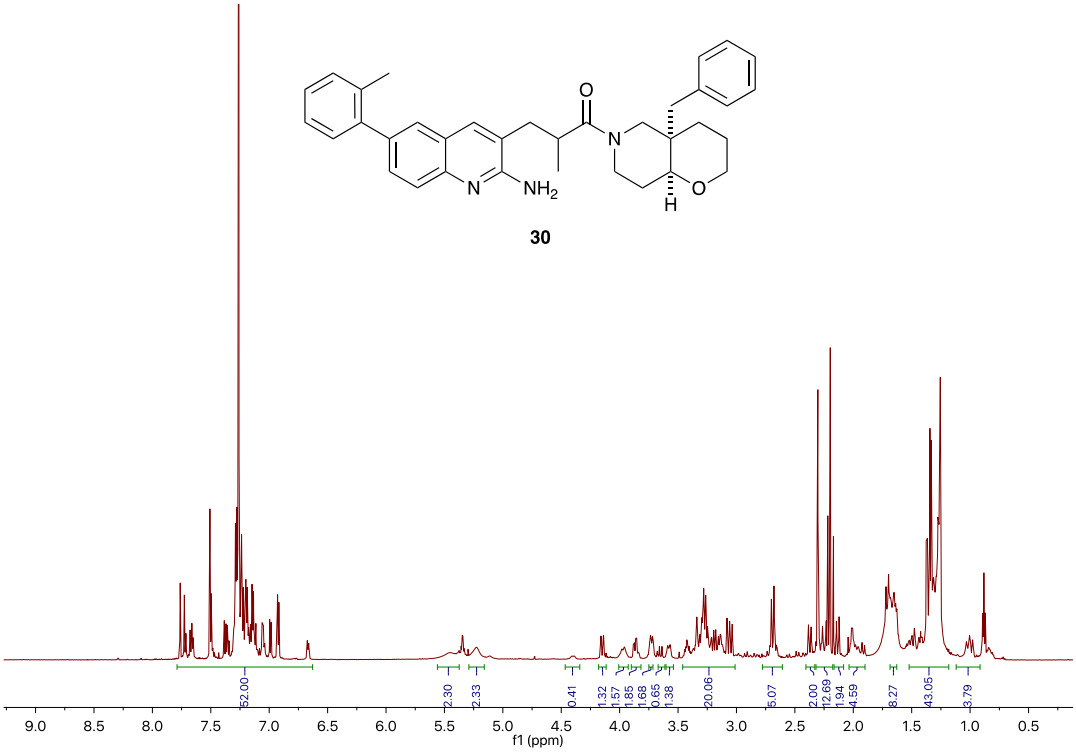
36.64
32.78
30.75
28.63
26.69
22.32
20.70
f1 (ppm)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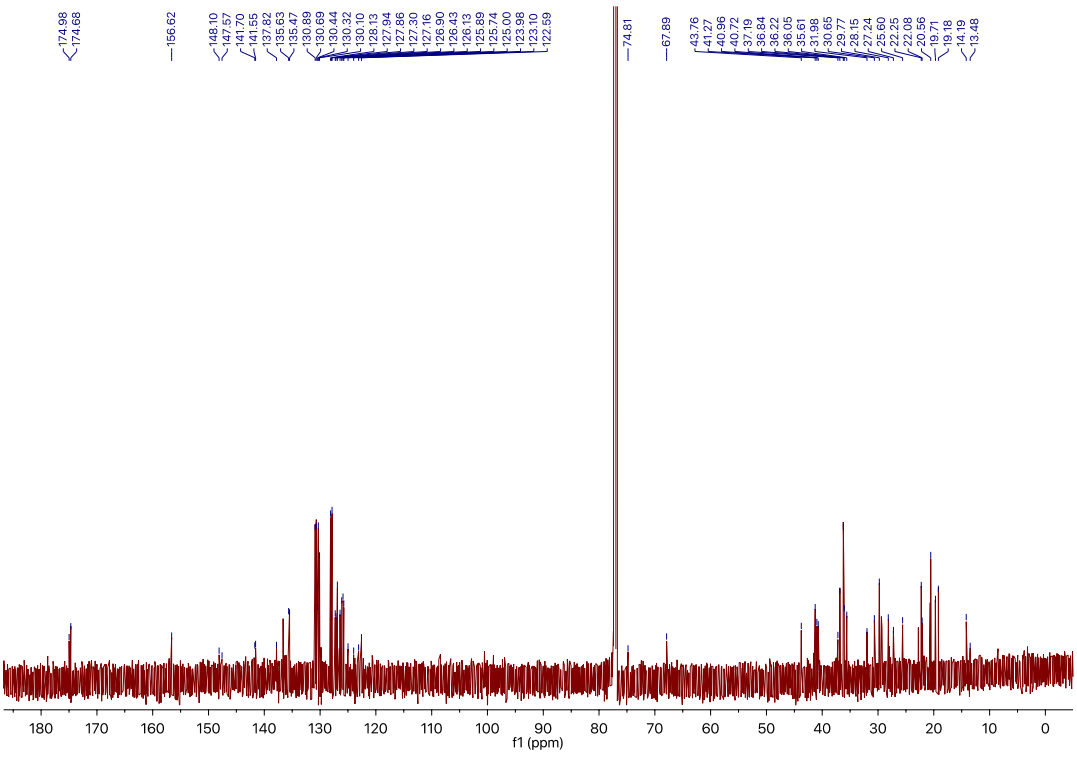
N
N
NH2
H
O
52.00
2.30
2.33
0.41
1.32
1.57
1.85
1.68
0.65
1.38
20.06
5.07
2.00
12.69
1.94
4.59
8.27
43.05
3.79
f1 (ppm)

30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174.68
156.62
148.10
147.57
141.70
141.55
137.82
135.63
135.47
130.89
130.89
130.44
130.32
130.10
128.13
127.94
127.86
127.30
127.16
126.90
126.43
126.13
125.89
125.74
125.00
123.98
123.10
122.59
74.81
67.89
43.76
41.27
40.96
40.72
37.19
36.84
36.22
36.05
35.61
31.98
30.65
29.77
28.15
27.24
25.60
22.25
22.08
20.56
19.71
19.18
14.19
13.48
f1 (ppm)

2. Determination of biological activity

2.1. Experimental for the determination of the biological activity

The derived compounds were assessed using a BACE1 red-shifted fluorescence-quenching assay kit supplied from ThermoFisher Scientific (PanVera®, Part Number P2985).[6] The kit was composed of a “Swedish” mutant APP peptide tagged with a rhodamine derivative (fluorescence donor) and a propietary quenching acceptor (rhodamine-EVNLDAEFK-quencher) in a 75 μM aqueous solution of 50 mM ammonium bicarbonate (PanVera®, Part Number P2986); purified baculovirus-expressed BACE1 in a 50 mM aqueous solution of tris(hydroxymethyl) aminomethane (pH 7.5) with 10% glycerol (PanVera®, Part Number P2947); and an assay buffer of 50 mM aqueous solution of sodium acetate (pH 4.5) (PanVera®, Part Number P2948). The assay was performed using black 384 round-bottom well plates (Corning®, Part number 4514).

The assay procedure was adapted from an existing protocol.[6] The BACE1 solution and the substrate solution provided were diluted in assay buffer to obtain 1 protein unit/mL and a 750 nM solution, respectively, as working solutions. The corresponding derived molecules were dissolved in DMSO (supplied by Sigma–Aldrich) to obtain a 200 mM or 100 mM solution. Lower concentrations of the derived compounds were achieved by serial dilution in DMSO in 10–12 steps to obtain different concentrations until 0.30 mM. Finally, each concentration in DMSO was diluted 100-fold with assay buffer to obtain the working solutions. For determination of inhibition activity, 5 μL of each of the working solutions (compound, BACE1 and substrate) was added to each well to obtain a total volume of 15 μL/well. For the positive control, a 1% DMSO solution in assay buffer was used instead of the working solution of the compounds. For the negative control, 1% DMSO solution in assay buffer and assay buffer were used instead of the working solutions of the compounds and BACE1. The compounds were added to the wells first, followed by the protein and 20 min later by the substrate. Each well was repeated in triplicate (Figure 2). The enzyme inhibition was measured at 25 ℃ by quantifying the fluorescence released using an Envision™ 2013 multilabel plate reader

(PerkinElmer), with BODIPY TMR mirror, $\lambda_{excitation}$ = 531 nm and $\lambda_{emission}$ = 595 nm. The measurements were taken every minute over 2 h.

A

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	24
A	The 13 derived compounds in																	
B	concentrations of 100 μM in triplicate																	
C	(each compound in a different column)																	
D																		
E	+	–																
F																		
G																		
P																		

B

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	24
A	Selected compound in concentrations from																	
B	up to 0.67 mM to 33.3 pM in triplicate																	
C	(each concentration in a different column)																	
D																		
E	+	–																
F																		
G																		
P																		

Figure 2: Well plate layout to assess BACE1 inhibition. The + and – means positive and negative control, respectively. Positive control does not contain compounds and negative control does not contain protein nor compounds. **Panel A:** First fluorescence-quenching assay to identify if the derived compounds **2** and **7**–**18** were inhibitors at 100 μM. **Panel B:** Successive fluorescence-quenching assays to determine the IC_{50} of the inhibitors **9**, **10** and **14** identified in the previous assay in panel A, the reference inhibitor **2** and the successive optimised inhibitors **22**–**30**.

All the data was processed using Graphpad Prism V.6 (Graphpad Software Inc. CA). To process the data the average value of fluorescence unit for each compound at the specific concentration, for the negative control and for the positive control was plotted against the time. A linear fit was applied, the slopes were obtained and the % of inhibition was determined (Equation 1).

$$\frac{\text{Compound slope–Positive control slope}}{\text{Negative control slope–Positive control slope}} \times 100$$

Equation 1: Calculation of the % of inhibition from the slopes.

The % of inhibition was reported as mean of the triplicate ± SEM (standard error of the mean). The dose-response data, expressed as % of inhibition vs log[compound] was represented with a sigmoidal dose-response model. This sigmoidal dose-response model allowed the determination of the IC_{50} (Table 1). The values were calculated from three independent experiments.

Derived compound	pIC_{50} ± SEM	IC_{50} (μM)
2	4.51 ± 0.06	31
9	4.26 ± 0.01	55
10	4.54 ± 0.02	29
14	4.07 ± 0.01	84
22	4.48 ± 0.08	34
23	7.11 ± 0.07	0.12
24	7.51 ± 0.06	0.031
25	5.43 ± 0.02	3.7
26	5.21 ± 0.06	6.1
27	5.29 ± 0.06	5.1
28	4.47 ± 0.03	34
29	5.50 ± 0.03	3.2
30	5.57 ± 0.03	2.7

Table 1: IC_{50} values for the active compounds obtained from the sigmoidal dose-response models. Normalised to negative and positive controls.

2.2. Sigmoidal dose-response models

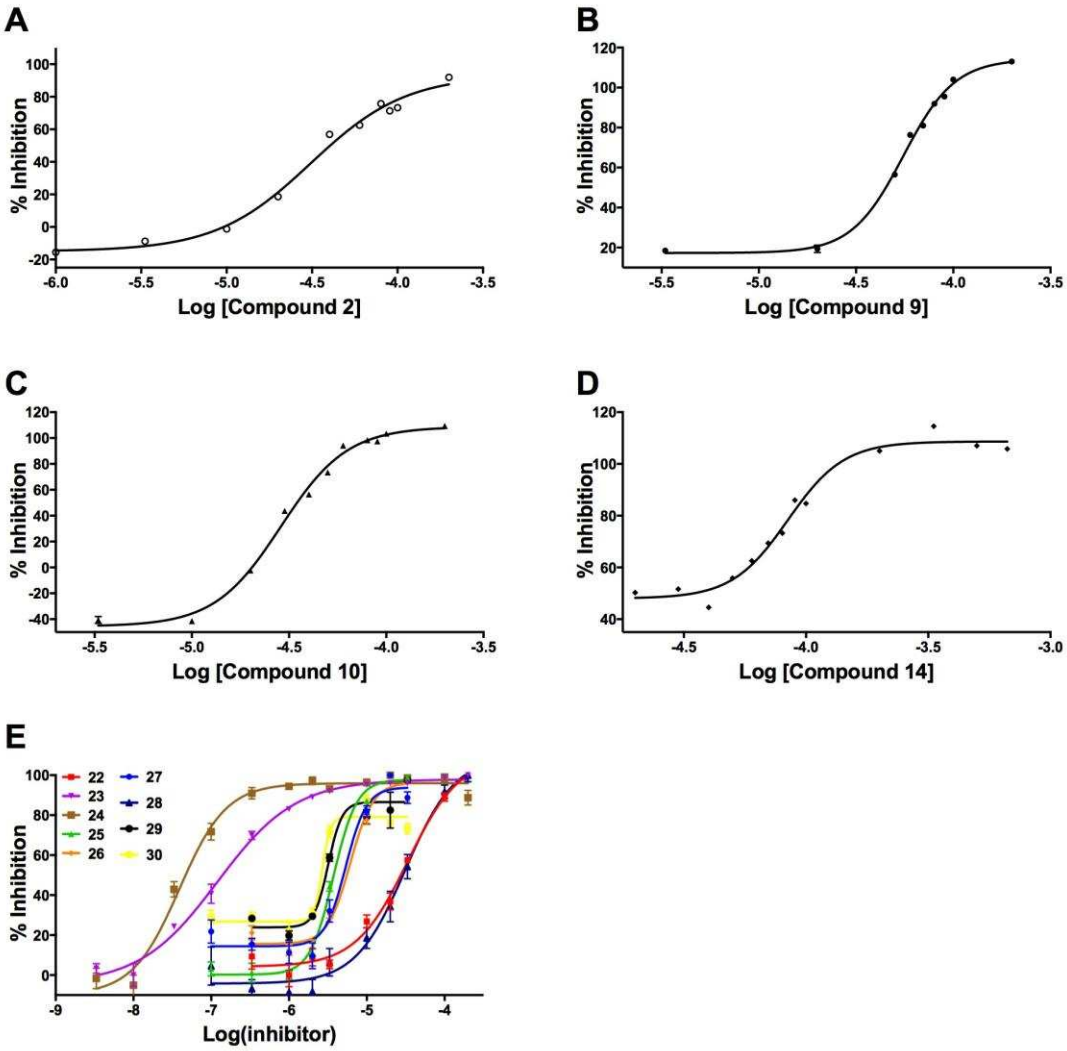


Figure 3: Sigmoidal dose-response models for the corresponding BACE1 inhibitors.

3. CNS drug–likeness

The CNS drug-likeness scores of compounds **3**–**4** and **23**–**24** were calculated using a literature procedure.[7]

4. Docking studies

4.1. Molecular docking studies

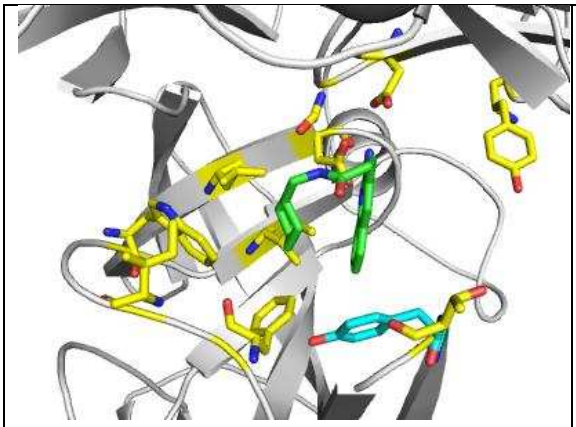
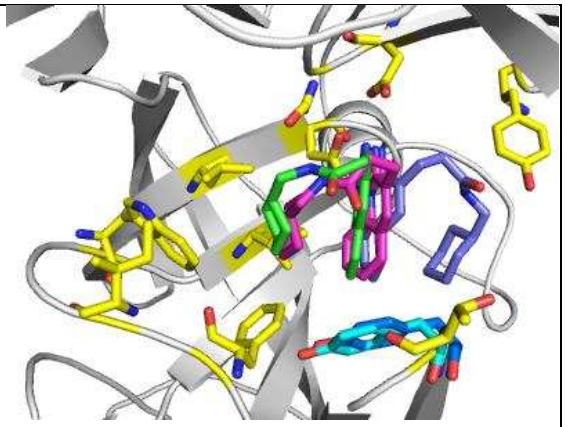
Protein preparation and molecular docking were carried out using GoldSuite ('Genetic Optimisation for Ligand Docking'; The Cambridge Crystallographic Data Centre, United Kingdom).[8] Protein structures were extracted from RCSB Protein Data Bank (RCSB.org) and subsequently prepared for docking using Hermes 1.9.3. Hydrogen atoms were first added to the protein structure, followed by removal of water molecules and ligand(s). Molecular docking was performed using Gold 5.6.3. The binding site was defined based on the conserved catalytic residues (Asp32 and Asp228) with a defined radius of 12 Å. Due to reported high mobility of Tyr71[2], side chain flexibility was introduced and four possible side chain rotamers (Table 2) were generated prior to docking. Two additional docking constraints based on previous protein co-crystal structures were introduced: (1) Asp32 and Asp228 were required to form H-bond(s), and (2) 2-aminoquinoline (PDB: 2OHL) was used as substructure template. The model was examined using PyMOL (version 2.0 Schrödinger, LLC) through visual inspection.[9]

Rotamer (Tyr71)	Chi 1	Delta 1	Chi 2	Delta 2
1	62	13	90	13
2	-177	11	80	14
3	-65	11	-85	21
4	-65	11	-30	18

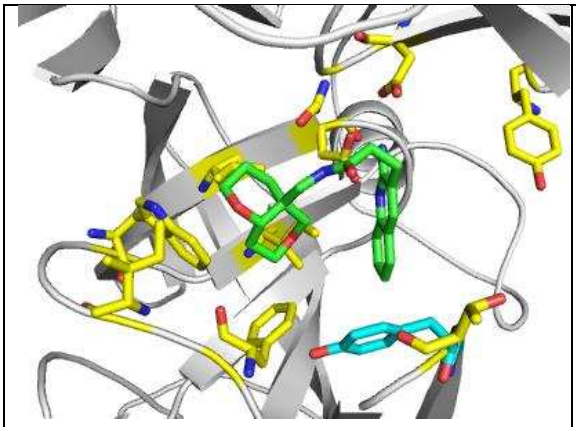
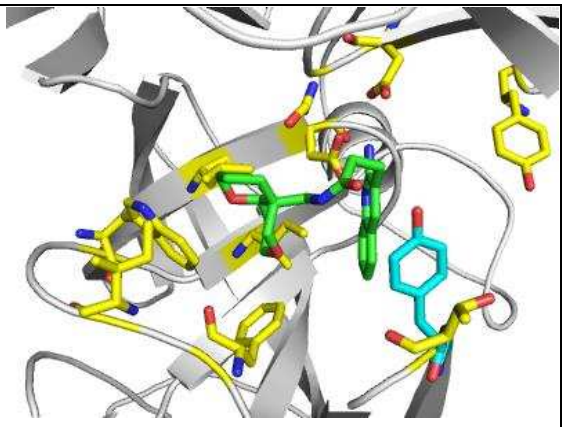
Table 2: Rotamers of Tyr71 used in GOLD docking studies. Chi and delta are dihedral angles.

4.2. Docked poses of compounds

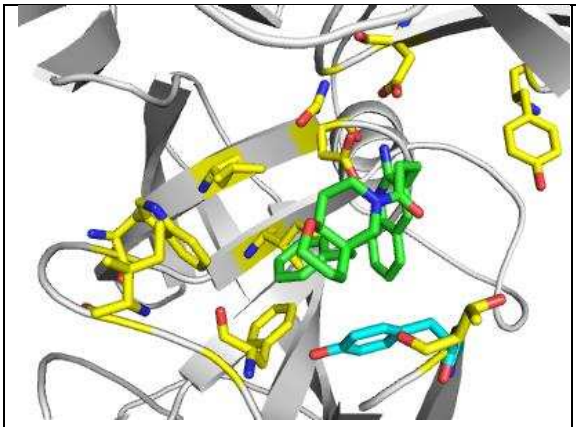
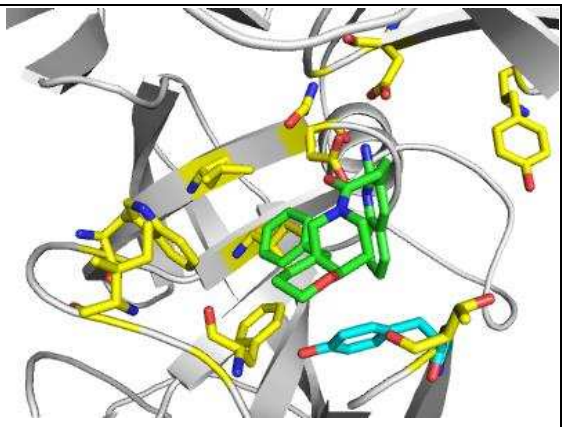
Compound 2

	
Docked pose of **2** **Tyr71 (cyan)**	Superimposition of **2** (Tyr71 in cyan) with PDB:3RU1 (Tyr71 in blue)

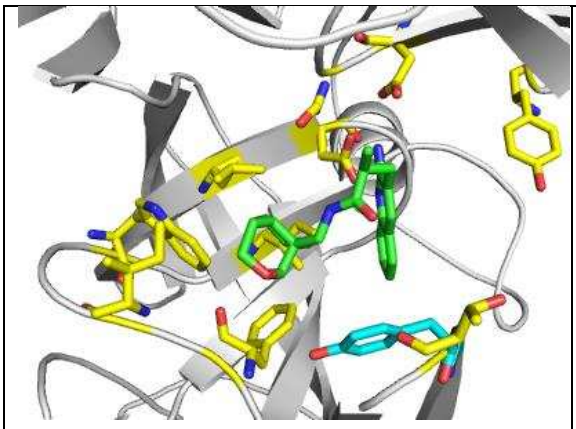
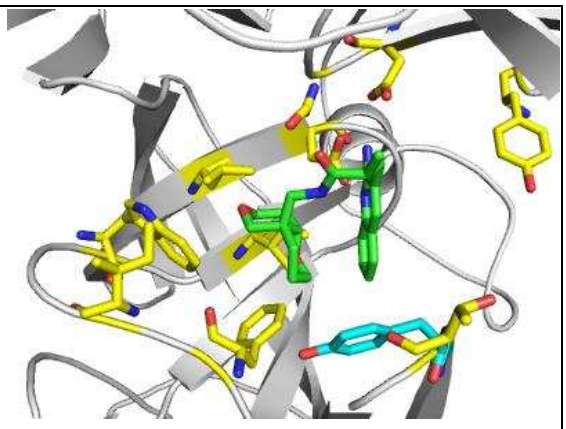
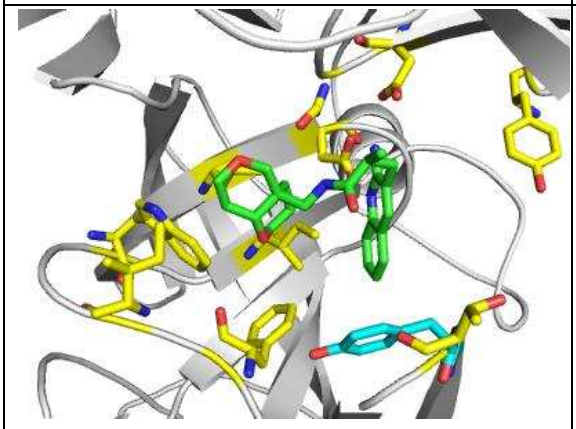
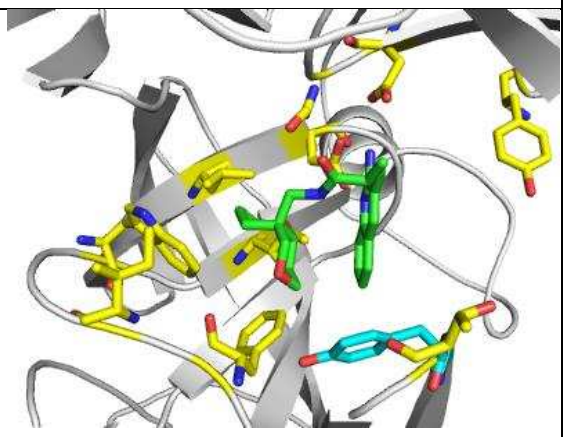
Compound 10

	
[S,S]	[R,R]

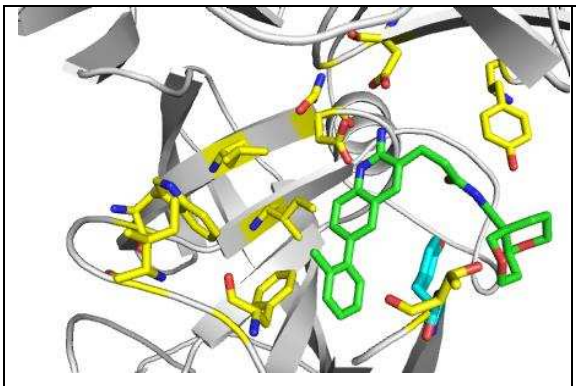
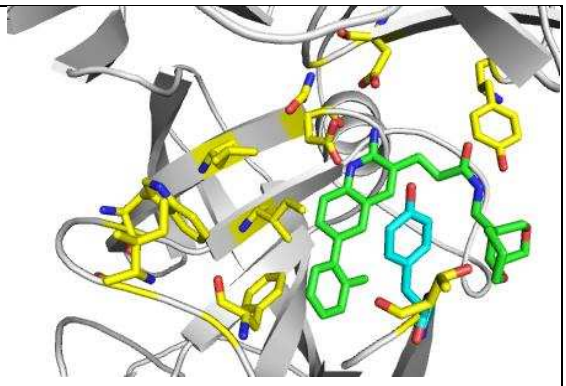
Compound 14

	
[S,S]	[R,R]

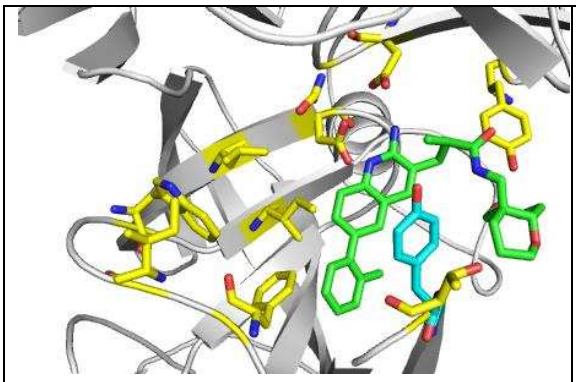
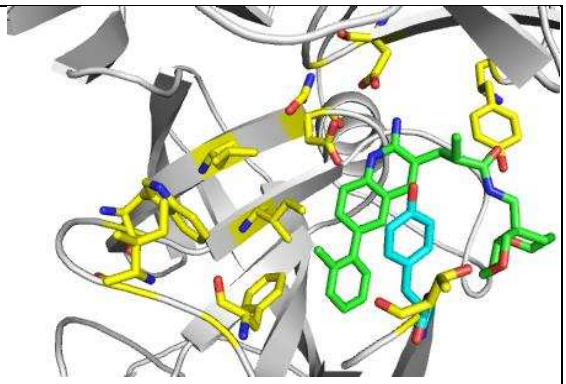
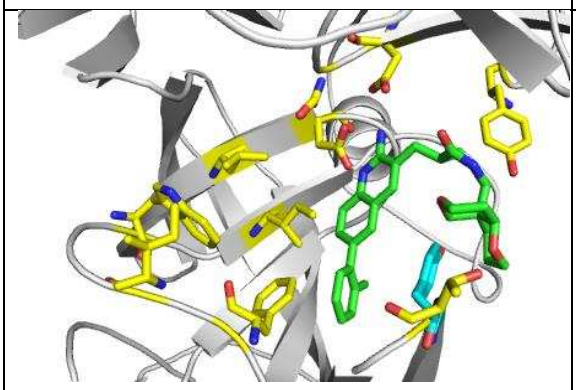
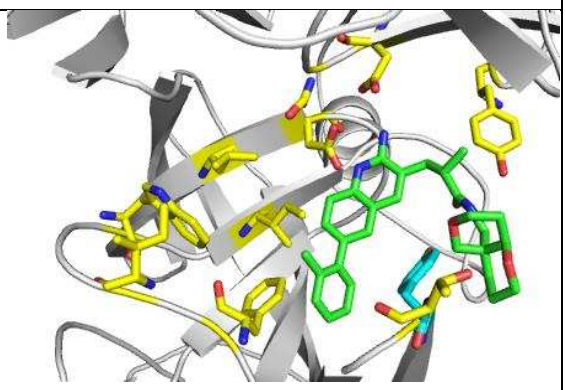
Compound 22

	
S-Methyl, [S,S]	R-Methyl, [S,S]
	
S-Methyl, [R,R]	R-Methyl, [R,R]

Compound 23

	
[S,S]	[R,R]

Compound 24

	
S-Methyl, [S,S]	R-Methyl, [S,S]
	
S-Methyl, [R,R]	R-Methyl, [R,R]

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