Supplementary Material

Synthesis, modeling and functional activity of substituted styrene-amides as small-molecule CXCR7 agonists

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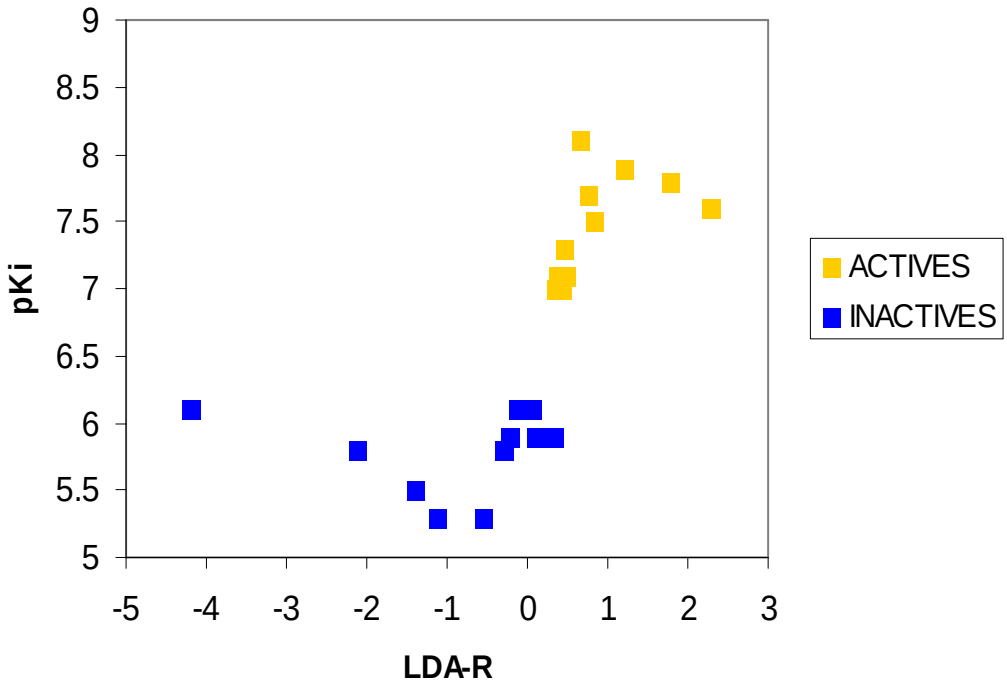


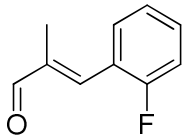
Figure S1. Scatter plot of LDA-R vs. pK_i showing the discrimination between actives and inactives for CXCR7. Positive values of LDA-R score indicate a candidate that is predicted to be active. Negative values are assigned by linear discriminant analysis when a candidate is predicted as inactive.

Synthesis.

General notes and general procedures A-E

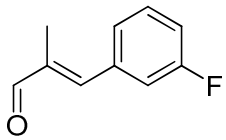
These can be found in the Experimental Section of the Main Text.

Aldol reaction



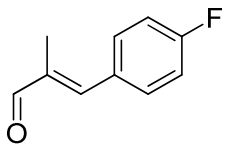
(E)-3-(2-Fluorophenyl)-2-methylacrylaldehyde (4b).

The general procedure A was followed, using 2-fluorobenzaldehyde (1.74 g, 14.0 mmol), 1-propanal (0.85 g, 14.6 mmol) and KOH (0.08 g, 1.4 mmol). The crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a yellow oil (1.57 g, 68 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.67 (s, 1H), 7.60-7.51 (m, 1H), 7.50-7.38 (m, 2H), 7.29-7.12 (m, 3H), 2.03 (s, 3H).



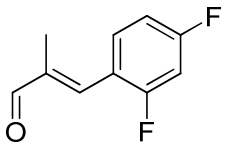
(*E*)-3-(3-Fluorophenyl)-2-methylacrylaldehyde (4c).

The general procedure A was followed, using 3-fluorobenzaldehyde (2.00 g, 16.1 mmol), 1-propanal (0.98 g, 16.9 mmol) and KOH (0.09 g, 1.6 mmol). The crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a yellow oil (2.07 g, 78 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ δ 9.45 (s, 1H), 7.36-7.26 (m, 1H), 7.22-6.91 (m, 5H), 1.95 (s, 3H).



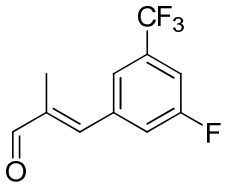
(*E*)-3-(4-Fluorophenyl)-2-methylacrylaldehyde (4d).

The general procedure A was followed, using 4-fluorobenzaldehyde (1.74 g, 14.0 mmol), 1-propanal (0.85 g, 14.6 mmol) and KOH (0.08 g, 1.4 mmol). The crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a yellow oil (1.00 g, 44 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.61 (s, 1H), 7.62-7.53 (m, 2H), 7.30-7.13 (m, 3H), 2.09 (s, 3H).



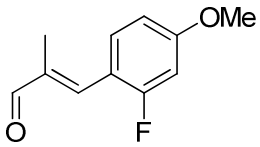
(*E*)-3-(2,4-Difluorophenyl)-2-methylacrylaldehyde (4e).

The general procedure A was followed, using 2,4-difluorobenzaldehyde (1.99 g, 14.0 mmol), 1-propanal (0.85 g, 14.6 mmol) and KOH (0.08 g, 1.4 mmol). The crude product was purified by recrystallization from hot methanol to give yellow crystals (1.22 g, 48 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (s, 1H), 7.58-7.48 (m, 1H), 7.36 (s, 1H), 7.02-6.87 (m, 2H), 2.02 (s, 3H).



(*E*)-3-(3-Fluoro-5-(trifluoromethyl)phenyl)-2-methylacrylaldehyde (4f).

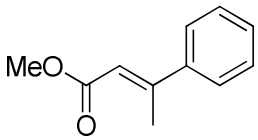
The general procedure A was followed, using 3-fluoro-5-trifluoromethylbenzaldehyde (2.00 g, 10.4 mmol), 1-propanal (0.63 g, 10.8 mmol) and KOH (0.06 g, 1.1 mmol). The crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a yellow oil (1.57 g, 65 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.52 (s, 1H), 7.46 (s, 1H), 7.34-7.29 (m, 1H), 7.20-7.09 (m, 2H), 1.95 (s, 3H).



(*E*)-3-(2-Fluoro-4-methoxyphenyl)-2-methylacrylaldehyde (4g).

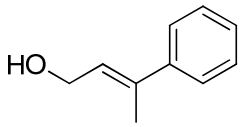
The general procedure A was followed, using 2-fluoro-4-methoxybenzaldehyde (0.71 g, 4.6 mmol), 1-propanal (0.28 g, 4.8 mmol) and KOH (0.02 g, 0.36 mmol). The crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a white solid (0.45 g, 50 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.46 (s, 1H), 7.43 (t, 1H, J=8.5 Hz), 7.26 (s, 1H), 6.71-6.57 (m, 2H), 3.73 (s, 3H), 1.92 (s, 3H).

Other aldehydes



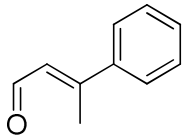
(*E*)-Methyl 3-phenylbut-2-enoate (5).

Acetophenone (1.62 g, 13.51 mmol) was mixed with methyl (triphenylphosphoranylidene) acetate (4.0 g, 11.96 mmol). The mixture was heated at 160°C overnight while stirring. After cooling, the crude product was purified by column chromatography (9.5:0.5, n-hexane: EtOAc) to give a brown oil (0.74 g, 35%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.39 (m, 2H), 7.33-7.22 (m, 3H), 6.12 (s, 1H), 3.69 (s, 3H), 2.55 (s, 3H).



(*E*)-3-Phenylbut-2-en-1-ol (6).

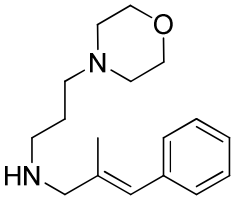
$LiAlH_4$ (0.27 g, 7.2 mmol) was added to dry diethylether (64 mL). Ester **5** (0.64 g, 3.63 mmol) was mixed with dry diethylether (1.8 mL) and the resulting solution was added dropwise to the LAH mixture at a temperature of -10°C. The mixture was stirred for 30 min at -10°C, after which TLC showed full conversion. The mixture was quenched with water (100 mL) and a solution of cold aq. H_2SO_4 (10%, 50 mL) was added. Extraction was performed with EtOAc (3x). The combined organic layers were washed with water (2x), with a solution of aq. K_2CO_3 (10%, 3x) and with water (2x). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a yellow oil (0.52 g, 97 %). It is noted that use of ether as solvent is important in this reaction, as use of THF led to side products. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.32-7.16 (m, 5H), 5.92-5.85 (m, 1H), 4.26 (d, 2H, J=6.25 Hz), 1.99 (s, 3H).



(*E*)-3-Phenylbut-2-enal (4i).

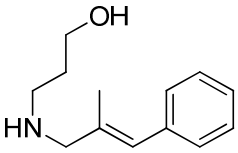
Alcohol **6** (0.43 g, 2.9 mmol) was dissolved in DCM (10 mL). An excess of MnO_2 (1.3 g, 14.9 mmol) was added. The mixture was stirred overnight at room temperature. TLC (eluent: EtOAc/Heptane=1/3) showed partial conversion. An extra amount of MnO_2 (0.41 g, 4.7 mmol) was added and stirring was continued for another 24 hours at room temperature. The mixture was filtered over Celite and the filtrate concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/heptane 1/3). This afforded the product (0.29 g, 68 %) as a yellow oil. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 10.19 (d, 1H, J= 7.8 Hz), 7.56-7.39 (m, 5H), 6.42 (d, 1H, J = 7.8 Hz), 2.57 (s, 3H). LR-MS $[M+H]^+$ 147.0.

Reductive amination



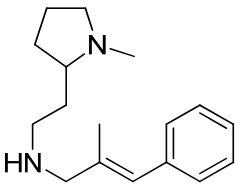
(*E*)-2-Methyl-*N*-(3-morpholinopropyl)-3-phenylprop-2-en-1-amine (8a).

This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7a** (0.57 g, 3.9 mmol), aldehyde **4a** (0.56 g, 3.8 mmol), $MgSO_4$ (5 g), DCM (20 mL) and a reaction time of 4 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1 hour. Purification with an SCX column (Si-SCX-2, 15 g) gave a yellowish oil (0.47 g, 45 %). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.37-7.19 (m, 5H), 6.46 (s, 1H), 3.75-3.69 (m, 4H), 3.34 (s, 2H), 2.72 (t, 2H, J=6.75 Hz), 2.49-2.40 (m, 6H), 1.91 (s, 3H), 1.80-1.62 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{27}N_2O^+$, Calc. 275.2, found 275.0.



(E)-3-(2-Methyl-3-phenylallylamino)propan-1-ol (8b).

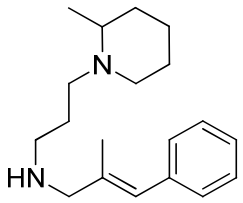
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7b** (0.30 g, 4.0 mmol), aldehyde **4a** (0.53 g, 3.6 mmol), $MgSO_4$ (5 g), DCM (20 mL) and a reaction time of 4 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 0.5 h. Purification was performed with an SCX column (Si-SCX-2, 15 g) to give a yellowish oil (0.56 g, 76 %). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.33-7.14 (m, 5H), 6.38 (s, 1H), 3.77 (t, 2H), 3.28 (s, 2H), 2.84 (t, 2H), 1.88 (s, 3H), 1.78-1.64 (m, 2H). LR-MS $[M+H]^+$ $C_{13}H_{20}NO^+$, Calc. 206.2, found 206.1.



(*E*)-2-Methyl-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-phenylprop-2-en-1-amine (8c).

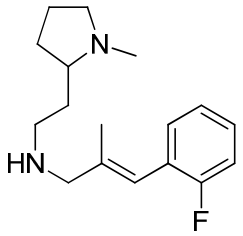
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (2.0 g, 15.6 mmol), aldehyde **4a** (2.32 g, 15.9 mmol), $MgSO_4$ (20.7 g), DCM (83 mL) and a reaction time of 4 days. For the imine reduction, the

following reagents and conditions were used: $NaBH_4$ (0.58 g, 15.3 mmol), MeOH (41 mL), acetone (4 mL) and a reaction time of 1 hour. The crude product was purified by column chromatography (74:13:13 EtOAc: Et_3N: MeOH) to give a yellow oil (2.15 g, 53 %). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33-7.17 (m, 5H), 6.42 (s, 1H), 3.30 (s, 2H), 3.09 – 2.98 (m, 1H), 2.74-2.55 (m, 2H), 2.32 (s, 3H), 2.15-2.00 (m, 2H), 1.94-1.80 (m, 2H), 1.85 (s, 3H), 1.80-1.59 (m, 2H), 1.55-1.41 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{27}N_2^+$, Calc. 259.2, found 259.0.



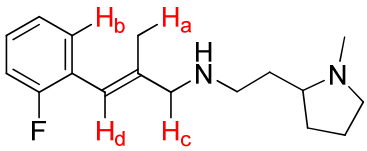
(E)-2-Methyl-N-(3-(2-methylpiperidin-1-yl)propyl)-3-phenylprop-2-en-1-amine (8d).

This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7d** (0.60 g, 3.8 mmol), aldehyde **4a** (0.53 g, 3.6 mmol), $MgSO_4$ (5 g), DCM (20 mL) and a reaction time of 4 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 3 hour. Purification was performed with an SCX column (Si-SCX-2, 10g) to give a yellowish oil (0.74 g, 72 %). ^1H-NMR ($CDCl_3$, 200 MHz) δ 7.31-7.12 (m, 5H), 6.40 (s, 1H), 3.25 (s, 2H), 2.90-2.65 (m, 4H), 2.40-2.02 (m, 4H), 1.85 (s, 3H), 1.70-1.15 (m, 8H), 1.02 (d, 3H). LR-MS $[M+H]^+$ $C_{19}H_{31}N_2^+$, Calc. 287.2, found 287.1.

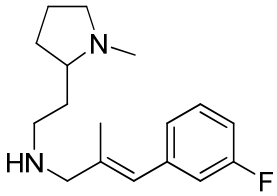


(E)-3-(2-Fluorophenyl)-2-methyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8e).

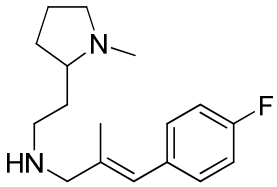
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.78 g, 6.1 mmol), aldehyde **4b** (1.0 g, 6.1 mmol), Na_2SO_4 (5.0 g), DCM (20 ml) and a reaction time of 24 hours. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.25 g, 6.6 mmol), MeOH (10 mL), acetone (1.0 mL) and a reaction time of 1 hour. The product was purified by column chromatography (eluent EtOAc/MeOH/Et_3N = 80/20/1) to give a light yellow oil (0.95 g, 56 %). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.30-6.90 (m, 4H), 6.35 (s, 1H), 3.29 (s, 2H), 3.05 – 2.94 (m, 1H), 2.68-2.55 (m, 2H), 2.25 (s, 3H), 2.14-1.98 (m, 2H), 1.94-1.79 (m, 2H), 1.75 (s, 3H), 1.79-1.62 (m, 2H), 1.55-1.41 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{26}FN_2^+$, Calc. 277.2, found 277.0.



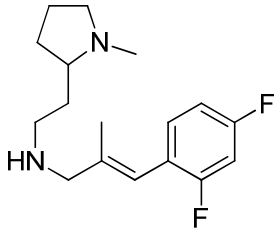
1D-NOESY: *Irradiation at H_o*: diagnostic couplings observed with H_c (large), H_b (large), H_d (small); *Irradiation at H_c*: diagnostic couplings observed with H_a (large), H_d (large); no coupling with H_b. Note: this compound is the precursor for both **29** and **30**.



(E)-3-(3-Fluorophenyl)-2-methyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8f).
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.50 g, 3.9 mmol), aldehyde **4c** (0.63 g, 3.8 mmol), $MgSO_4$ (5.0 g), DCM (20 mL) and a reaction time of 5 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1 hour. The product was purified by column chromatography (85:10:5 EtOAc:MeOH: Et_3N) to give a light yellow oil (0.235 g, 22 %). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.33-7.20 (m, 1H), 7.12-6.84 (m, 3H), 6.42 (s, 1H), 3.33 (s, 2H), 3.14-3.00 (m, 1H), 2.71-2.52 (m, 2H), 2.32 (s, 3H), 2.20-2.03 (m, 2H), 1.99-1.82 (m, 2H), 1.87 (s, 3H), 1.80-1.61 (m, 2H), 1.60-1.41 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{26}FN_2^+$, Calc. 277.2, observed 277.0.

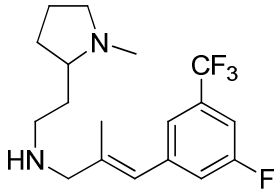


(E)-3-(4-Fluorophenyl)-2-methyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8g).
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.50 g, 3.9 mmol), aldehyde **4d** (0.63 g, 3.8 mmol), $MgSO_4$ (5.0 g), DCM (20 mL) and a reaction time of 5 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1 hour. The product was purified by column chromatography (85:10:5 EtOAc:MeOH:Et_3N) to give a light yellow oil (0.639 g, 61 %). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.29-7.20 (m, 2H), 7.05 (t, 2H, J=7.5 Hz), 6.45 (s, 1H), 3.37 (s, 2H), 3.18-3.09 (m, 1H), 2.78-2.62 (m, 2H), 2.39 (s, 3H), 2.25-2.11 (m, 2H), 2.03-1.86 (m, 2H), 1.87 (s, 3H), 1.85-1.69 (m, 2H), 1.69-1.49 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{26}FN_2^+$, Calc. 277.2, observed 277.0.



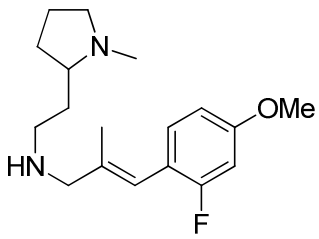
(*E*)-3-(2,4-Difluorophenyl)-2-methyl-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8h).

This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.50 g, 3.9 mmol), aldehyde **4e** (0.70 g, 3.8 mmol), $MgSO_4$ (5 g), DCM (20 mL mL) and a reaction time of 4 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1 hour. The crude product was purified by column chromatography (85:10:5 EtOAc: MeOH: Et_3N) to give a yellow oil (0.608 g, 54 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.15 (m, 1H), 6.82-6.73 (m, 2H), 6.30 (s, 1H), 3.31 (s, 2H), 3.09 – 2.98 (m, 1H), 2.74-2.55 (m, 2H), 2.32 (s, 3H), 2.15-1.99 (m, 2H), 1.93-1.78 (m, 2H), 1.75 (s, 3H), 1.78-1.59 (m, 2H), 1.53-1.41 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{25}N_2F_2^+$, Calc. 295.2, found 295.0.



(*E*)-3-(3-Fluoro-5-(trifluoromethyl)phenyl)-2-methyl-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8i).

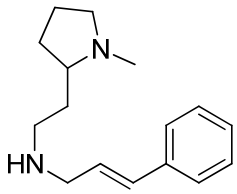
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.50 g, 3.9 mmol), aldehyde **4f** (0.89 g, 3.8 mmol), $MgSO_4$ (4.96 g), DCM (20 mL) and a reaction time of 4 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.14 g, 3.7 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1 hour. The crude product was purified by column chromatography (85:10:5 EtOAc: MeOH: Et_3N) to give a yellow oil (0.064 g, 5 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.22 (app s, 1H), 7.09 (app s, 1H), 7.05 (app s, 1H), 6.38 (s, 1H), 3.25 (s, 2H), 3.01 – 2.92 (m, 1H), 2.71-2.50 (m, 2H), 2.22 (s, 3H), 2.15-1.92 (m, 2H), 1.91-1.75 (m, 2H), 1.82 (s, 3H), 1.72-1.55 (m, 2H), 1.55-1.34 (m, 2H). LR-MS $[M+H]^+$ $C_{18}H_{25}N_2F_4^+$, Calc. 345.2, found 345.1.



(*E*)-3-(2-Fluoro-4-methoxyphenyl)-2-methyl-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)prop-2-en-1-amine (8j).

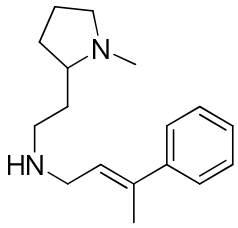
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.20 g, 1.6 mmol), aldehyde **4g** (0.30 g, 1.5 mmol), $MgSO_4$ (2.0 g), DCM (8 mL) and a reaction time of 4 days. For the imine reduction, the

following reagents and conditions were used: $NaBH_4$ (0.06 g, 1.6 mmol), MeOH (4 mL), acetone (1 mL) and a reaction time of 1 hour. The crude product was purified by column chromatography (85:10:5 EtOAc: MeOH: Et_3N) to give a yellow oil (0.228 g, 49 %). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.12 (t, 1H, J=8.5 Hz), 6.63-6.51 (m, 2H), 6.29 (s, 1H), 3.72 (s, 3H), 3.28 (s, 2H), 3.04 – 2.94 (m, 1H), 2.71-2.50 (m, 2H), 2.25 (s, 3H), 2.15-1.96 (m, 2H), 1.95-1.75 (m, 2H), 1.76 (s, 3H), 1.75-1.53 (m, 2H), 1.53-1.35 (m, 2H). LR-MS $[M+H]^+$ $C_{18}H_{28}N_2FO^+$, Calc. 307.2, found 307.1



(E)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-phenylprop-2-en-1-amine (8k).

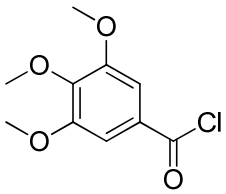
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (0.71 g, 5.5 mmol), cinnamaldehyde **4h** (1.46 g, 11.0 mmol), Na_2SO_4 (1.57 g), DCM (100 mL) and a reaction time of 1 day. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (0.42 g, 11.0 mmol), MeOH (100 mL), acetone (40 mL) and a reaction time of 2 hour. The crude product was purified by column chromatography (DCM/8% Et_3N, MeOH gradient 0% to 8%) to give yellow oil (0.35 g, 26 %). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 5H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.9 Hz, 6.2 Hz, 1H), 3.44 (d, *J* = 6.2 Hz, 2H), 3.15 – 3.04 (m, 1H), 2.80-2.63 (m, 2H), 2.33 (s, 3H), 2.20-2.05 (m, 2H), 2.02-1.85 (m, 2H), 1.85-1.60 (m, 2H), 1.60-1.44 (m, 2H). The *trans*-configuration of **8k** was confirmed by the large J-constant for coupling of the vinylic protons. LR-MS $[M+H]^+$ $C_{16}H_{25}N_2^+$, Calc. 245.2, found 245.1.



(E)-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-phenylbut-2-en-1-amine (8l).

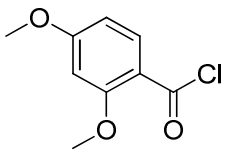
This compound was prepared according to general procedure B. For the imine formation, the following reagents and conditions were used: amine **7c** (256 mg, 2.00 mmol), aldehyde **4i** (289 mg, 1.98 mmol), Na_2SO_4 (10 g), DCM (20 mL) and a reaction time of 5 days. For the imine reduction, the following reagents and conditions were used: $NaBH_4$ (73 mg, 1.93 mmol), MeOH (10 mL), acetone (1 mL) and a reaction time of 1.5 hour. The crude product was purified by column chromatography (EtOAc-MeOH (4:1)) to give an oil (357 mg, 70 %). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34-7.08 (m, 5H), 5.80 (t, 1H, J=7.5 Hz), 3.35 (d, 2H, J= 7.5 Hz), 3.04 – 2.93 (m, 1H), 2.71-2.55 (m, 2H), 2.22 (s, 3H), 2.11-1.98 (m, 2H), 2.00 (s, 3H), 1.92-1.72 (m, 2H), 1.72-1.52 (m, 2H), 1.52-1.31 (m, 2H). LR-MS $[M+H]^+$ $C_{17}H_{27}N_2^+$, Calc. 259.2, found 259.1.

Acid chloride synthesis



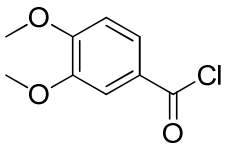
3,4,5-Trimethoxybenzoyl chloride (10a).

The general procedure C was followed, using acid **9a** (2.00 g, 9.42 mmol) and $SOCl_2$ (13.8 mL, 190.2 mmol). The product was a white solid (2.10 g, 97 %).[1]



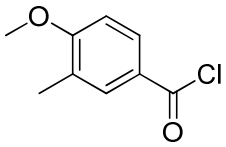
2,4-Dimethoxybenzoyl chloride (10b).

Anhydrous DMF (8 µL, 0.1 mmol) was added to anhydrous DCM (7 mL). Acid **9b** (1.00 g, 5.49 mmol) was added and the mixture was cooled to 0°C. Oxalylchloride (1.0 mL, 11.7 mmol) was added dropwise and the resulting solution was allowed to warm to r.t. (ca. 30 min.), after which it was concentrated *in vacuo* and dried. The product was a white solid (1.06 g, 96 %) and was used without purification. [2]



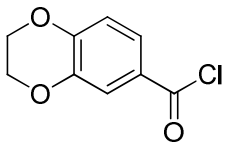
3,4-Dimethoxybenzoyl chloride (10c).

The general procedure C was followed, using acid **9c** (1.00 g, 5.49 mmol) and $SOCl_2$ (5.13 mL, 70.7 mmol). The product was a purple solid (1.07 g, 97 %).[3]



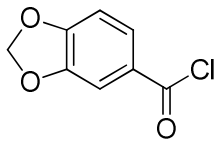
4-Methoxy-3-methylbenzoyl chloride (10d).

The general procedure C was followed, using acid **9d** (0.10 g, 0.60 mmol) and $SOCl_2$ (0.56 mL, 7.7 mmol). The product was a white-cream solid (0.10 g, 90 %).[4]



2,3-Dihydrobenzo[*b*][1,4]dioxine-6-carbonyl chloride (10e).

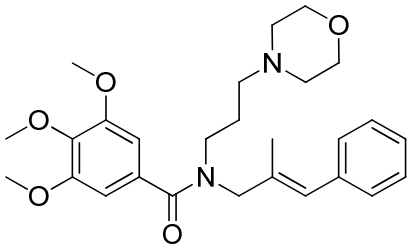
The general procedure C was followed, using acid **9e** (1.00 g, 5.55 mmol) and $SOCl_2$ (5.19 mL, 71.5 mmol). The product was a brown solid (1.03 g, 93 %).[5]



Benzo[*d*][1,3]dioxole-5-carbonyl chloride (10f).

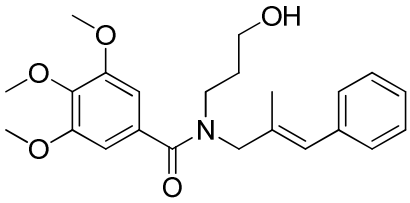
The general procedure C was followed, using acid **9f** (1.55 g, 9.33 mmol) and $SOCl_2$ (8.72 mL, 120.2 mmol). The product was a yellow solid (1.65 g, 96 %).[6]

EDCI coupling



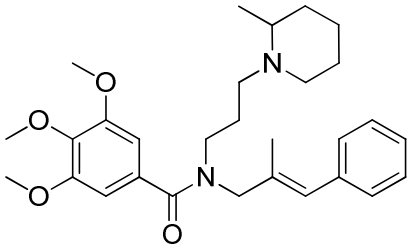
(E)-3,4,5-Trimethoxy-N-(2-methyl-3-phenylallyl)-N-(3-morpholinopropyl)-benzamide (11).

The general procedure D was followed, using THF (11 mL), EDCI.HCl (0.25 g, 1.3 mmol), Et_3N (0.18 mL, 1.3 mmol), HOBt.H_2O (0.13 g, 0.85 mmol), acid **9a** (0.28 g, 1.3 mmol), amine **8a** (0.23 g, 0.84 mmol) and a reaction time of 20 h. Purification was performed by sequential column chromatography, first with eluent DCM:MeOH:Et_3N 10:0.1:0.1, then with eluent DCM:MeOH 9.7:0.3. This afforded the product as a yellow oil (0.287 g, 73 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.38-7.33 (m, 2H), 7.30-7.21 (m, 3H), 6.69 (s, 2H), 6.42 (s, 1H), 4.10 (s, 2H), 3.79 (s, 6H), 3.74 (s, 3H), 3.53-3.48 (m, 4H), 3.42-3.37 (m, 2H), 2.33-2.27 (m, 6H), 1.79 (s, 3H), 1.79-1.72 (m, 2H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz, 300 K) δ 171.5, 153.0, 138.6, 136.7, 133.6, 131.9, 128.5, 128.1, 126.6, 126.0, 103.6, 66.7, 60.5, 56.7, 56.0, 55.9, 53.4, 43.6, 23.9, 15.8. LC-purity: 99.3 %. HR-MS $[M+H]^+$ $C_{27}H_{37}N_2O_5^+$, Calc. 469.2697, found 469.2690.



(E)-N-(3-Hydroxypropyl)-3,4,5-trimethoxy-N-(2-methyl-3-phenylallyl)benzamide (12).

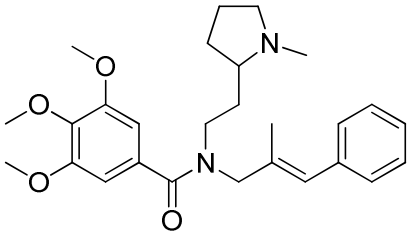
The general procedure D was followed, using THF (17 mL), EDCI.HCl (0.35 g, 1.83 mmol), Et_3N (0.29 mL, 2.08 mmol), HOBt.H_2O (0.20 g, 1.3 mmol), acid **9a** (0.44 g, 2.07 mmol), amine **8b** (0.28 g, 1.36 mmol) and a reaction time of 20 h. Purification was performed by column chromatography (gradient DCM:MeOH 9.97:0.03 to DCM:MeOH 9.7:0.3). This gave the product as a yellowish oil (0.222 g, 41%). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ δ 7.36-7.33 (m, 2H), 7.28-7.21 (m, 3H), 6.69 (s, 2H), 6.40 (s, 1H), 4.12 -4.08 (m, 1H), 4.10 (s, 2H), 3.78 (s, 6H), 3.73 (s, 3H), 3.50-3.40 (m, 4H), 1.86-1.75 (m, 2H), 1.75 (s, 3H). ^{13}C-NMR ($CDCl_3$, 62.5 MHz, 300 K) δ 172.8, 153.0, 139.3, 136.8, 133.4, 131.0, 128.7, 128.1, 126.8, 126.1, 104.5, 60.8, 58.9, 56.4, 56.2, 41.7, 30.0, 16.0. LC-purity: 97.2 %. HR-MS $[M+H]^+$ $C_{23}H_{30}NO_5^+$, Calc. 400.2118, found 400.2103.



(E)-3,4,5-Trimethoxy-N-(2-methyl-3-phenylallyl)-N-(3-(2-methylpiperidin-1-yl)propyl)benzamide (13).

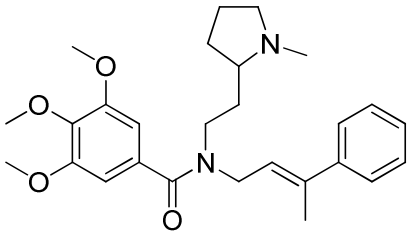
The general procedure D was followed, using THF (16 mL), EDCI.HCl (0.37 g, 1.93 mmol), Et_3N (0.27 mL, 1.93 mmol), HOBt.H_2O (0.19 g, 1.24 mmol), acid **9a** (0.41 g, 1.93 mmol), amine **8d** (0.37 g, 1.29 mmol) and a reaction time of 36 hour. Purification was performed by column chromatography (eluent DCM:MeOH 9:1). This afforded the product as a yellowish oil (0.144 g, 23 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.37-7.33 (m, 2H), 7.28-7.21 (m, 3H), 6.68 (s, 2H), 6.42 (s, 1H), 4.10 (s, 2H), 3.79 (s, 6H), 3.74 (s, 3H), 3.42-3.26 (m, 2H), 2.72-2.66 (m, 1H), 2.62-2.50 (m, 1H), 2.34-2.25 (m, 1H), 2.25-2.17 (m, 1H), 2.12-2.02 (m, 1H), 1.79 (s, 3H), 1.79-1.69 (m, 2H), 1.61-1.12 (m, 6H), 0.95 (d, 3H, J=6.4 Hz). ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ 171.5, 153.0, 138.7, 136.8, 133.6, 131.6, 128.6, 128.1, 126.6, 126.1, 104.0, 60.7, 56.5, 56.0, 51.7, 51.0, 46.3, 43.6, 34.2, 29.5, 25.9, 23.9, 18.7, 15.8. IR (neat) 1624 cm^{-1}. LC-purity: 98.8 %. HR-MS $[M+H]^+$ $C_{29}H_{41}N_2O_4^+$, Calc. 481.3061, found 481.3046.

Acid chloride coupling



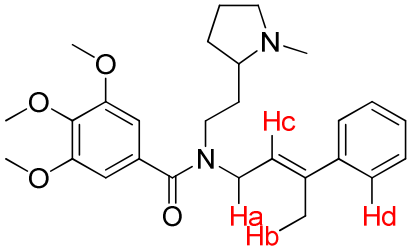
(*E*)-3,4,5-Trimethoxy-*N*-(2-methyl-3-phenylallyl)-*N*-(2-1-methylpyrrolidin-2-yl)ethyl)benzamide (14).

This compound was prepared following the general procedure E, using amine **8c** (50 mg, 0.19 mmol), acid chloride **10a** (48 mg, 0.21 mmol), Et_3N (0.030 mL, 0.22 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (56 mg, 65%). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.37-7.33 (m, 2H), 7.30-7.21 (m, 3H), 6.68 (s, 2H), 6.43 (s, 1H), 4.10 (s, 2H), 3.79 (s, 6H), 3.73 (s, 3H), 3.38-3.33 (m, 2H), 2.95-2.87 (m, 1H, overlaps with H_2O signal), 2.18 (s, 3H), 2.12-2.02 (m, 2H), 1.92-1.73 (m, 2H), 1.78 (s, 3H), 1.62-1.55 (m, 3H), 1.49-1.35 (m, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz, 300 K) δ 171.6, 153.2, 138.9, 137.0, 132.2, 131.8, 128.8, 128.3, 126.8, 104.2, 103.9, 64.4 (br), 60.9, 57.1, 56.2, 45.3, 44.8, 40.4, 30.8, 30.4, 21.8, 15.7. LC-purity: 98.9 %. HR-MS $[M+H]^+$ $C_{27}H_{37}N_2O_4^+$, Calc. 453.2748, found 453.2741.



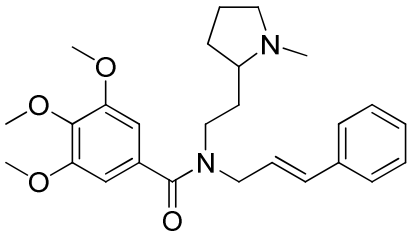
(*E*)-3,4,5-trimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-N-(3-phenylbut-2-enyl)benzamide (15).

This compound was prepared following the general procedure E, using amine **8l** (67 mg, 0.26 mmol), acid chloride **10a** (111 mg, 0.48 mmol), Et_3N (0.07 mL, 0.50 mmol), DCM (1.0 mL + 1.0 mL) and a reaction time of 2 days. The product was purified using sequential column chromatography (1st column: EtOAc/MeOH/TEA = 4/1/0.1; 2nd column: DCM/EtOAc/TEA = 1/1/0.05) to give an oil (24 mg, 20 %). ^{1}H-NMR (400 MHz, DMSO-d6, 373 K) δ 7.43-7.40 (m, 2H), 7.36-7.27 (m, 3H), 6.68 (s, 2H), 5.82 (t, 1H, J=6.4 Hz), 4.16 (d, 2H, J=6.4 Hz), 3.79 (s, 6H), 3.73 (s, 3H), 3.41-3.33 (m, 2H), 2.26 (s, 3H), 2.28-2.15 (m, 2H), 1.97 (s, 3H), 1.97-1.79 (m, 2H), 1.69-1.59 (m, 3H), 1.43-1.32 (m, 1H), an 1H signal overlaps with H_2O peak according to 2D-NOESY. LC-purity: 93.1 %. HR-MS $[M+H]^+$ $C_{27}H_{37}N_2O_4^+$, Calc. 453.2748, found 453.2707.



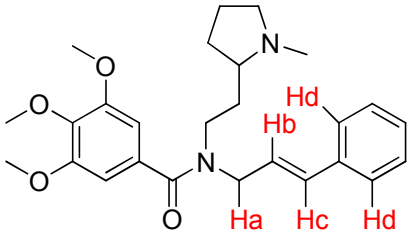
The *trans*-configuration of **15** was confirmed by high-temperature NOESY NMR:

- Coupling Ha and Hb
- Absence coupling Ha and Hd



(*E*)-*N*-Cinnamyl-3,4,5-trimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (16).

This compound was prepared following the general procedure E, using amine **8k** (0.150 g, 0.61 mmol), acid chloride **10a** (0.170 g, 0.74 mmol), Et_3N (0.075 g, 0.74 mmol), DCM (7.5 mL + 7.5 mL) and a reaction time of 20 hours. The product was purified using column chromatography (EtOAc/5% Et_3N, MeOH gradient 0% to 10%) to give a yellow oil (0.197 g, 73 %). ^{1}H NMR (400 MHz, DMSO-d6, 375 K) δ 7.43 (d, *J* = 7.3, 2H), 7.35-7.30 (m, 2H), 7.27-7.23 (m, 1H), 6.70 (s, 2H), 6.55 (d, *J* = 15.9, 1H), 6.28 (dt, *J* = 15.9 Hz, 5.6 Hz, 1H), 4.12 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 6H), 3.74 (s, 3H), 3.40-3.33 (m, 2H), 2.95-2.87 (m, 1H, overlaps with H_2O signal), 2.19 (s, 3H), 2.15-2.05 (m, 2H), 1.95-1.75 (m, 2H), 1.65-1.54 (m, 3H), 1.41-1.25 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6, 375 K) δ 170.6, 153.5, 137.1, 132.8, 132.5, 129.0, 128.0, 126.7, 126.4, 121.0, 105.7, 64.3, 60.6, 57.0, 56.7, 45.1, 40.1, 31.5, 30.3, 22.3, one signal overlaps with another one or with DMSO signal. LC-purity: 99.0 %. HR-MS $[M+H]^+$ $C_{26}H_{35}N_2O_4^+$, Calc. 439.2591, found 439.2552.

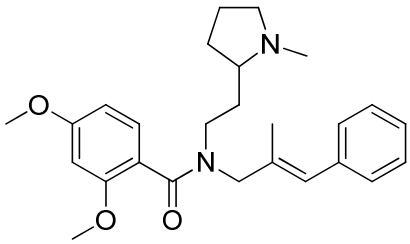


The *trans*-configuration for **16** was confirmed by:

1) The large J-constant for coupling of Hb and Hc

2) High-temperature NOESY NMR, revealing:

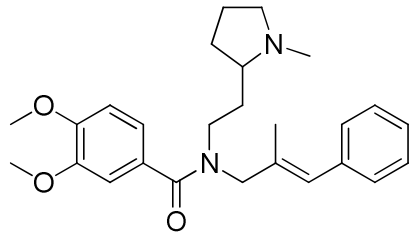
- Coupling of both Hb and Hc with Hd and with Ha
- Absence of a coupling of Ha with Hd



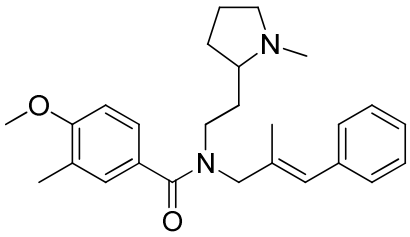
(*E*)-2,4-Dimethoxy-*N*-(2-methyl-3-phenylallyl)-*N*-(2-1-methylpyrrolidin-2-yl)ethyl)benzamide (17).

This compound was prepared following the general procedure E, using amine **8c** (50 mg, 0.19 mmol), acid chloride **10b** (69 mg, 0.34 mmol), Et_3N (0.050 mL, 0.36 mmol), DCM (5 mL + 5 mL) and a reaction time of 3 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (34 mg, 42 %). The ^{1}H-NMR spectrum is complex and shows rotamers in a ca. 1:3 ratio. Some signals below 5.0 ppm are broad and cannot be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) **Major rotamer** δ 7.35-7.15 (m, 6H), 6.52-6.43 (m, 3 overlapping H),

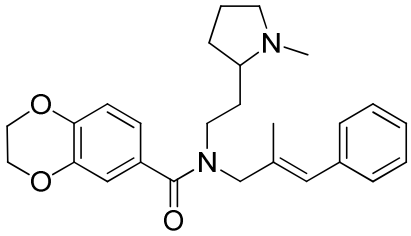
4.9-4.4 (br, 2H?), 3.81 (s, 3H), 3.79 (s, 3H), 3.20-3.00 (m, 2H), 2.15 (s, 3H), 2.20-1.30 (br m, 12 H). LC-purity: 97.2 %. HR-MS $[M+H]^+$ $C_{26}H_{35}N_2O_3^+$, Calc. 423.2642, found 423.2628.



(*E*)-3,4-Dimethoxy-*N*-(2-methyl-3-phenylallyl)-*N*-(2-1-methylpyrrolidin-2-yl)ethyl)benzamide (18).
This compound was prepared following the general procedure E, using amine **8c** (50 mg, 0.19 mmol), acid chloride **10c** (69 mg, 0.34 mmol), Et_3N (0.050 mL, 0.36 mmol), DCM (5 mL + 5 mL) and a reaction time of 3 hours. The crude product was purified by column chromatography (8.0:1.5:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (48 mg, 60 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.37-7.20 (m, 5H), 7.04-6.98 (m, 2H), 6.84 (d, 1H, J=8.75 Hz), 6.44 (s, 1H), 4.40-3.95 (br, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.75-3.25 (br m, 2H), 3.09-2.95 (br m, 1H), 2.40-1.40 (br m, 14 H). LC-purity: 98.8 %. HR-MS $[M+H]^+$ $C_{26}H_{35}N_2O_3^+$, Calc. 423.2642, found 423.2626.

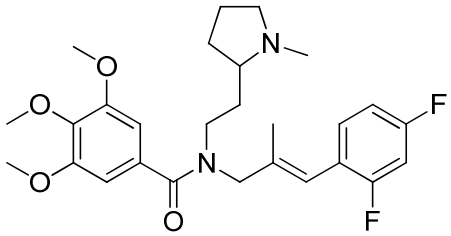


(*E*)-4-Methoxy-3-methyl-*N*-(2-methyl-3-phenylallyl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (19).
This compound was prepared following the general procedure E, using amine **8c** (50 mg, 0.19 mmol), acid chloride **10d** (70 mg, 0.38 mmol), Et_3N (0.052 mL, 0.37 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (4.5:5:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (20 mg, 26 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ 7.36-7.32 (m, 2H), 7.28-7.21 (m, 5H), 6.80 (d, 1H, J=8.4 Hz), 6.43 (s, 1H), 4.50-3.95 (br, 2H), 3.84 (s, 3H), 3.75-3.25 (br m, 2H), 3.10-2.95 (br m, 1H), 2.22 (s, 3H), 2.45-1.30 (br m, 14 H). LC-purity: 99.0 %. HR-MS $[M+H]^+$ $C_{26}H_{35}N_2O_2^+$, Calc. 407.2693, found 407.2695.



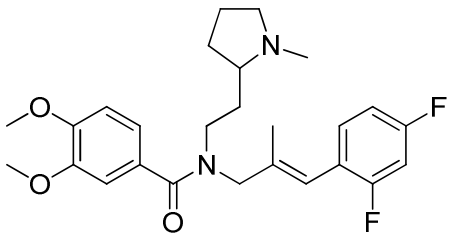
(*E*)-*N*-(2-Methyl-3phenylallyl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (20).

This compound was prepared following the general procedure E, using amine **8c** (194 mg, 0.75 mmol), acid chloride **10e** (270 mg, 1.36 mmol), Et_3N (0.20 mL, 1.43 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (192 mg, 61 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.31-7.11 (m, 5H), 6.95-6.77 (m, 3H), 6.37 (s, 1H), 4.30-3.85 (br, 2H), 4.19 (br s, 4H), 3.72-3.20 (br m, 2H), 3.05-2.90 (br m, 1H), 2.40-1.40 (br m, 14 H). LC-purity: 98.1 %. HR-MS $[M+H]^+$ $C_{26}H_{33}N_2O_3^+$, Calc. 421.2486, found 421.2467.



(*E*)-*N*-(3-(2,4-Difluorophenyl)-2-methylallyl)-3,4,5-trimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (21).

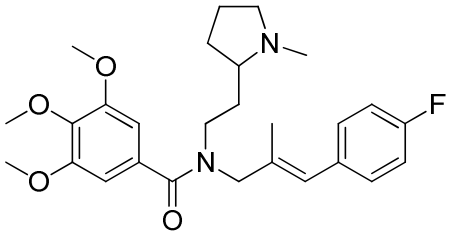
This compound was prepared following the general procedure E, using amine **8h** (55 mg, 0.19 mmol), acid chloride **10a** (79 mg, 0.34 mmol), Et_3N (0.050 mL, 0.36 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (72 mg, 78 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.40-7.30 (m, 1H), 7.15-7.00 (m, 2H), 6.69 (s, 2H), 6.33 (s, 1H), 4.11 (s, 2H), 3.79 (s, 6H), 3.73 (s, 3H), 3.38-3.30 (m, 2H), 2.95-2.87 (m, 1H, overlaps with H_2O signal), 2.19 (s, 3H), 2.12-1.98 (m, 2H), 1.94-1.73 (m, 2H), 1.70 (s, 3H), 1.65-1.55 (m, 3H), 1.40-1.28 (m, 1H). LC-purity: 98.3 %. HR-MS $[M+H]^+$ $C_{27}H_{35}F_2N_2O_4^+$, Calc. 489.2559, found 489.2561.



(*E*)-*N*-(3-(2,4-Difluorophenyl)-2-methylallyl)-3,4-dimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (22).

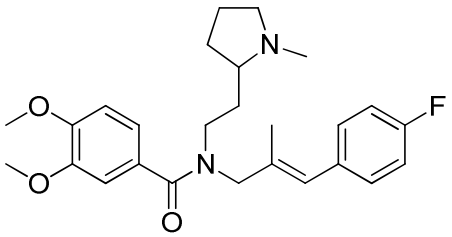
This compound was prepared following the general procedure E, using amine **8h** (0.50 g, 1.7 mmol), acid chloride **10c** (0.60 g, 2.99 mmol), Et_3N (0.47 mL, 3.37 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5

EtOAc:Hex:TEA) to give an orange oil (0.50 g, 64 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.11-7.00 (m, 1H), 6.92-6.85 (m, 2H), 6.75-6.63 (m, 3H), 6.22 (s, 1H), 4.30-3.70 (br, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.65-3.12 (br m, 2H), 2.92-2.80 (br m, 1H),2.20-1.30 (br m, 14 H). LC-purity: 95.7 %. HR-MS $[M+H]^+$ $C_{26}H_{33}F_2N_2O_3^+$, Calc. 459.2454, found 459.2451.



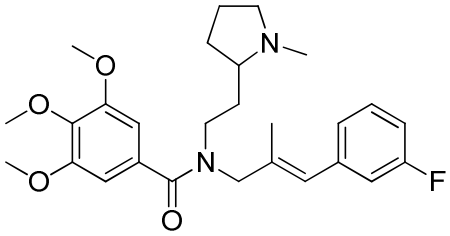
(*E*)-*N*-(3-(4-Fluorophenyl)-2-methylallyl)-3,4,5-trimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (23).

This compound was prepared following the general procedure E, using amine **8g** (0.349 g, 1.26 mmol), acid chloride **10a** (0.51 g, 2.21 mmol), Et_3N (0.35 mL, 2.51 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (0.420 g, 71 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.32-7.26 (m, 2H), 7.17-7.11 (m, 2H), 6.69 (s, 2H), 6.41 (s, 1H), 4.10 (s, 2H), 3.79 (s, 6H), 3.73 (s, 3H), 3.39-3.29 (m, 2H), 2.95-2.87 (m, 1H, overlaps with H_2O signal), 2.19 (s, 3H), 2.15-2.00 (m, 2H), 1.94-1.73 (m, 2H), 1.76 (s, 3H), 1.64-1.54 (m, 3H), 1.41-1.28 (m, 1H). LC-purity: 96.4 %. HR-MS $[M+H]^+$ $C_{27}H_{36}FN_2O_4^+$, Calc. 471.2654, found 471.2634.



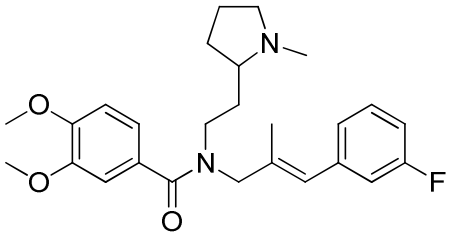
(E)-N-(3-(4-Fluorophenyl)-2-methylallyl)-3,4-dimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (24).

This compound was prepared following the general procedure E, using amine **8g** (0.168 g, 0.61 mmol), acid chloride **10c** (0.219 g, 1.09 mmol), Et_3N (0.17 mL, 1.22 mmol), DCM (5 mL + 5 mL) and a reaction time of 4 hours. The product was purified using column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.111 g, 41 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR (DMSO-d6, 250 MHz, 300 K) δ 7.38-7.29 (m, 2H), 7.26-7.13 (t, 2H), 7.03-6.94 (m, 3H), 6.42 (br s, 1H), 4.30-3.90 (br, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.50-3.10 (br, 2H, overlaps with H_2O peak), 2.95-2.81 (br m, 1H), 2.30-1.40 (br m, 14 H). LC-purity: 97.3 %. HR-MS $[M+H]^+$ $C_{26}H_{34}FN_2O_3^+$, Calc. 441.2548, found 441.2546.



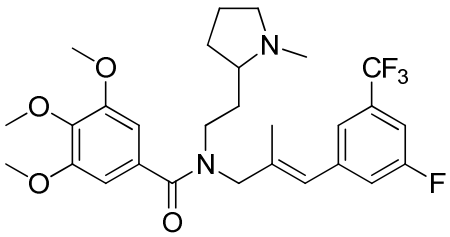
(*E*)-*N*-(3-(3-Fluorophenyl)-2-methylallyl)-3,4,5-trimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (25).

This compound was prepared following the general procedure E, using amine **8f** (0.40 g, 1.45 mmol), acid chloride **10a** (1.12 g, 4.86 mmol), Et_3N (0.74 mL, 5.3 mmol), DCM (5 mL + 5 mL) and a reaction time of 18 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (0.40 g, 59 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 400 MHz, 300 K) δ 7.19-7.14 (app q, 1H), 6.90 (d, 1H, J=7.6 Hz), 6.84-6.76 (m, 2H), 6.61-6.50 (br, 2H), 6.29 (s, 1H), 4.30-3.80 (br, 2H), 3.72 (s, 6H), 3.70 (br s, 3H), 3.60-2.80 (br m, 3 H), 2.30-1.40 (br m, 14 H). LC-purity: 96.6 %. HR-MS $[M+H]^+$ $C_{27}H_{36}FN_2O_4^+$, Calc. 471.2654, found 471.2633.



(E)-N-(3-(3-Fluorophenyl)-2-methylallyl)-3,4-dimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (26).

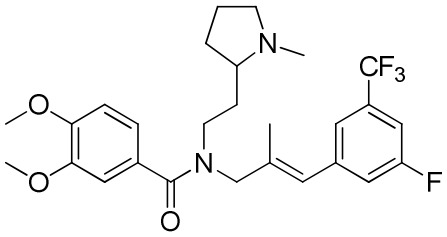
This compound was prepared following the general procedure E, using amine **8f** (0.235 g, 0.85 mmol), acid chloride **10c** (0.307 g, 1.53 mmol), Et_3N (0.24 mL, 1.7 mmol), DCM (5 mL + 5 mL) and a reaction time of 4 hours. The product was purified using column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.187 g, 50 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.42-7.36 (m, 1H), 7.09 (d, 1H, J=7.6 Hz), 7.03-6.96 (m, 5H), 6.40 (s, 1H), 4.10 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.35 (t, 2H, J=7.6 Hz), 2.95-2.85 (m, 1H), 2.18 (s, 3H), 2.13-2.02 (m, 2H), 1.92-1.75 (m, 2H), 1.77 (s, 3H), 1.64-1.51 (m, 3H), 1.39-1.24 (m, 1H). LC-purity: 95.3 %. HR-MS $[M+H]^+$ $C_{26}H_{34}FN_2O_3^+$, Calc. 441.2548, found 441.2536.



(*E*)-N-(3-(3-Fluoro-5-(trifluoromethyl)phenyl)-2-methylallyl)-3,4,5-trimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (27).

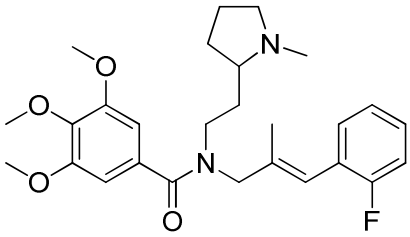
This compound was prepared following the general procedure E, using amine **8i** (0.30 g, 0.87 mmol), acid chloride **10a** (0.36 g, 1.57 mmol), Et_3N (0.25 mL, 1.79 mmol), DCM (5 mL + 5 mL) and a reaction

time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (0.31 g, 66 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.43-7.39 (m, 3H), 6.70 (s, 2H), 6.51 (s, 1H), 4.12 (s, 2H), 3.80 (s, 6H), 3.75 (s, 3H), 3.35 (t, 2H, J=7.6 Hz), 2.95-2.87 (m, 1H), 2.17 (s, 3H), 2.11-2.02 (m, 2H), 1.92-1.75 (m, 2H), 1.82 (s, 3H), 1.62-1.54 (m, 3H), 1.48-1.36 (m, 1H). ^{13}C-NMR (DMSO-d6, 100 MHz, 373 K) δ 170.9, 163.7, 161.3, 153.5, 141.7 (d, J=8 Hz), 138.8, 132.7, 124.3, 121.8, 119.5 (d, J=21 Hz), 110.9 (m), 105.7, 64.0, 60.6, 57.0, 56.9, 44.5, 40,4, 31.5, 30.4, 22.3, 16.1, one signal overlaps with another one or with DMSO signal. The signals for the quaternary C-F and CF_3 carbons were not visible under these conditions. LC-purity: 97 %. HR-MS $[M+H]^+$ $C_{28}H_{35}F_4N_2O_4^+$, Calc. 539.2527, found 539.2504. A trace of DCM remains as solvate and could not be removed after prolonged drying (ca. 15 mole %).



(*E*)-*N*-(3-(3-Fluoro-5-(trifluoromethyl)phenyl)-2-methylallyl)-3,4-dimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (28).

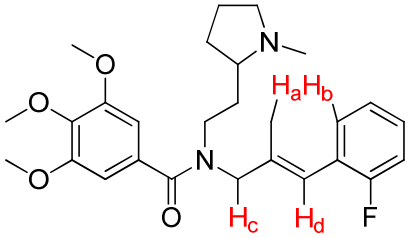
This compound was prepared following the general procedure E, using amine **8i** (0.30 g, 0.87 mmol), acid chloride **10c** (0.31 g, 1.55 mmol), Et_3N (0.25 mL, 1.79 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.34 g, 77 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.20 (s, 1H), 7.12-7.02 (m, 2H), 6.95-6.87 (m, 2H), 6.77 (d, 1H, J=8 Hz), 6.33 (s, 1H), 4.30-3.90 (br, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.65-3.20 (br m, 2H), 2.98-2.85 (br m, 1H), 2.30-1.40 (br m, 14 H). LC-purity: 96.8 %. HR-MS $[M+H]^+$ $C_{27}H_{33}F_4N_2O_3^+$, Calc. 509.2422, found 509.2423.



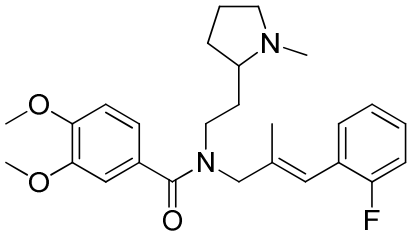
(*E*)-*N*-(3-(2-Fluorophenyl)-2-methylallyl)-3,4,5-trimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (29, VUF11207)

This compound was prepared following the general procedure E, using amine **8e** (50 mg, 0.18 mmol), acid chloride **10a** (75 mg, 0.33 mmol), Et_3N (0.050 mL, 0.36 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a colorless oil (63 mg, 74 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.33-7.25 (m, 2H), 7.21-7.12 (m, 2H), 6.69 (s, 2H), 6.41 (s, 1H), 4.13 (s, 2H), 3.81 (s, 6H), 3.74 (s, 3H), 3.35 (t, 2H, J=8.0 Hz), 2.93-2.87 (m, 1H), 2.18 (s, 3H), 2.11-1.99 (m, 2H), 1.92-1.75 (m, 2H), 1.72 (s, 3H), 1.63-1.55 (m, 3H), 1.40-1.28 (m, 1H). ^{13}C-NMR (DMSO-d6, 100 MHz, 373 K) δ 170.9, 160.0 (d, J=245

Hz), 153.5, 139.9, 137.6, 132.7, 130.9, 129.2, 125.1 (d, J=15 Hz), 124.5, 119.3, 115.7 (d, J=22 Hz), 106.6, 64.1, 60.6, 56.9, 56.8, 44.2, 40.4, 31.4, 30.3, 22.3, 16.2, one signal overlaps with another one or with DMSO signal. LC-purity: 98.7 %. HR-MS $[M+H]^+$ $C_{27}H_{36}FN_2O_4^+$, Calc. 471.2654, found 471.2643. When prepared at larger scale, a trace of EtOAc solvate remained and could not be removed by prolonged drying (13 mole %).

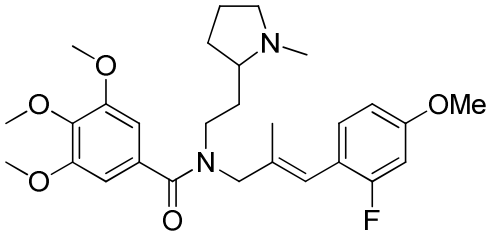


2D-NOESY (DMSO-d6, 400 MHz, 373 K): Diagnostic couplings for *E*-configuration: Ha x Hc, Ha x Hb; absent: Hc x Hb.



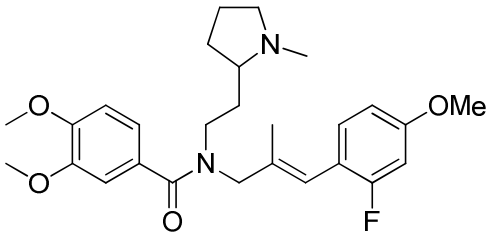
(E)-N-(3-(2-Fluorophenyl)-2-methylallyl)-3,4-dimethoxy-N-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (30, VUF11403)

This compound was prepared following the general procedure E, using amine **8e** (0.244 g; 0.88 mmol), acid chloride **10c** (0.319 g, 1.59 mmol), Et_3N (0.25 mL, 1.79 mmol), DCM (5 mL + 5 mL) and a reaction time of 4 hours. The product was purified using column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.123 g, 32 %). ^{1}H-NMR (DMSO-d6, 400 MHz, 373 K) δ 7.34-7.28 (m, 2H), 7.22-7.14 (m, 2H), 7.02-6.95 (m, 3H), 6.40 (s, 1H), 4.14 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.37 (t, 2H, J=8.0 Hz), 2.95-2.86 (m, 1H), 2.18 (s, 3H), 2.10-2.00 (m, 2H), 1.92-1.75 (m, 2H), 1.70 (s, 3H), 1.62-1.52 (m, 3H), 1.42-1.35 (m, 1H). ^{13}C-NMR (DMSO-d6, 100 MHz, 373 K) δ 171.2, 160.0 (d, J=243 Hz), 150.7, 149.5, 137.7, 131.0, 130.2, 129.2, 125.1 (d, J=15 Hz), 124.5, 120.1, 119.2, 115.7 (d, J=22 Hz), 113.0, 112.2, 64.0, 56.9, 56.6, 56.6, 44.2, 40.4, 31.5, 30.4, 22.4, 16.2, one signal overlaps with another one or with DMSO signal. LC-purity: 98.3 %. HR-MS $[M+H]^+$ $C_{26}H_{34}FN_2O_3^+$, Calc. 441.2548, found 441.2551. When prepared at larger scale, a trace of EtOAc solvate remained and could not be removed by prolonged drying (18 mole %).



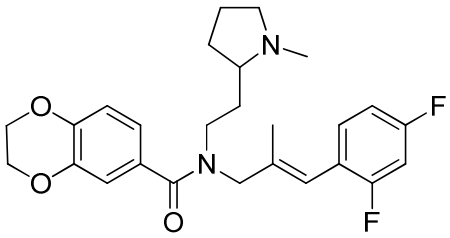
(*E*)-*N*-(3-(2-Fluoro-4-methoxyphenyl)-2-methylallyl)-3,4,5-trimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (31).

This compound was prepared following the general procedure E, using amine **8j** (0.17 g, 0.56 mmol), acid chloride **10a** (0.20 g, 0.87 mmol), Et_3N (0.14 mL, 1.00 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:Et_3N) to give a yellow oil (0.23 g, 82 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.19-7.03 (br m, 1H), 6.69-6.52 (m, 4H), 6.33 (s, 1H), 4.40-3.80 (br, 2H), 3.81-3.71 (m, 12H), 3.70-3.10 (br m, 2H), 3.05-2.88 (br m, 1H), 2.30-1.40 (br m, 14 H). LC-purity: 93.7 %. HR-MS $[M+H]^+$ $C_{28}H_{38}FN_2O_5^+$, Calc. 501.2759, found 501.2750.



(*E*)-*N*-(3-(2-Fluoro-4-methoxyphenyl)-2-methylallyl)-3,4-dimethoxy-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzamide (32)

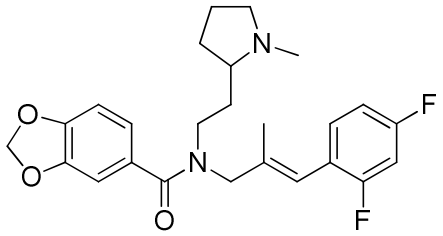
This compound was prepared following the general procedure E, using amine **8j** (16 mg, 0.05 mmol), acid chloride **10c** (40 mg, 0.20 mmol), Et_3N (0.020 mL, 0.14 mmol), DCM (5 mL + 5 mL) and a reaction time of 4 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (5 mg, 21 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.19-7.07 (br m, 1H), 7.06-6.95 (m, 2H), 6.85 (d, 1H, J=7.8 Hz), 6.70-6.55 (m, 2H), 6.36 (s, 1H), 4.40-3.90 (br, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.70-3.15 (br m, 2H), 3.10-2.94 (br m, 1H), 2.40-1.40 (br m, 14 H). LC-purity: 92.0 %. HR-MS $[M+H]^+$ $C_{27}H_{36}FN_2O_4^+$, Calc. 471.2654, found 471.2643.



(*E*)-*N*-(3-(2,4-Difluorophenyl)-2-methylallyl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (33).

This compound was prepared following the general procedure E, using amine **8h** (0.41 g, 1.39 mmol), acid chloride **10e** (0.49 g, 2.47 mmol), Et_3N (0.38 mL, 2.72 mmol), DCM (5 mL + 5 mL) and a reaction

time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.47 g, 74 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.21-7.05 (m, 1H), 6.95-6.68 (m, 5H), 6.27 (s, 1H), 4.40-3.80 (br, 2H), 4.20 (br s, 4H), 3.75-3.20 (br m, 2H), 3.05-2.88 (br m, 1H), 2.40-1.40 (br m, 14 H). LC-purity: 96.5 %. HR-MS $[M+H]^+$ $C_{26}H_{31}F_2N_2O_3^+$, Calc. 457.2297, found 457.2305.



(*E*)-*N*-(3-(2,4-Difluorophenyl)-2-methylallyl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)benzo[*d*][1,3]dioxole-5-carboxamide (34)

This compound was prepared following the general procedure E, using amine **8h** (0.61 g, 2.07 mmol), acid chloride **10f** (0.69 g, 3.73 mmol), Et_3N (0.57 mL, 4.09 mmol), DCM (5 mL + 5 mL) and a reaction time of 2 hours. The crude product was purified by column chromatography (8.5:1:0.5 EtOAc:Hex:TEA) to give a yellow oil (0.78 g, 85 %). The ^{1}H-NMR spectrum is complex and indicates rotamers. Many signals below 5.0 ppm are broad and cannot always be clearly interpreted. ^{1}H-NMR ($CDCl_3$, 250 MHz, 300 K) δ 7.06-6.95 (m, 1H), 6.78-6.70 (m, 2H), 6.69-6.56 (m, 3H), 6.14 (s, 1H), 5.76 (s, 2H), 4.20-3.70 (br, 2H), 3.60-2.90 (br m, 2H), 2.85-2.72 (br m, 1H), 2.20-1.30 (br m, 14 H). LC-purity: 96.4 %. HR-MS $[M+H]^+$ $C_{25}H_{29}F_2N_2O_3^+$, Calc. 443.2141, found 443.2139.

Exemplary spectra

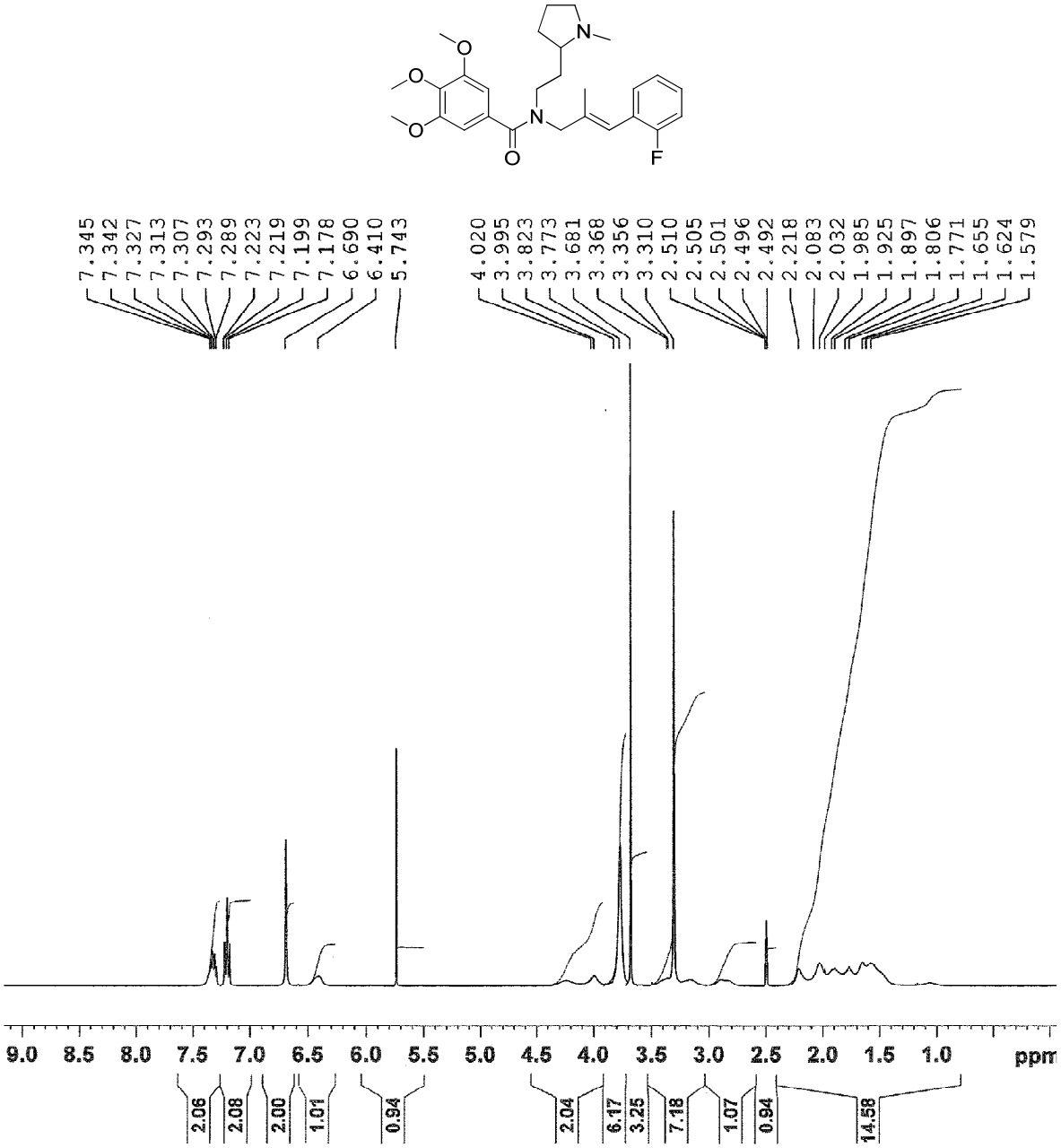


Figure S2. ^{1}H-NMR spectrum of compound **29** in DMSO-d6 at 300 K. This particular NMR sample had a trace of DCM left (at 5.74 ppm).

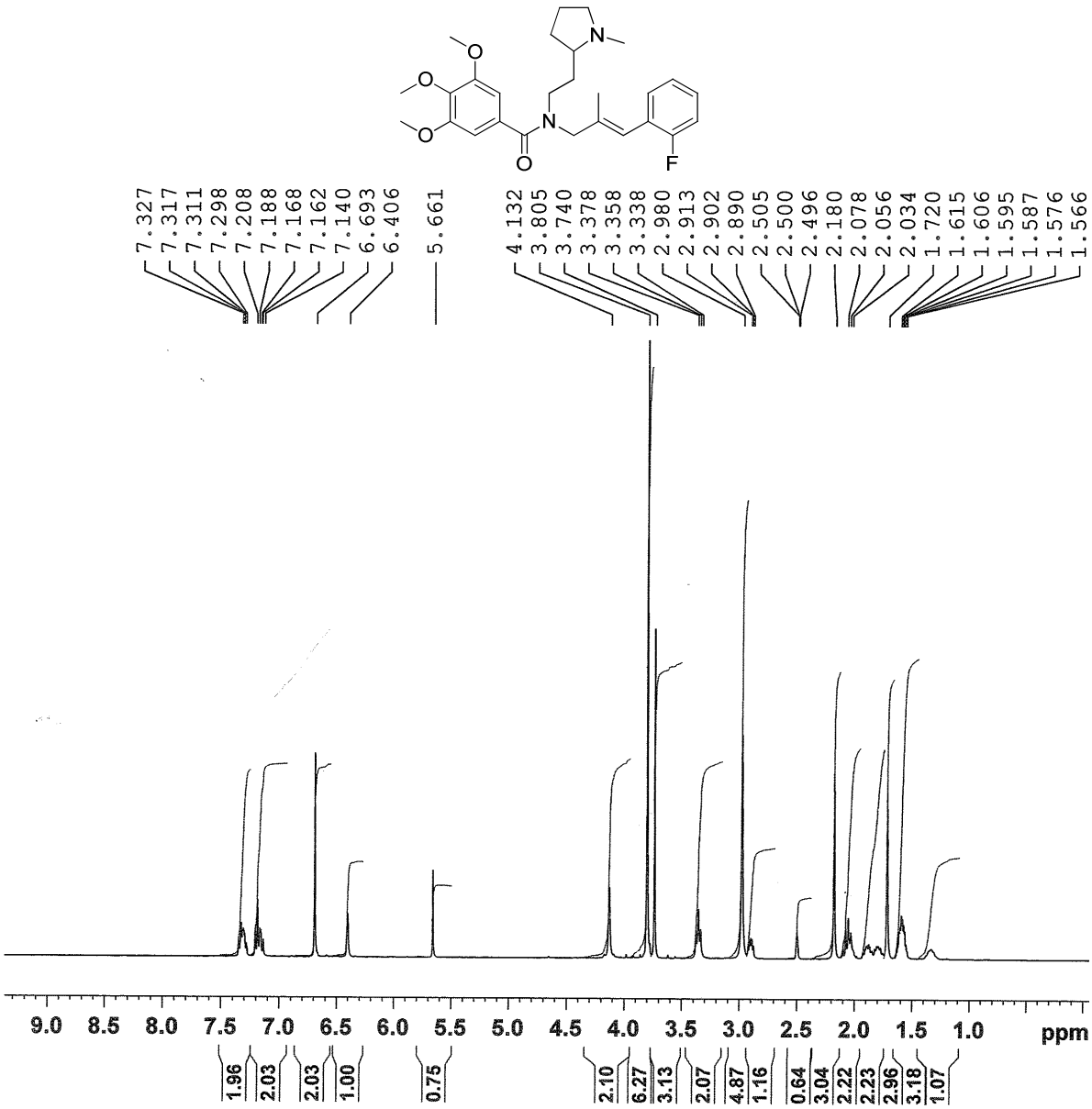


Figure S3. ^{1}H-NMR spectrum of compound **29** in DMSO-d6 at 373 K. This particular NMR sample had a trace of DCM left (at 5.66 ppm).

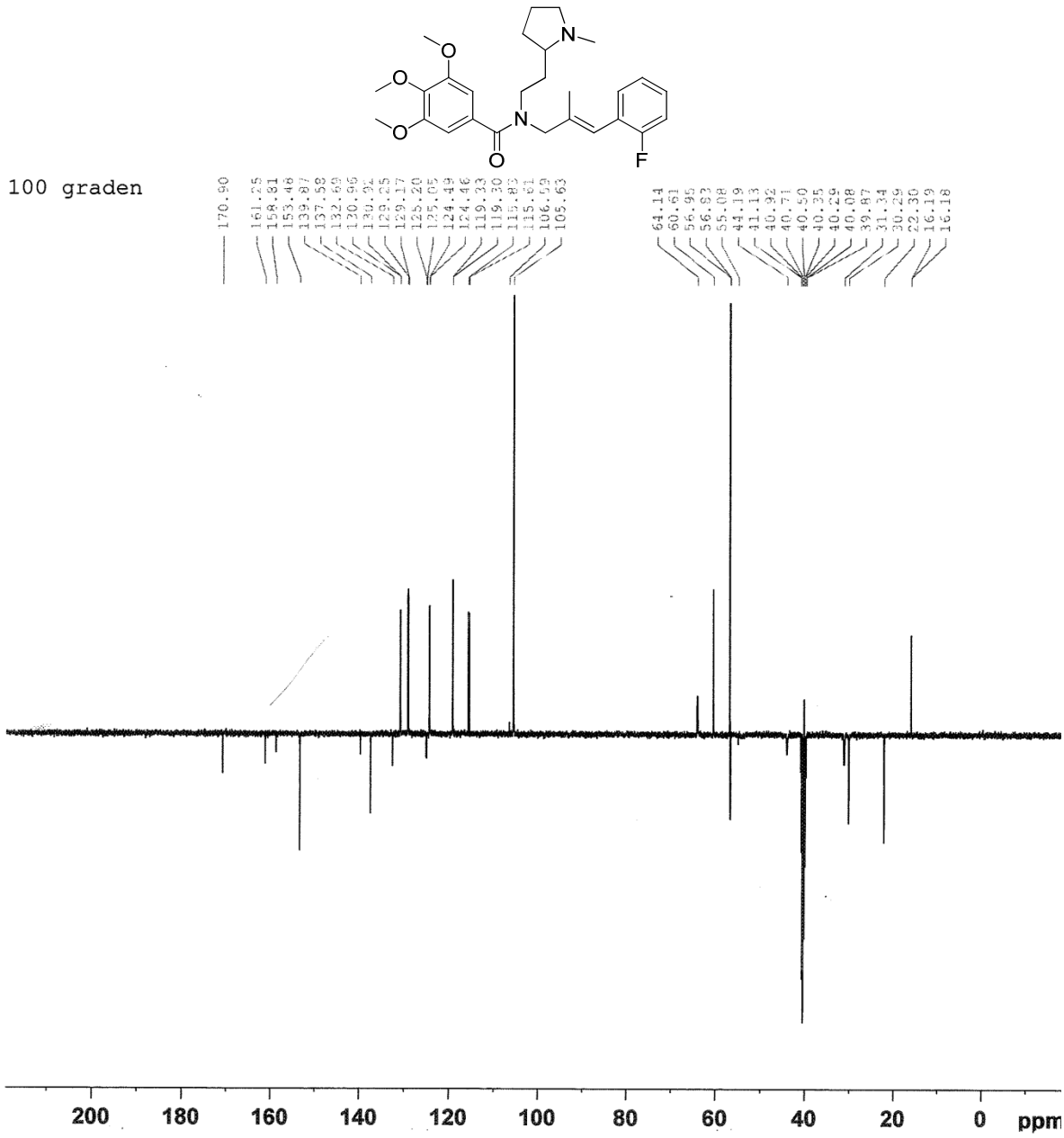


Figure S4. ^{13}C-APT-NMR spectrum of compound **29** in DMSO-d6 at 373 K. This particular NMR sample had a trace of DCM left (at 55.1 ppm).

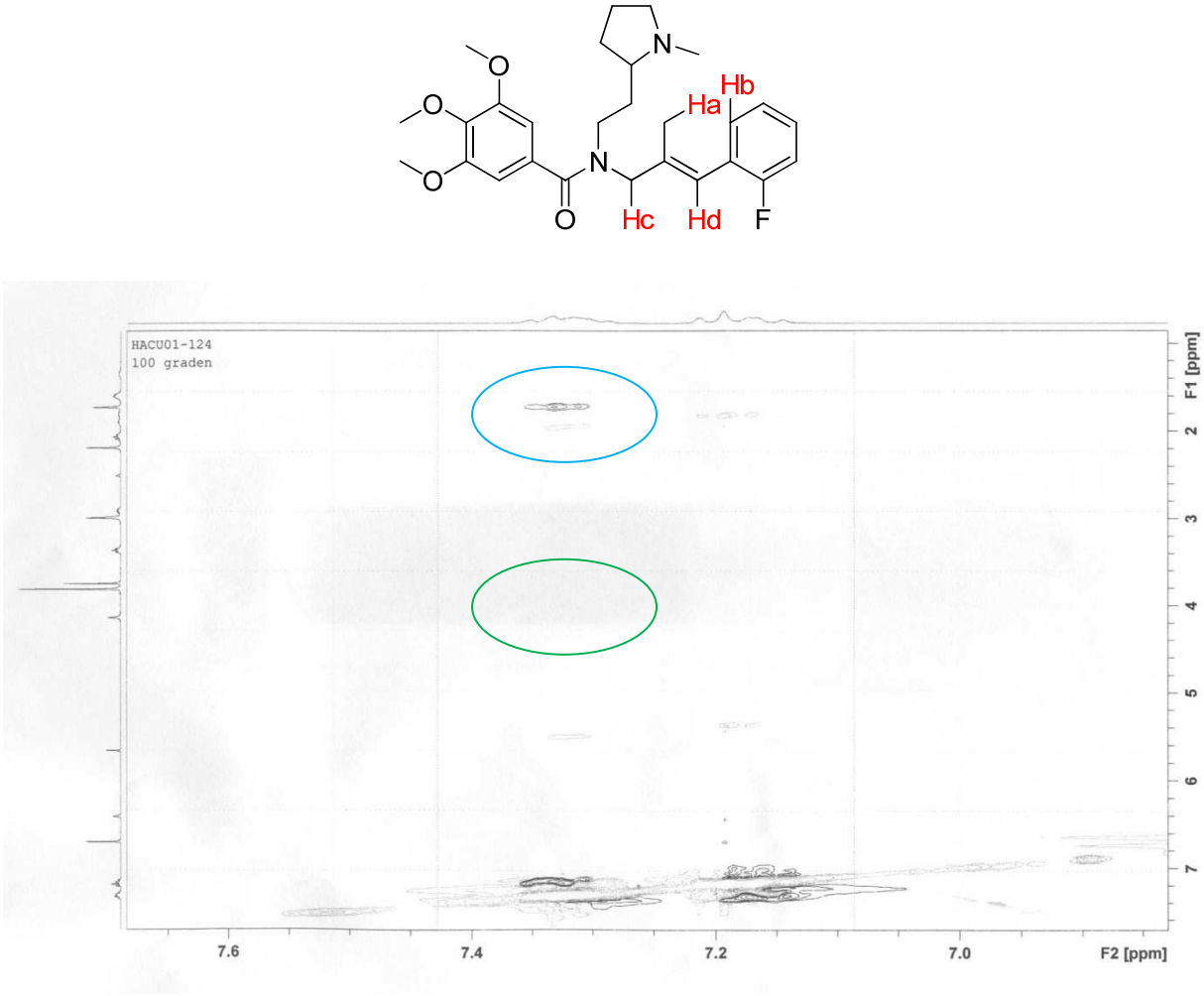


Figure S5. Blow-up of 2D-NOESY spectrum of compound **29** in DMSO-d6 at 373 K. This particular NMR sample had a trace of DCM left (at 5.66 ppm). Clearly visible is the Ha x Hb coupling (blue, indicative for *trans*-configuration) and the absence of Hc x Hb couping (green, if present this would be indicative of *cis*-configuration).

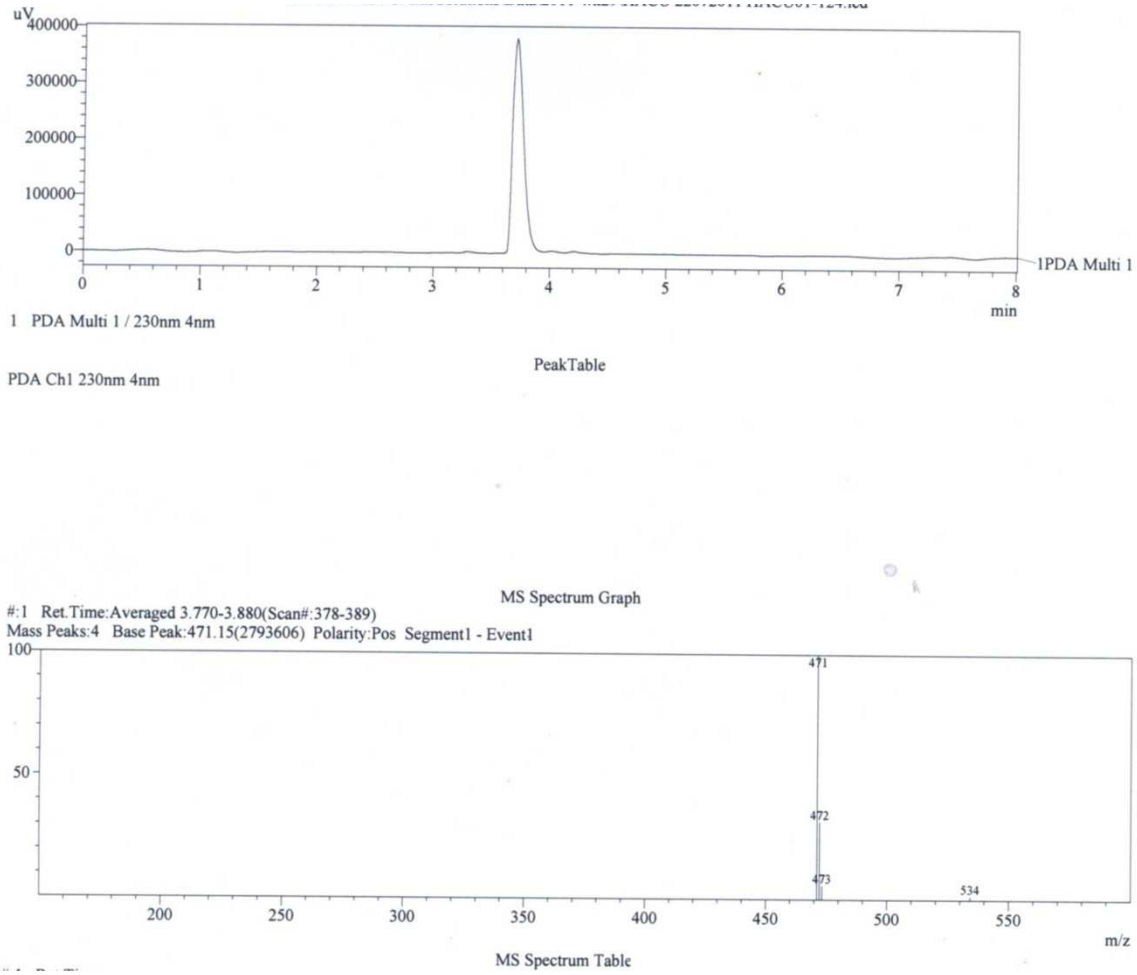


Figure S6. LC-MS chromatogram of compound **29** (detection at 230 nm).

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