

Supplementary materials

***N*-Skatyltryptamines – Dual 5-HT₆R/D₂R Ligands with Antipsychotic and Procognitive Potential**

Agata Hogendorf¹, Adam S. Hogendorf¹, Rafał Kurczab¹, Grzegorz Satała¹, Bernadeta Szewczyk², Paulina Cieślik², Gniewomir Latacz³, Jadwiga Handzlik³, Tomasz Lenda⁴, Katarzyna Kaczorowska¹, Jakub Staroń¹, Ryszard Bugno¹, Beata Duszyńska¹ and Andrzej J. Bojarski.^{1,*}

¹ Department of Medicinal Chemistry, Maj Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 30-343 Kraków, Poland; agatah@if-pan.krakow.pl (A.H.), ahogen@if-pan.krakow.pl (A.S.H.); kurczab@if-pan.krakow.pl (R.K.); satala@if-pan.krakow.pl (G.S.); k.kaczor@if-pan.krakow.pl (K.K.); staron@if-pan.krakow.pl (J.S.); bugno@if-pan.krakow.pl (R.B.); duszyn@if-pan.krakow.pl (B.D.).

² Department of Neurobiology, Maj Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, 30-343 Kraków, Poland; szewczyk@if-pan.krakow.pl (B.S.); cieslik@if-pan.krakow.pl (P.C.).

³ Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, Medyczna 9, PL 30-688 Kraków, Poland; glatacz@cm-uj.krakow.pl (G.L.); j.handzlik@uj.edu.pl (J.H.).

⁴ Department of Neuropsychopharmacology, Maj Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 30-343 Kraków, Poland; lenda@if-pan.krakow.pl (T.L.).

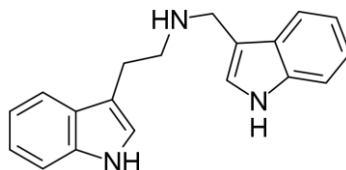
* Correspondence: bojarski@if-pan.krakow.pl

Table of contents

1. Chemical characterization of synthesized compounds.....	2
2. In vitro pharmacology	56
2.1 Radioligand binding assay	56
3. Metabolic stability	57

1. Chemical characterization of synthesized compounds.

[2-(1*H*-indol-3-yl)ethyl][[1(*H*-indol-3-yl)methyl]amine (1)

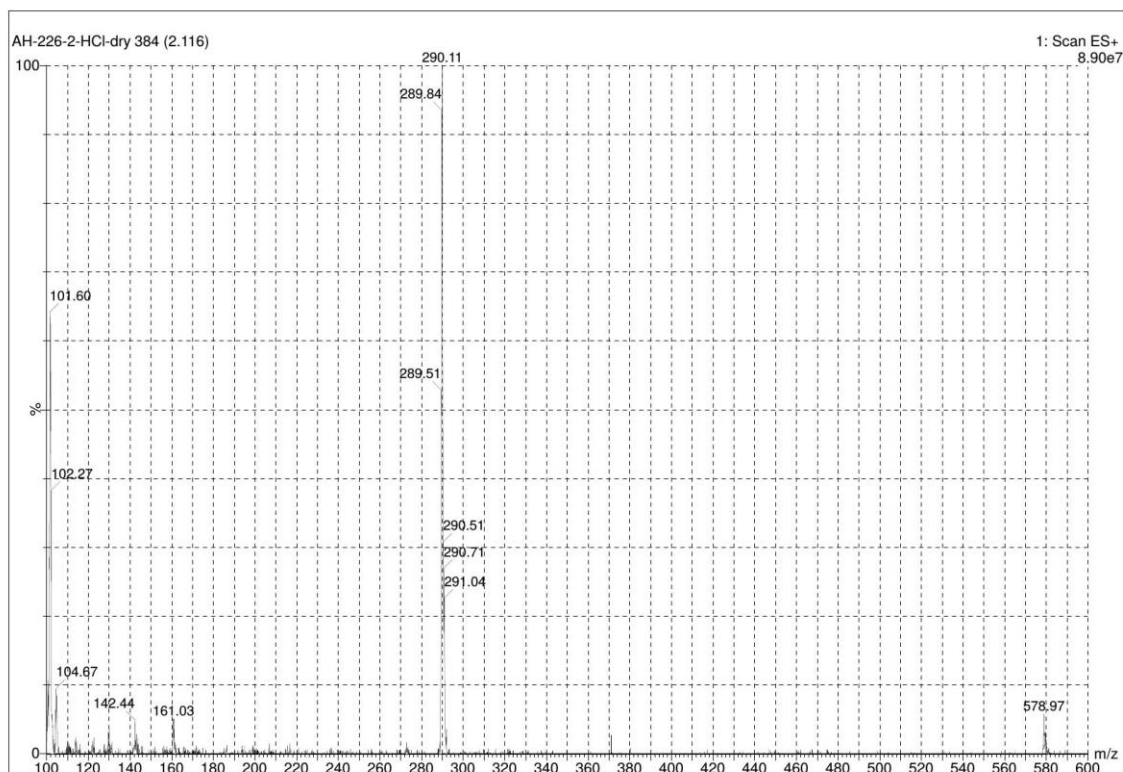


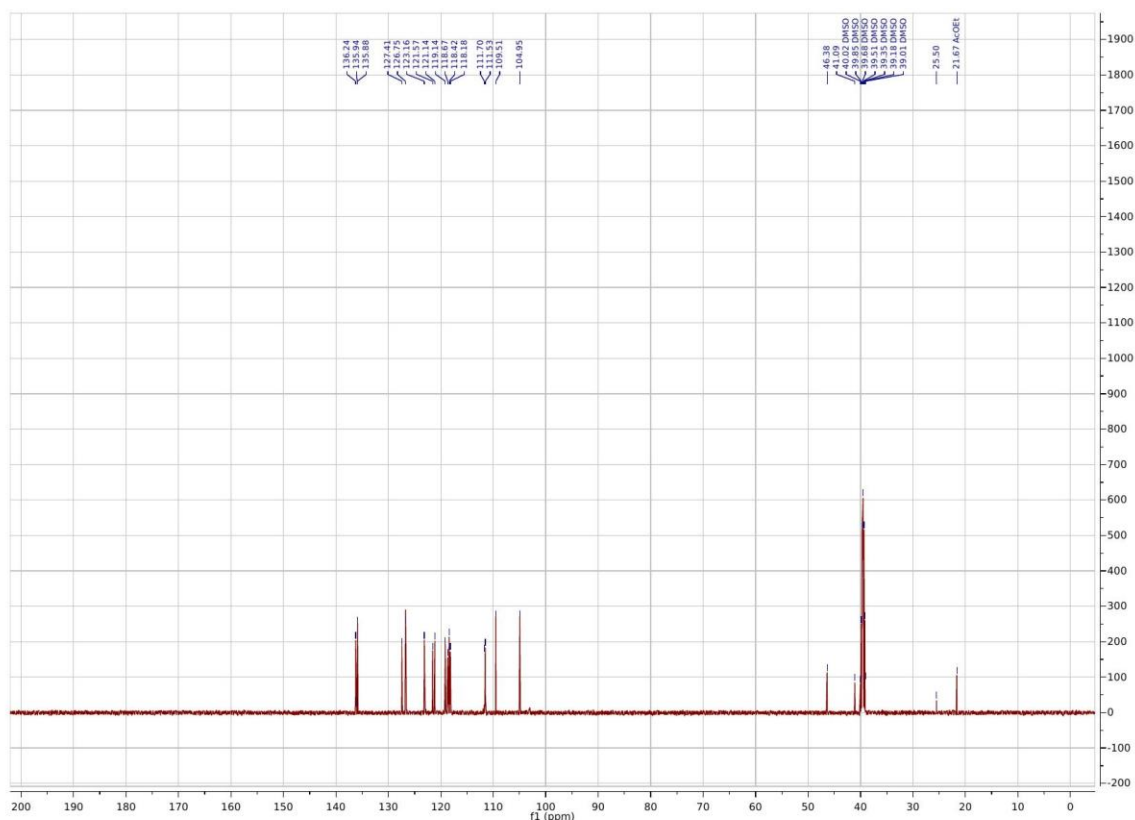
The product was obtained as a white solid. Yield: 48%.

LCMS [M+1] = 290,11 (290,17 calculated).

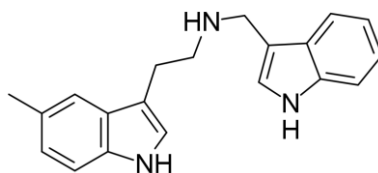
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.44 (d, $J = 2.6$ Hz, 1H), 11.00 (d, $J = 2.4$ Hz, 1H), 9.29 (d, $J = 7.1$ Hz, 2H), 7.79 (dq, $J = 7.9, 0.9$ Hz, 1H), 7.63 (d, $J = 2.6$ Hz, 1H), 7.55 (dt, $J = 7.9, 0.9$ Hz, 1H), 7.43 (dt, $J = 8.1, 0.9$ Hz, 1H), 7.36 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.20 (d, $J = 2.4$ Hz, 1H), 7.14 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.07 (dtd, $J = 8.0, 6.9, 1.1$ Hz, 2H), 6.98 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 4.34 (t, $J = 5.4$ Hz, 2H), 3.15 (d, $J = 8.3$ Hz, 4H), 2.50 (p, $J = 1.8$ Hz, 2H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 136.24, 135.94, 135.88, 127.41, 126.75, 123.16, 121.57, 121.14, 119.14, 118.67, 118.42, 118.18, 111.70, 111.53, 109.51, 104.95, 46.38, 41.09, 25.50, 21.67.





[(1*H*-indol-3-yl)methyl][2-(5-methyl-1*H*-indol-3-yl)ethyl]amine (2)

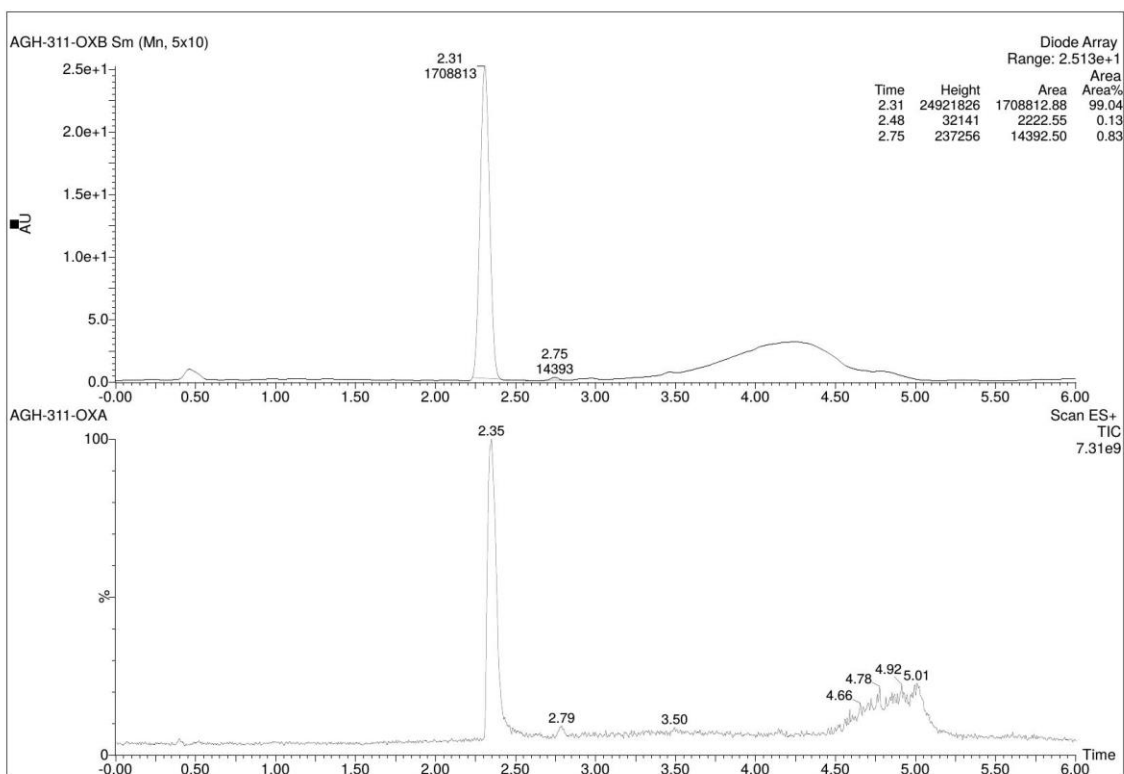
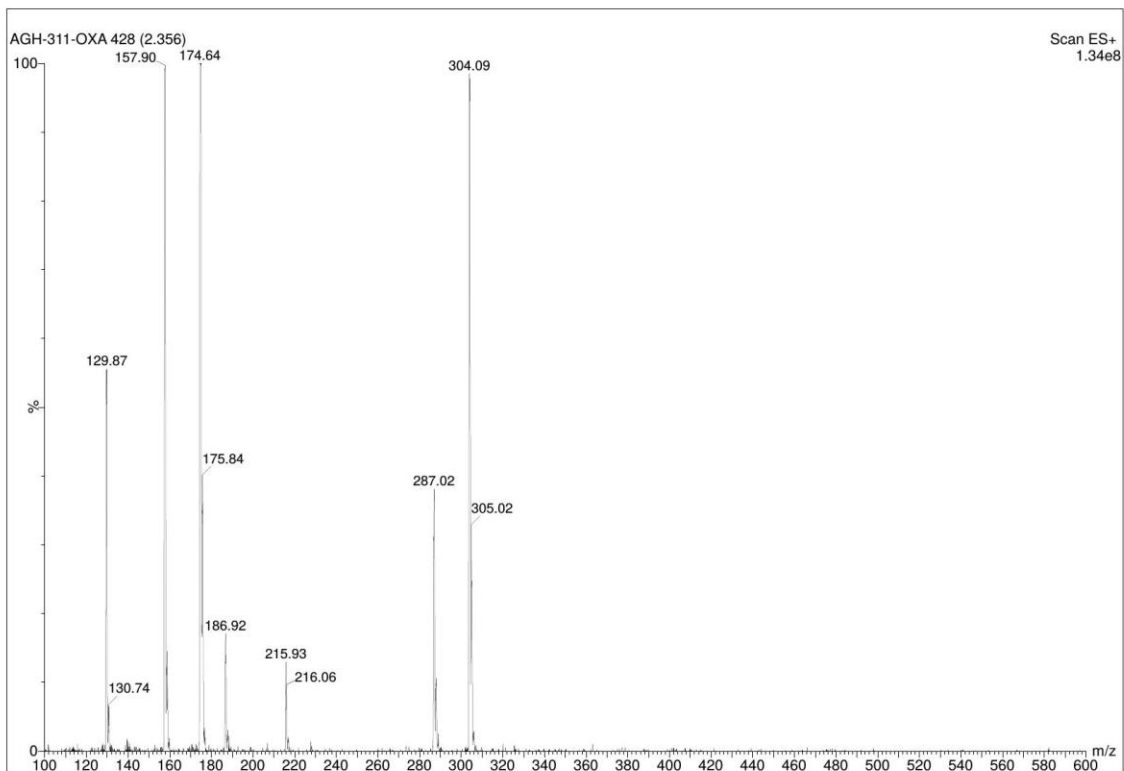


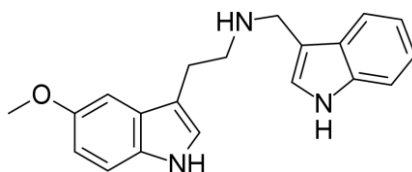
The product was obtained as a beige solid. Yield: 50%.

LCMS [M+1] = 304,09 (304,18 calculated).

¹H NMR (500 MHz, DMSO-*d*₆) δ 11.43 (s, 1H), 10.83 (s, 1H), 7.76 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.55 (d, *J* = 2.6 Hz, 1H), 7.44 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.18 – 7.11 (m, 2H), 7.07 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.37 (s, 2H), 3.20 – 3.13 (m, 2H), 3.04 (dd, *J* = 9.9, 6.4 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.79, 135.94, 134.63, 127.23, 126.95, 126.88, 126.78, 123.26, 122.76, 121.60, 119.17, 118.58, 117.66, 111.76, 111.26, 108.95, 105.10, 46.40, 41.15, 21.74, 21.27.



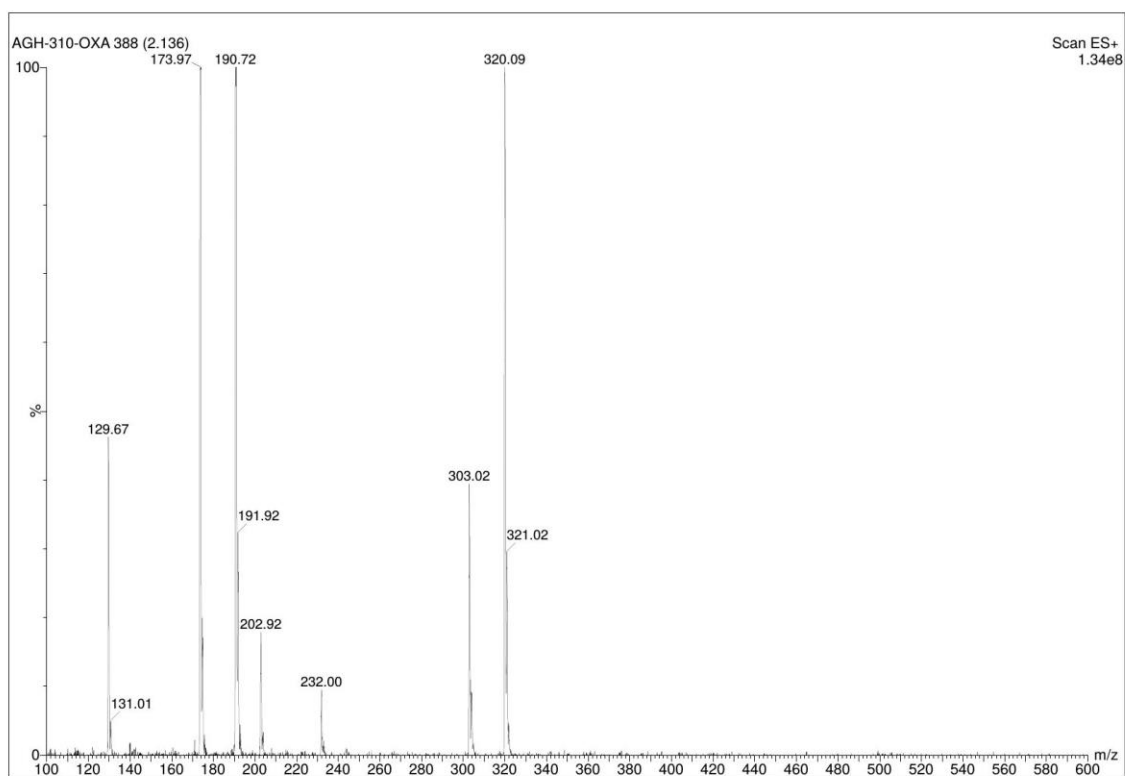


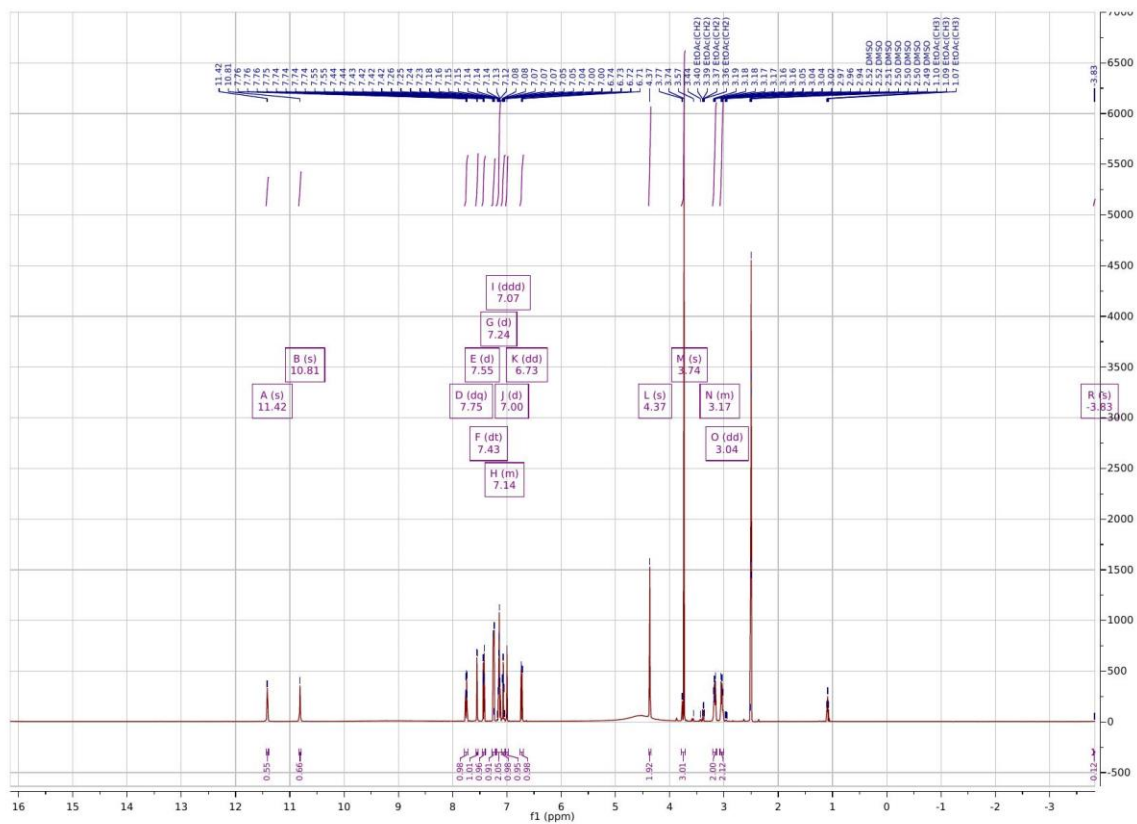
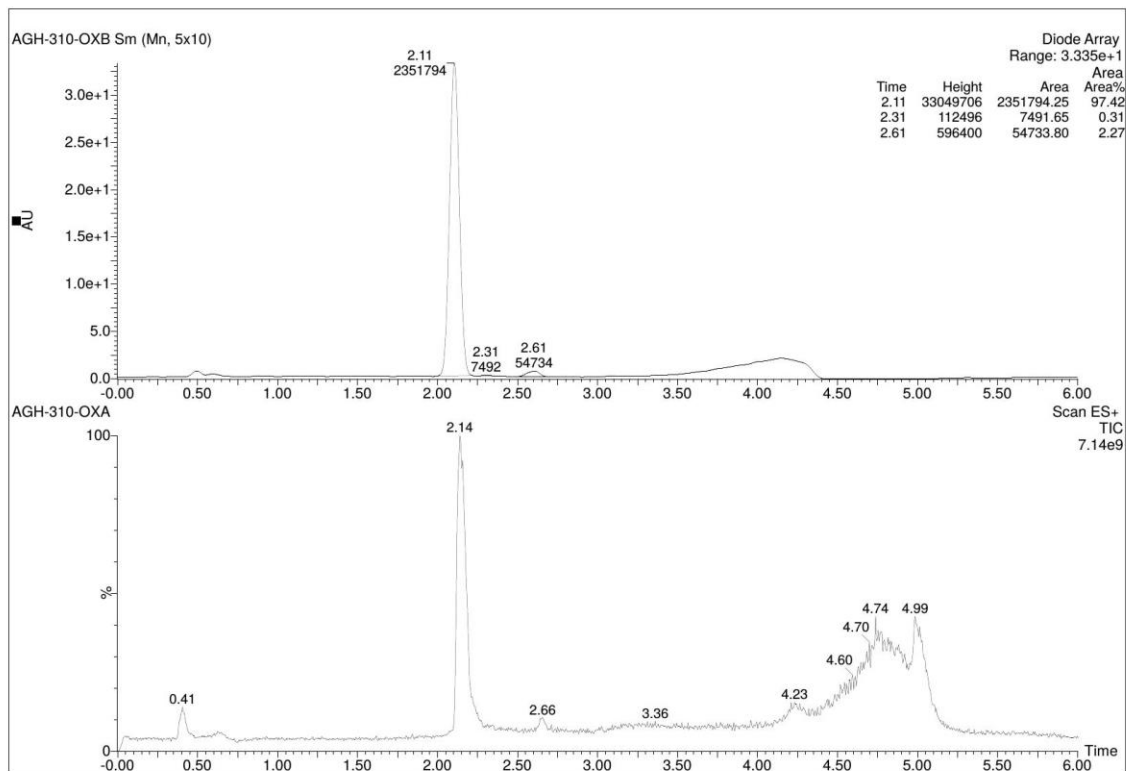
The product was obtained as a off-white solid. Yield: 63%.

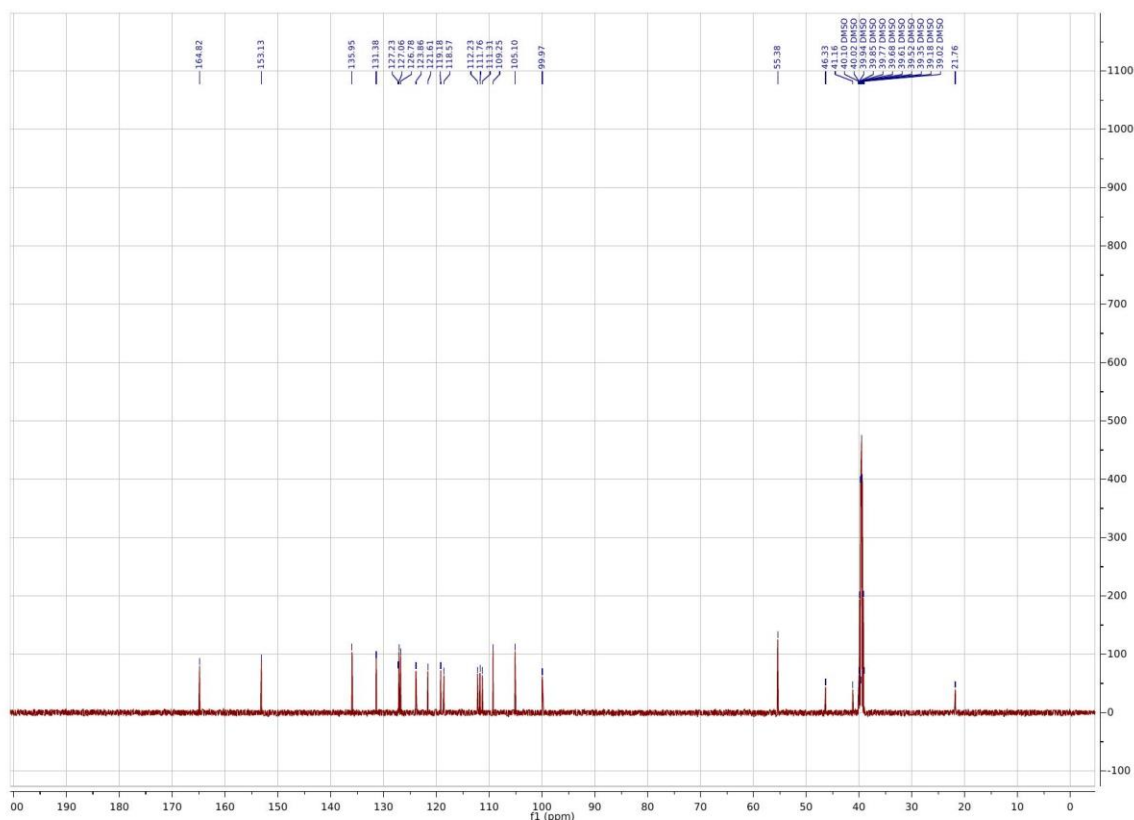
LCMS [M+1] = 320,09 (320,18 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.42 (s, 1H), 10.81 (s, 1H), 7.75 (dq, J = 7.9, 0.9 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.43 (dt, J = 8.1, 0.9 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.20 – 7.10 (m, 2H), 7.07 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.73 (dd, J = 8.8, 2.4 Hz, 1H), 4.37 (s, 2H), 3.74 (s, 3H), 3.21 – 3.14 (m, 2H), 3.04 (dd, J = 9.8, 6.5 Hz, 2H).

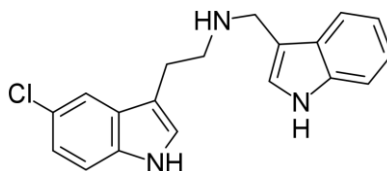
^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 164.82, 153.13, 135.95, 131.38, 127.23, 127.06, 126.78, 123.86, 121.61, 119.18, 118.57, 112.23, 111.76, 111.31, 109.25, 105.10, 99.97, 55.38, 46.33, 41.16, 21.76.







[2-(5-chloro-1*H*-indol-3-yl)ethyl][(1*H*-indol-3-yl)methyl]amine (4)

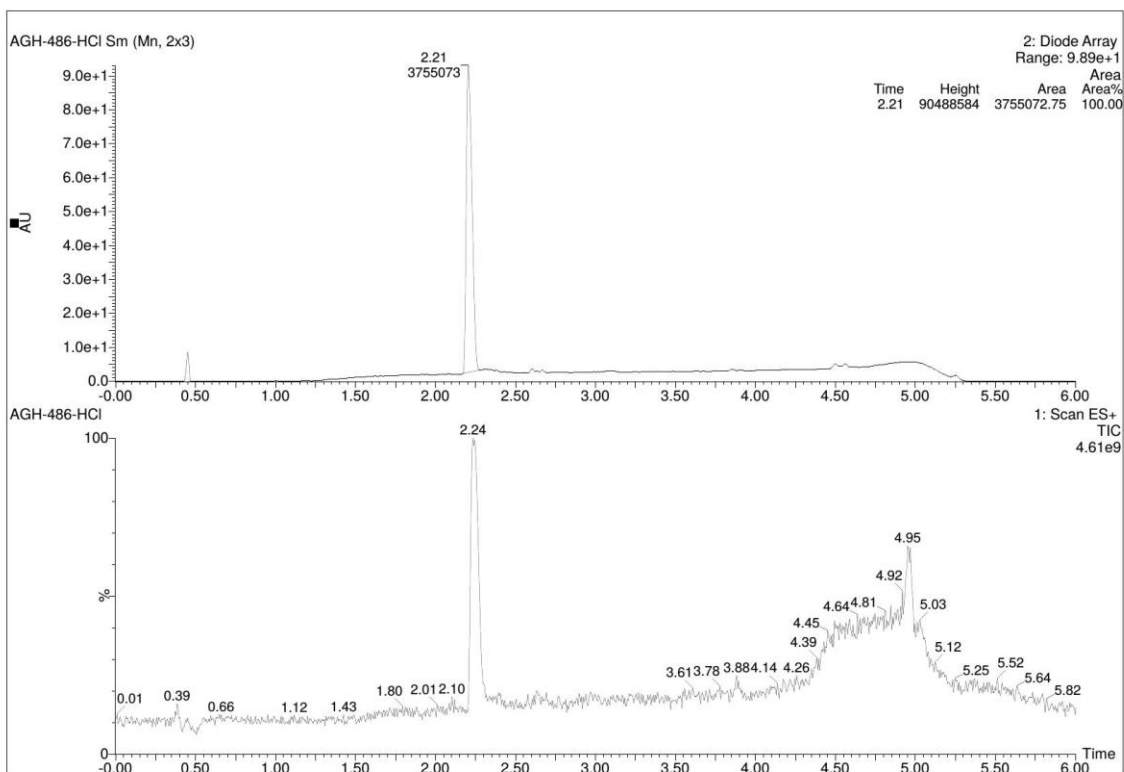
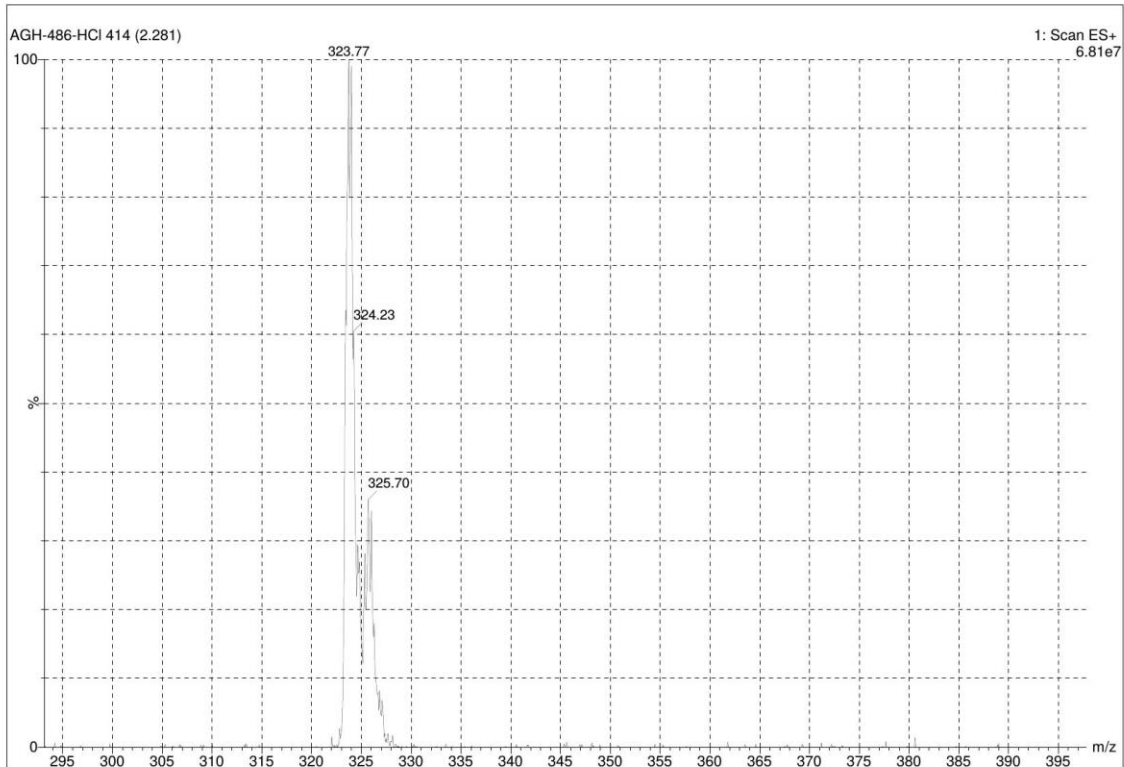


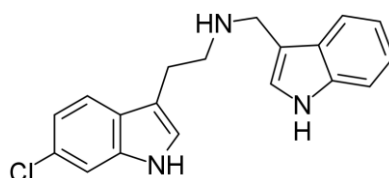
The product was obtained as a white solid. Yield: 68%.

LCMS [M+1] = 323,77 (324,13 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.41 (d, $J = 2.6$ Hz, 1H), 11.22 (d, $J = 2.4$ Hz, 1H), 9.16 (s, 2H), 7.79 (dt, $J = 7.9, 1.0$ Hz, 1H), 7.62 (dd, $J = 13.2, 2.3$ Hz, 2H), 7.43 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.41 – 7.34 (m, 1H), 7.30 (d, $J = 2.4$ Hz, 1H), 7.14 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.11 – 7.03 (m, 2H), 4.34 (t, $J = 5.3$ Hz, 2H), 3.18 – 3.06 (m, 4H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 135.88, 134.71, 127.93, 127.37, 126.72, 125.23, 123.23, 121.60, 121.11, 119.15, 118.65, 117.52, 113.08, 111.72, 109.49, 104.98, 46.37, 41.11, 21.47.



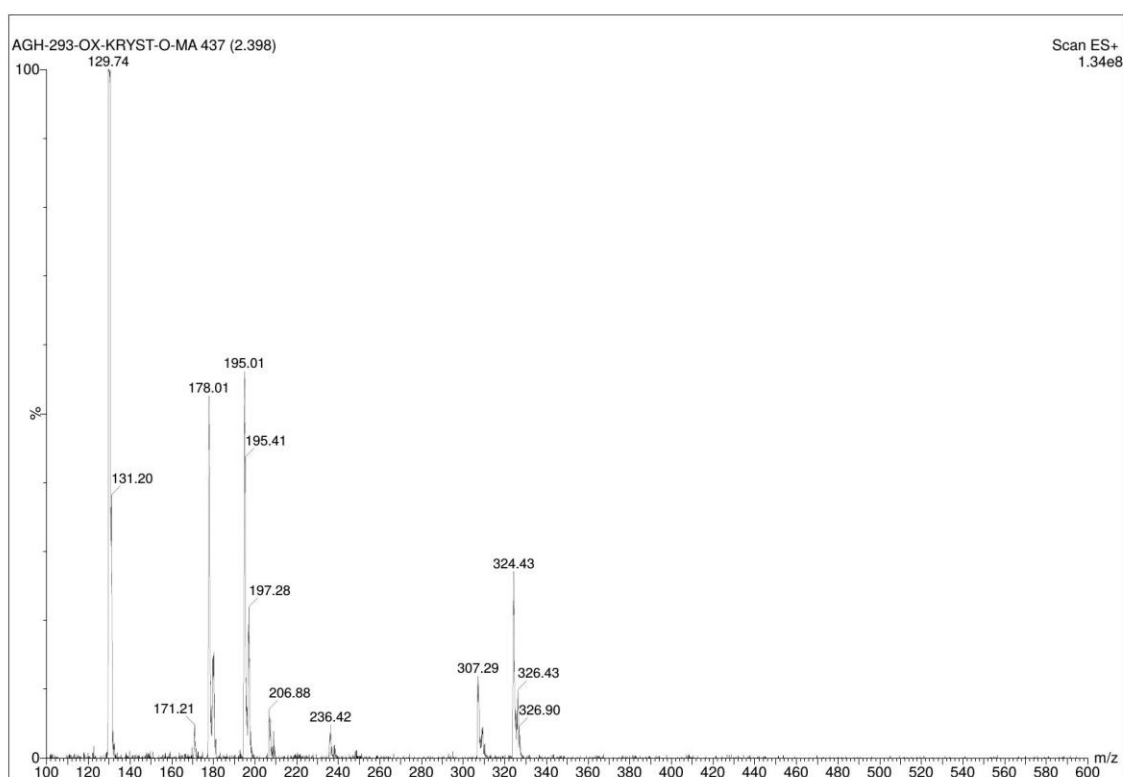


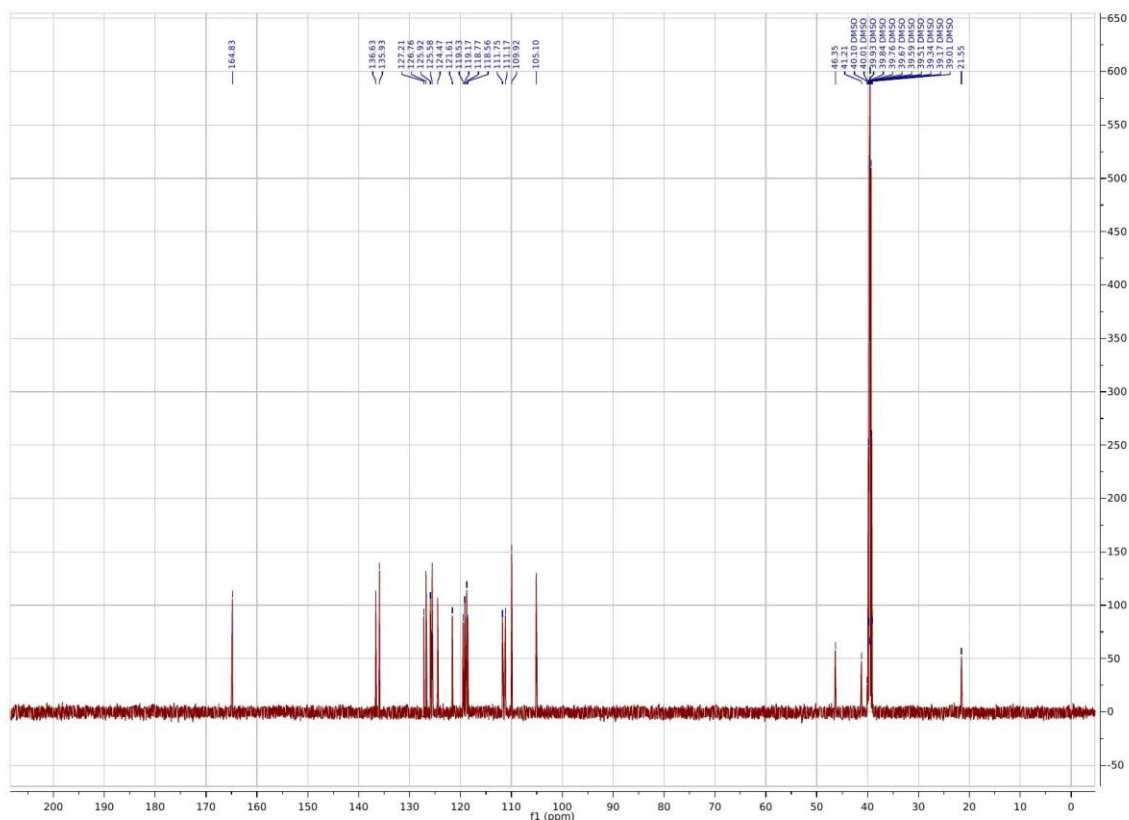
The product was obtained as a beige solid. Yield: 44%.

LCMS [M+1] = 324,43 (324,13 calculated).

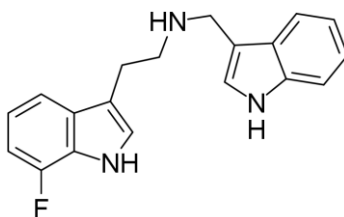
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.41 (s, 0H), 11.18 (s, 1H), 7.74 (dt, $J = 7.8, 0.9$ Hz, 1H), 7.59 – 7.49 (m, 2H), 7.46 – 7.39 (m, 2H), 7.25 (d, $J = 2.3$ Hz, 1H), 7.14 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.07 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 7.00 (dd, $J = 8.5, 1.9$ Hz, 1H), 4.36 (s, 2H), 3.21 – 3.14 (m, 2H), 3.06 (dd, $J = 9.6, 6.5$ Hz, 2H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 164.83, 136.63, 135.93, 127.21, 126.76, 125.92, 125.58, 124.47, 121.61, 119.53, 119.17, 118.77, 118.56, 111.75, 111.17, 109.92, 105.10, 46.35, 41.21, 21.55.





[2-(7-fluoro-1*H*-indol-3-yl)ethyl][(1*H*-indol-3-yl)methyl]amine (6)

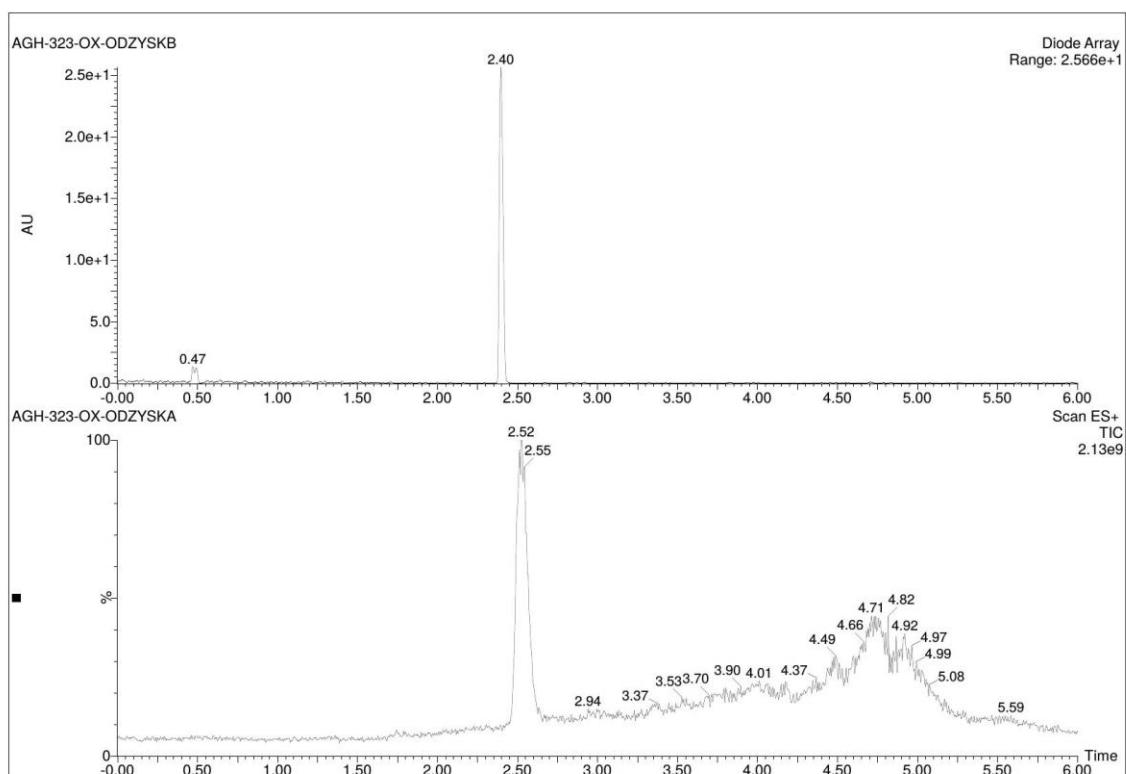
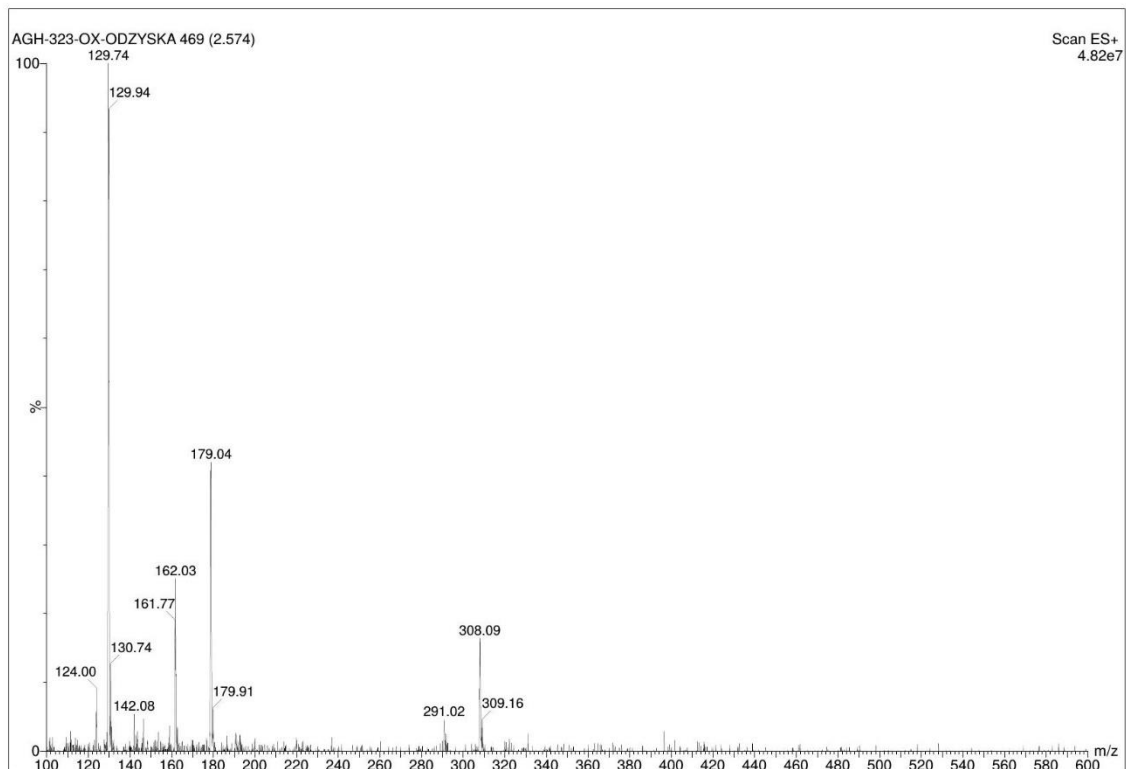


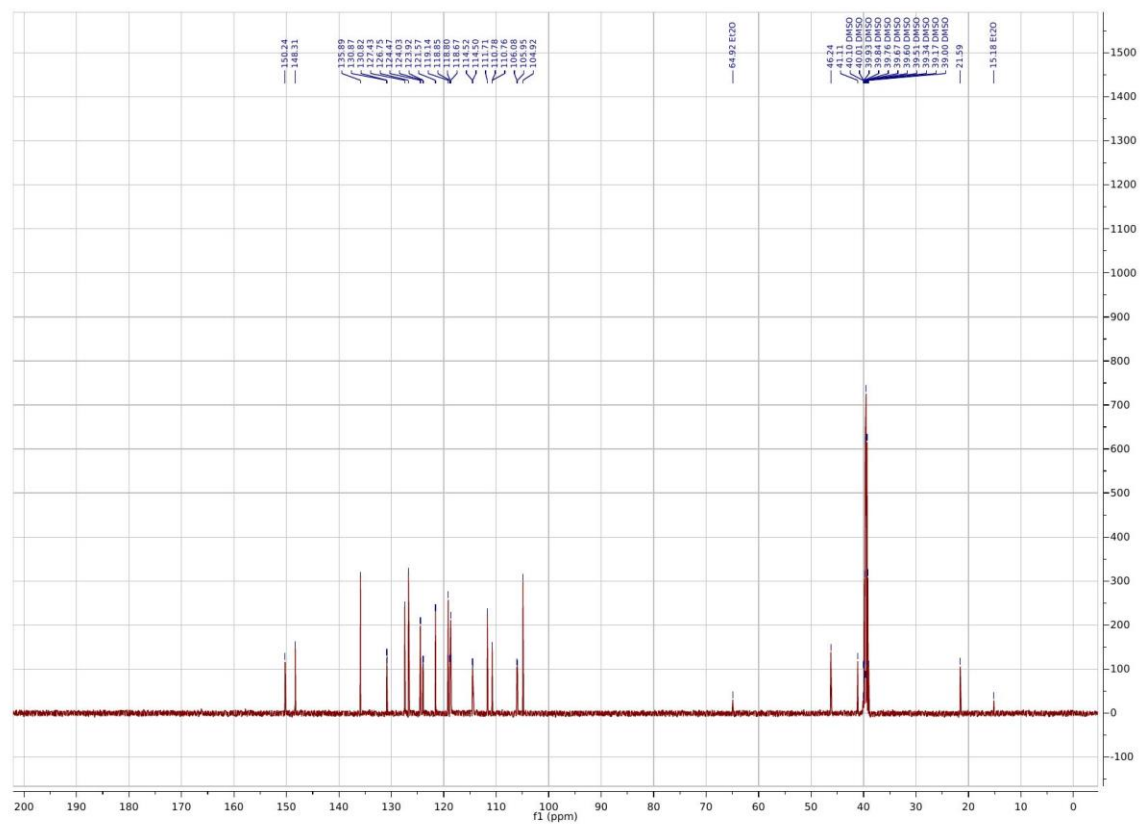
The product was obtained as a yellow solid. Yield: 90%.

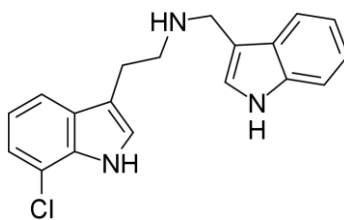
LCMS [M+1] = 308,09 (308,16 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.48 (s, 1H), 11.45 (s, 1H), 9.31 (s, 2H), 7.79 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.63 (d, $J = 2.6$ Hz, 1H), 7.43 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.41 – 7.36 (m, 1H), 7.28 (d, $J = 2.5$ Hz, 1H), 7.14 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.06 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.00 – 6.86 (m, 2H), 4.34 (s, 2H), 3.15 (t, $J = 3.1$ Hz, 4H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 150.24, 148.31, 135.89, 130.87, 130.82, 127.43, 126.75, 124.47, 124.03, 123.92, 121.57, 119.14, 118.85, 118.80, 118.67, 114.52, 114.50, 111.71, 110.78, 110.76, 106.08, 105.95, 104.92, 46.24, 41.11, 21.59.





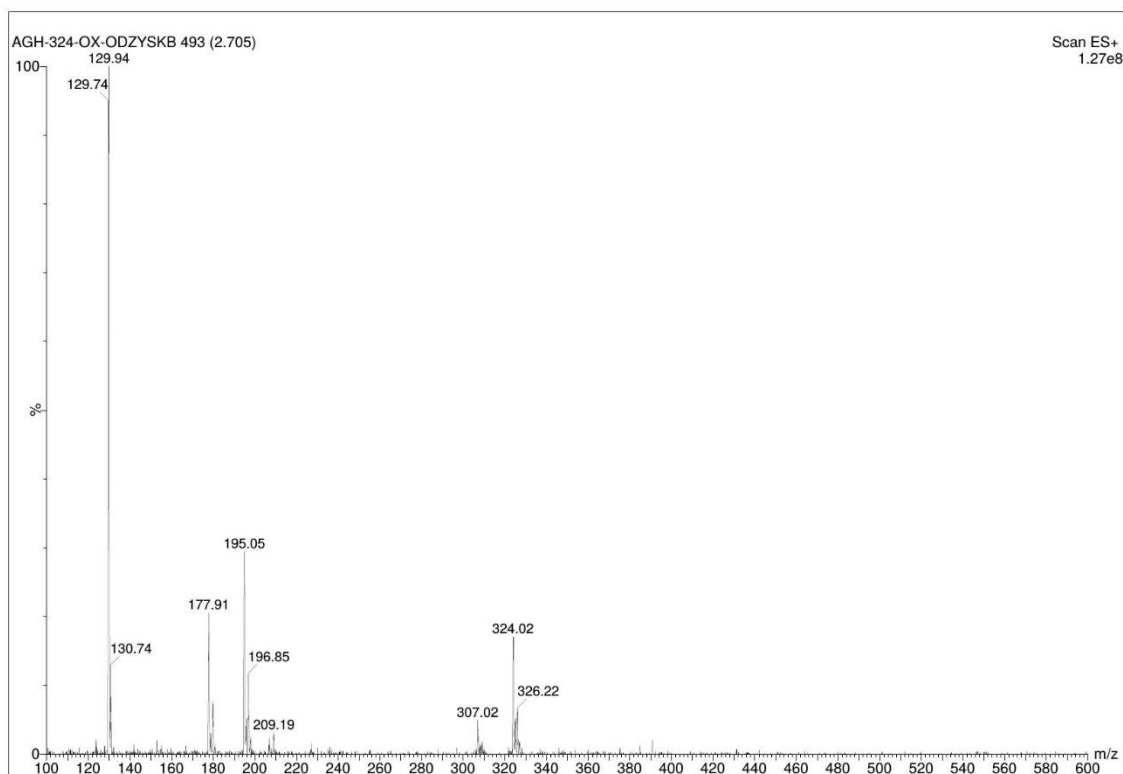


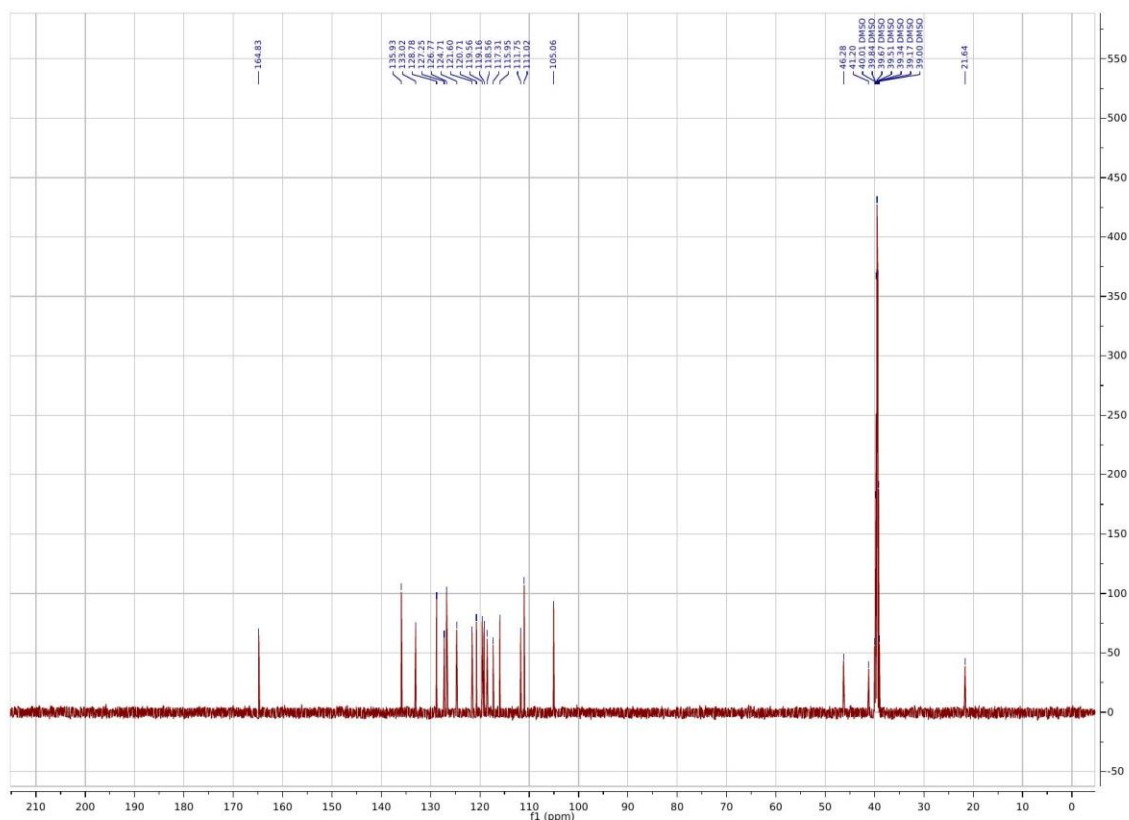
The product was obtained as a light brown solid. Yield: 61%.

LCMS [M+1] = 324,02 (324,13 calculated).

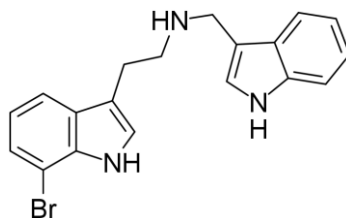
^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.47 – 11.38 (m, 1H), 11.38 – 11.29 (m, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.43 (dt, J = 8.1, 0.9 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.17 (dd, J = 7.5, 0.8 Hz, 1H), 7.14 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.07 (td, J = 7.4, 6.9, 1.0 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 4.36 (s, 2H), 3.19 (dd, J = 9.7, 6.3 Hz, 2H), 3.08 (dd, J = 9.6, 6.4 Hz, 2H).

^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ 164.83, 135.93, 133.02, 128.78, 127.25, 126.77, 124.71, 121.60, 120.71, 119.56, 119.16, 118.56, 117.31, 115.95, 111.75, 111.02, 105.06, 46.28, 41.20, 21.64.





[2-(7-bromo-1H-indol-3-yl)ethyl][(1H-indol-3-yl)methyl]amine (8)

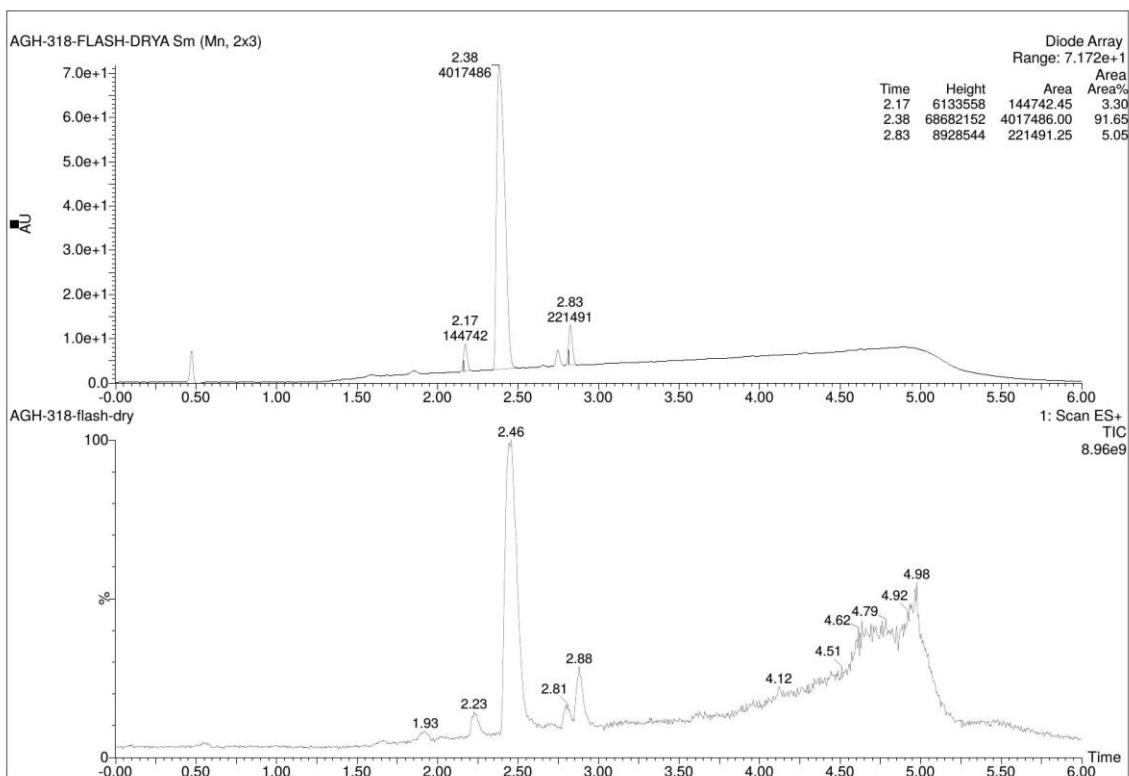
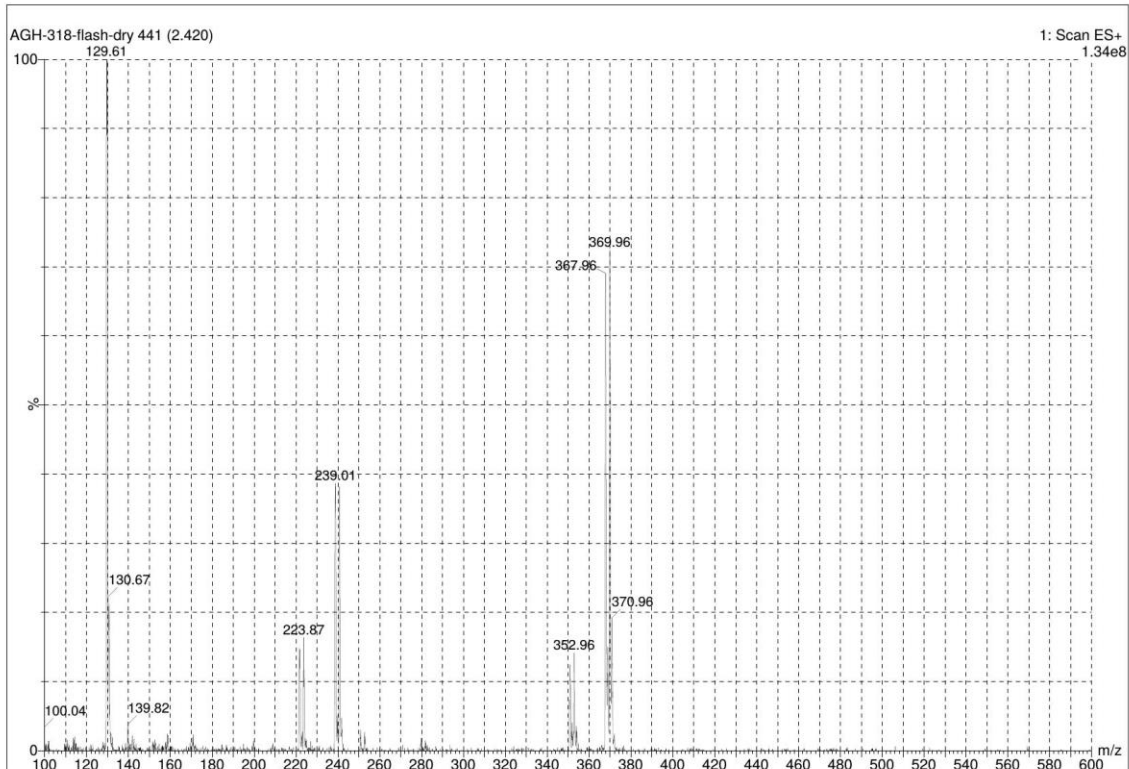


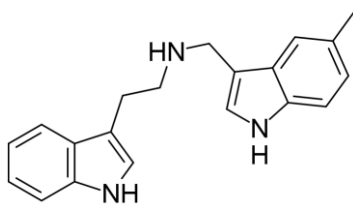
The product was obtained as a white solid. Yield: 43%.

LCMS [M+1] = 369,96 (368,08 calculated).

^1H NMR (500 MHz, DMSO- d_6) δ 11.41 (d, J = 2.5 Hz, 1H), 11.20 (d, J = 2.5 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.61 – 7.52 (m, 2H), 7.43 (dt, J = 8.1, 1.0 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.29 (d, J = 2.5 Hz, 1H), 7.14 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 6.95 (t, J = 7.7 Hz, 1H), 4.36 (s, 2H), 3.23 – 3.16 (m, 2H), 3.07 (dd, J = 9.3, 6.6 Hz, 2H).

^{13}C NMR (126 MHz, DMSO- d_6) δ 164.79, 135.93, 134.52, 128.54, 127.23, 126.76, 124.71, 123.76, 121.60, 119.98, 119.17, 118.56, 117.79, 117.75, 111.09, 105.07, 104.30, 46.28, 41.22, 25.50, 21.70.



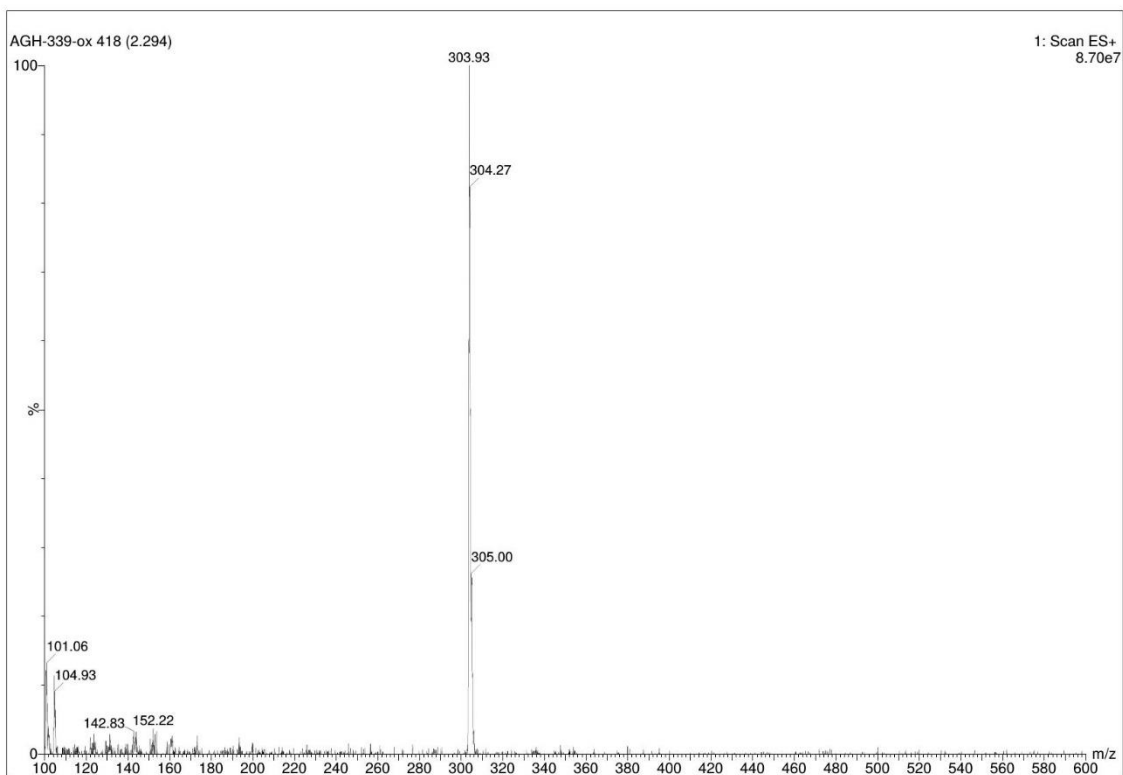


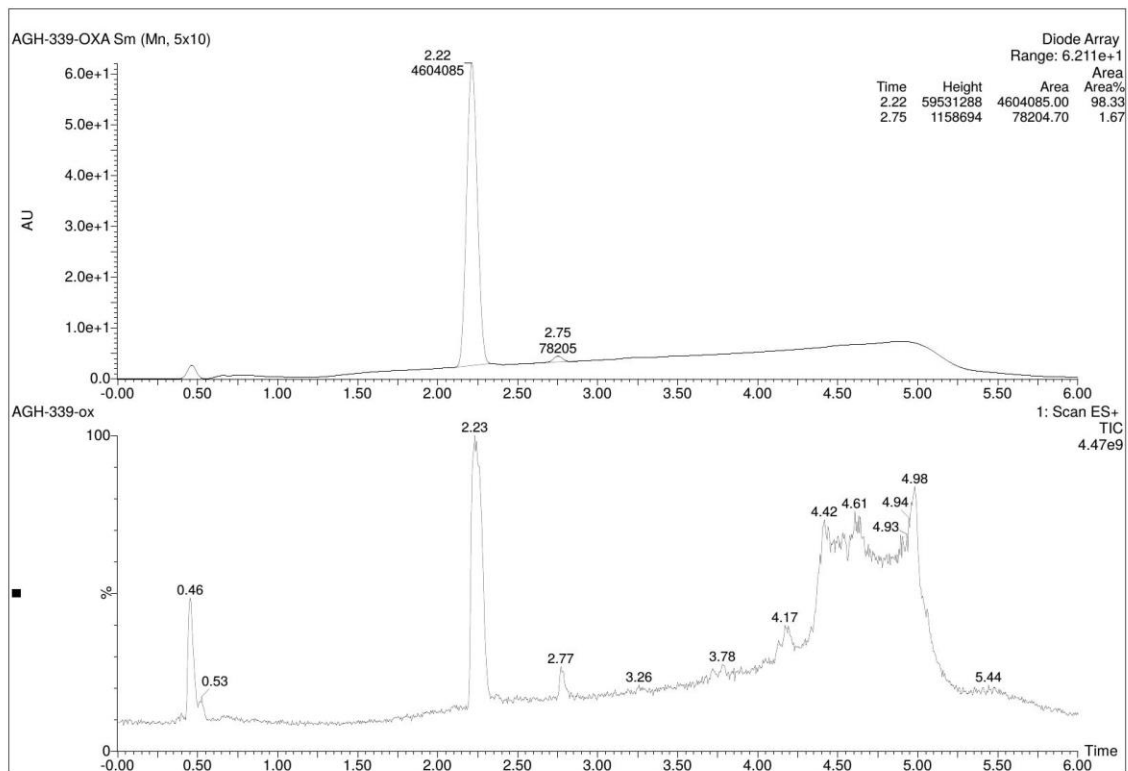
The product was obtained as a beige solid. Yield: 40%.

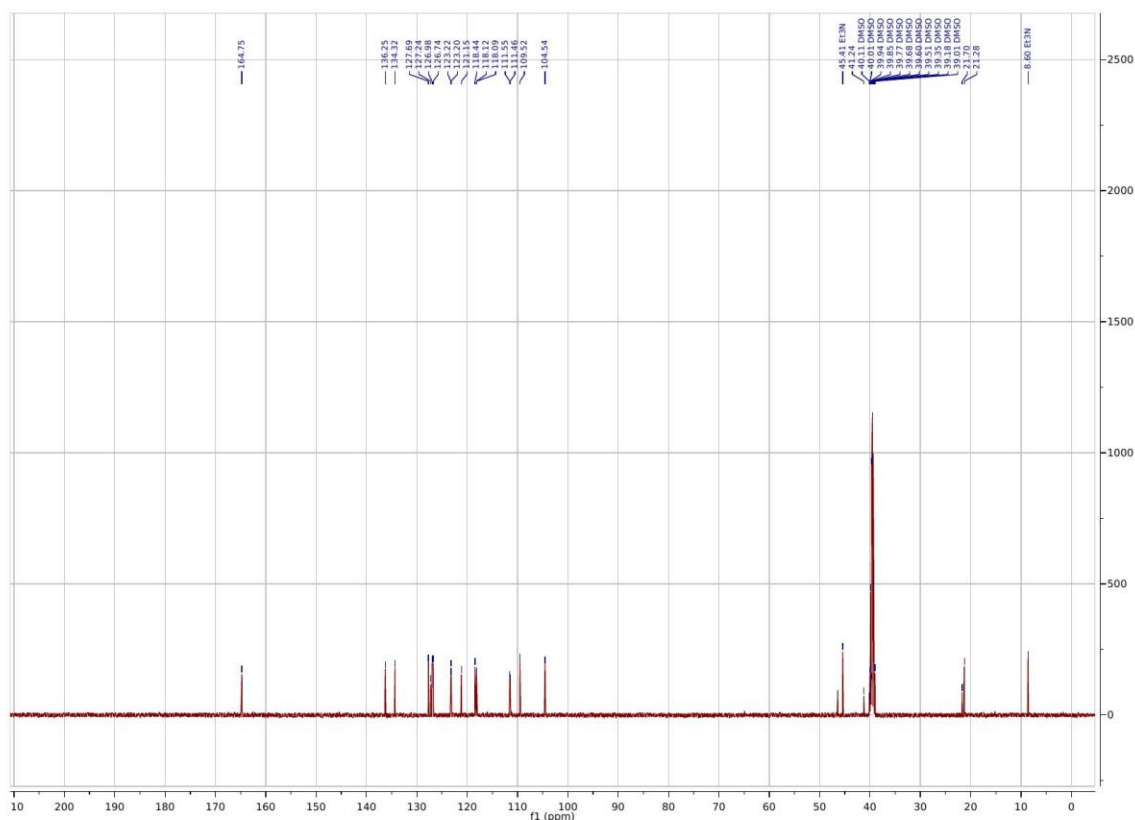
LCMS [M+1] = 303,93 (304,18 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.27 (d, $J = 2.4$ Hz, 1H), 10.98 (d, $J = 2.4$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 2.6$ Hz, 1H), 7.36 (dd, $J = 8.1, 1.0$ Hz, 1H), 7.37 – 7.28 (m, 1H), 7.20 (d, $J = 2.4$ Hz, 1H), 7.08 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.05 – 6.94 (m, 2H), 4.33 (s, 2H), 3.18 (dd, $J = 10.5, 5.7$ Hz, 2H), 3.11 – 2.99 (m, 4H), 2.39 (s, 3H).

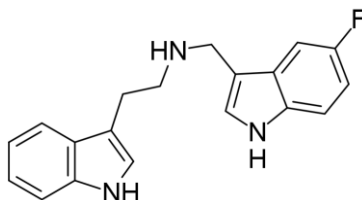
^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 164.75, 136.25, 134.32, 127.69, 127.24, 126.98, 126.74, 123.22, 123.20, 121.15, 118.44, 118.12, 118.09, 111.55, 111.46, 109.52, 104.54, 41.24, 21.70, 21.28.







[(5-fluoro-1*H*-indol-3-yl)methyl][2-(1*H*-indol-3-yl)ethyl]amine (10)

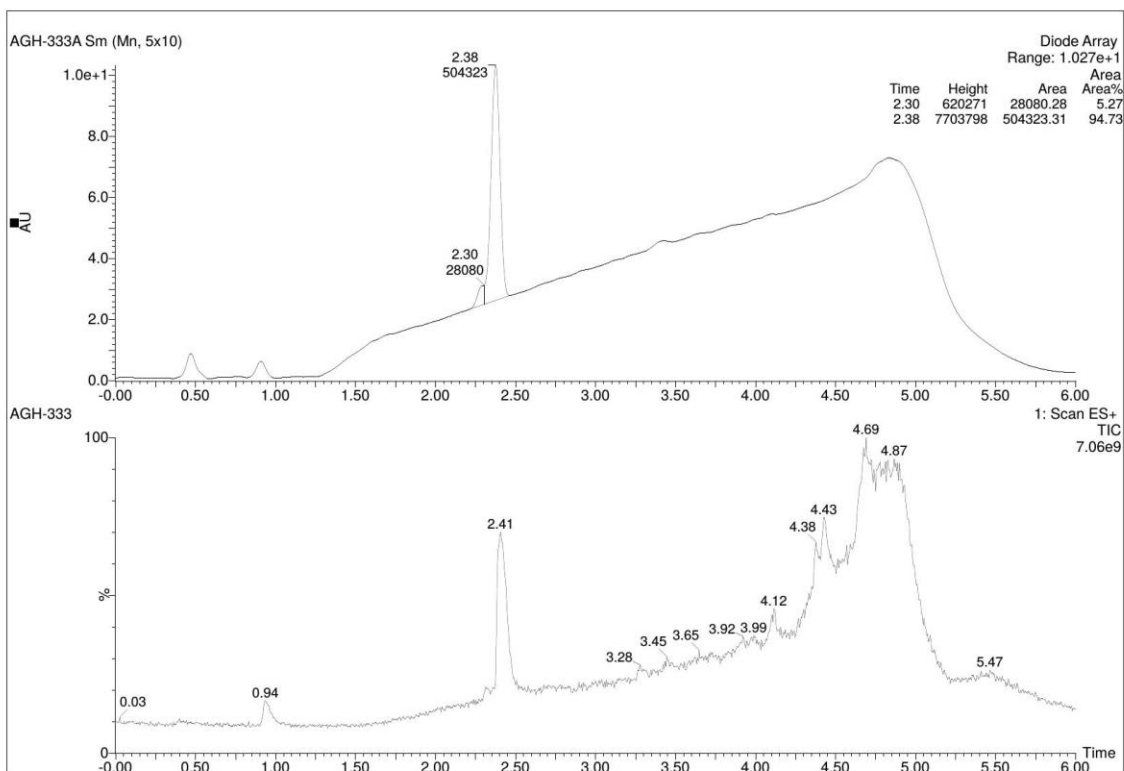
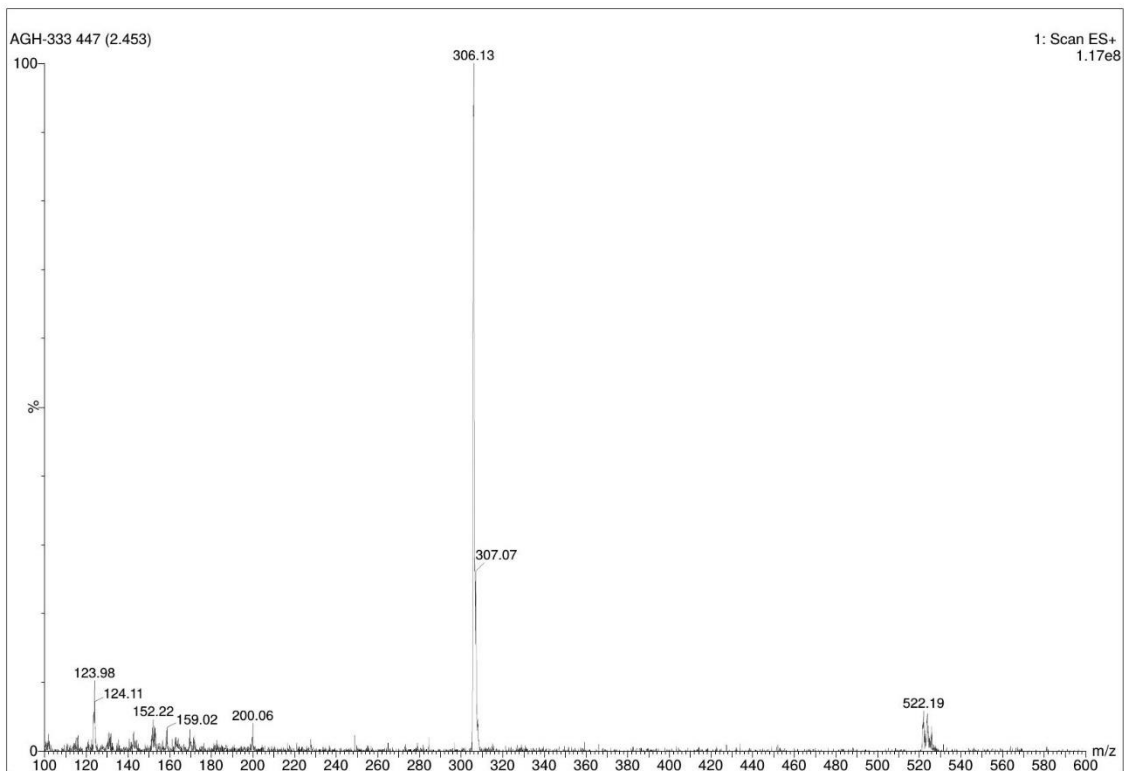


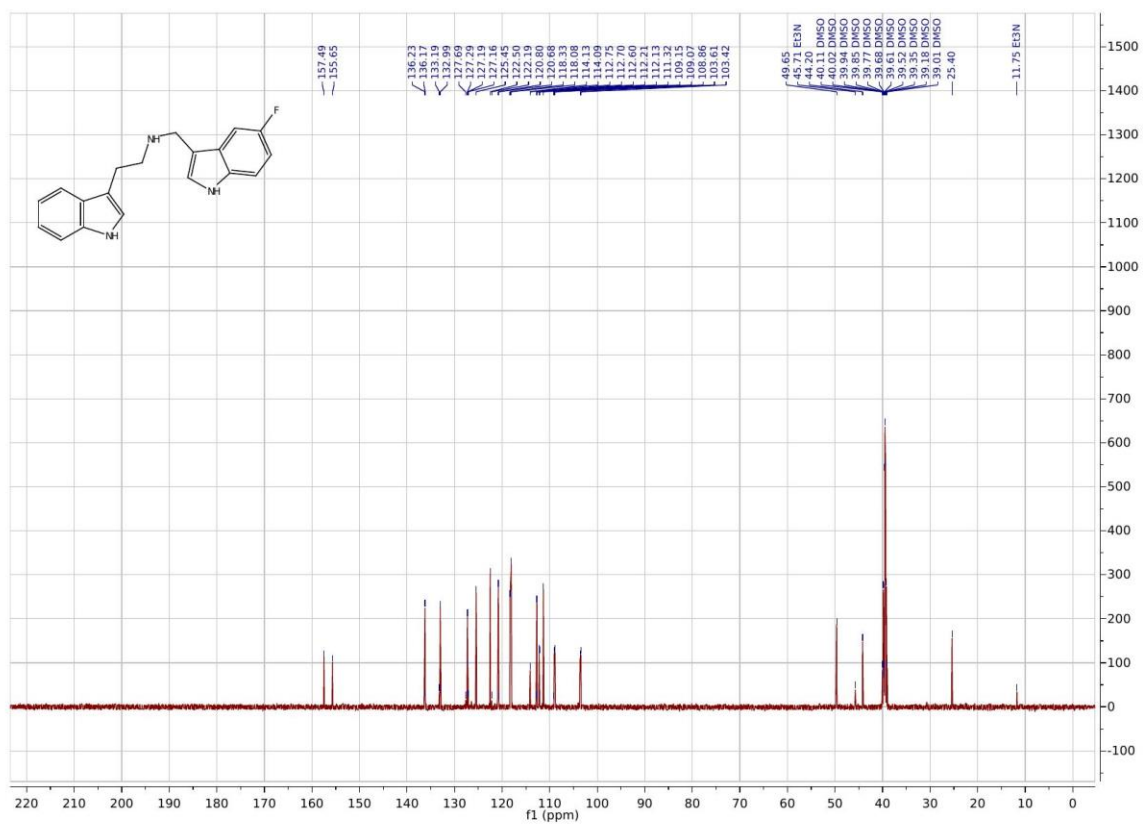
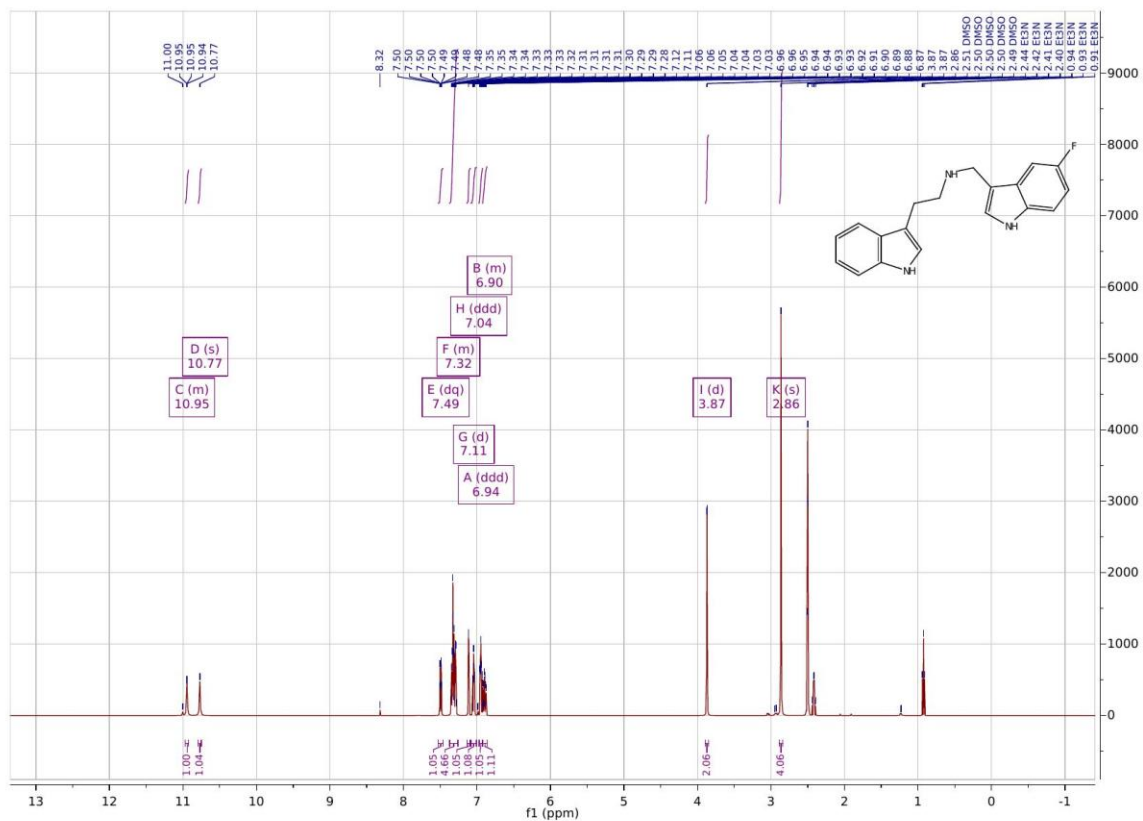
The product was obtained as a light yellow solid. Yield: 66%.

LCMS [M+1] = 306,13 (308,16 calculated).

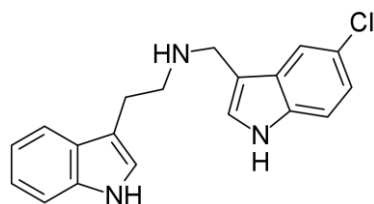
¹H NMR (500 MHz, DMSO-*d*₆) δ 10.97 – 10.92 (m, 1H), 10.77 (s, 1H), 7.49 (dq, *J* = 8.0, 0.9 Hz, 1H), 7.37 – 7.26 (m, 5H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.92 – 6.87 (m, 1H), 3.87 (d, *J* = 0.8 Hz, 2H), 2.86 (s, 4H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 157.49, 155.65, 136.23, 136.17, 133.19, 132.99, 127.69, 127.29, 127.19, 127.16, 125.45, 122.50, 122.19, 120.80, 120.68, 118.33, 118.08, 114.13, 114.09, 112.75, 112.70, 112.60, 112.21, 112.13, 111.32, 109.15, 109.07, 108.86, 103.61, 103.42, 49.65, 44.20, 25.40.



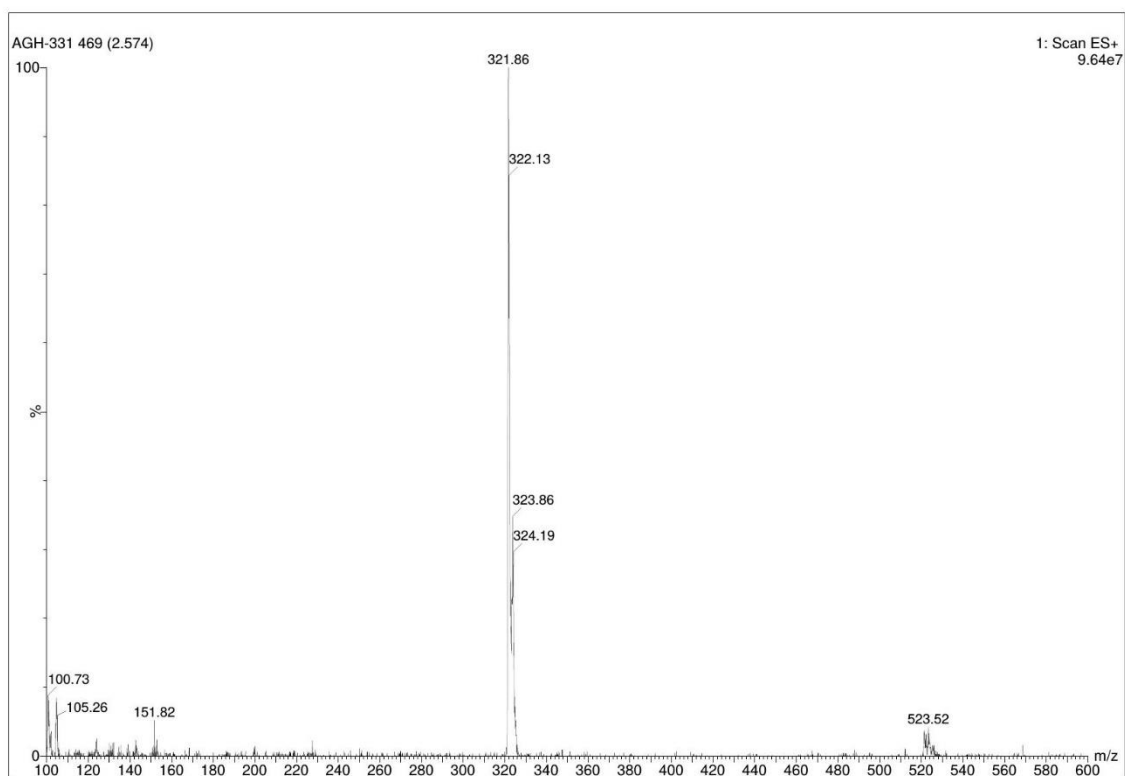


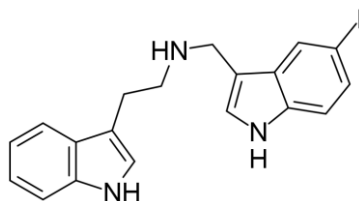
[(5-chloro-1*H*-indol-3-yl)methyl][2-(1*H*-indol-3-yl)ethyl]amine (11)



The product was obtained as a light brown solid. Yield: 56%.
 LCMS [M+1] = 322,13 (324,13 calculated).

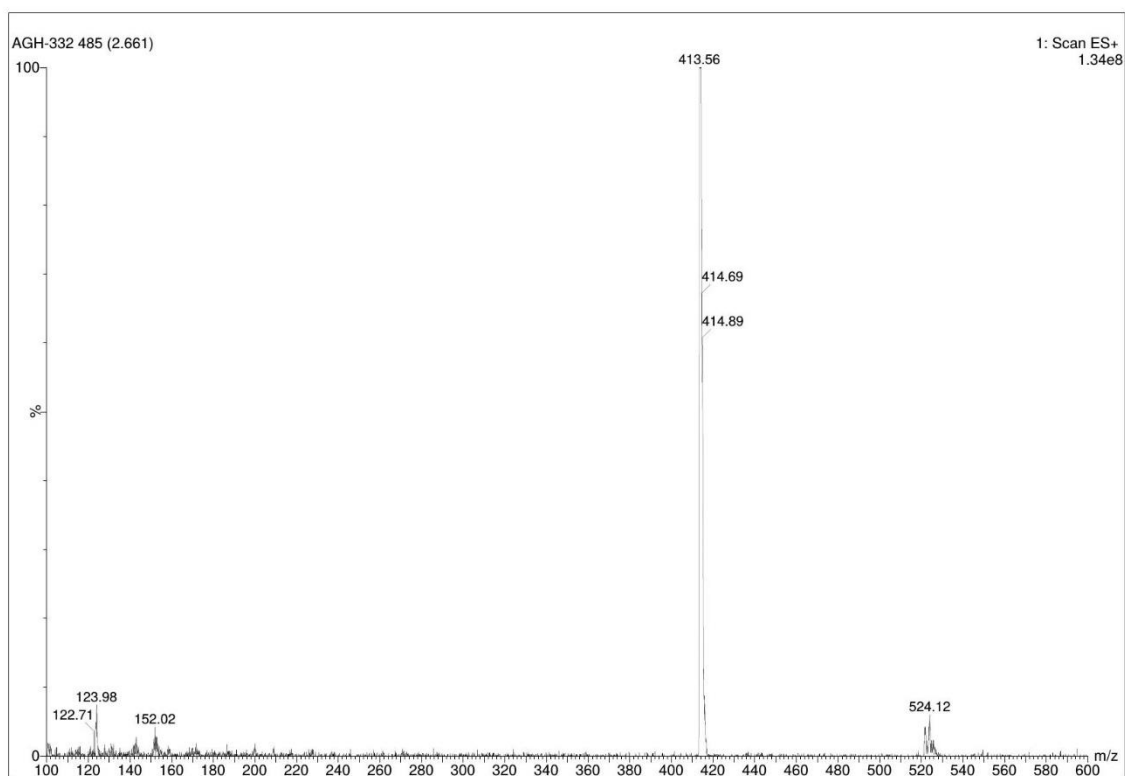
^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.06 (s, 1H), 10.78 (s, 1H), 7.68 – 7.63 (m, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.37 – 7.30 (m, 4H), 7.12 (dd, J = 10.2, 2.3 Hz, 2H), 7.08 – 7.01 (m, 4H), 3.88 (d, J = 0.9 Hz, 2H), 2.42 (s, 1H), 2.41 (s, 1H).

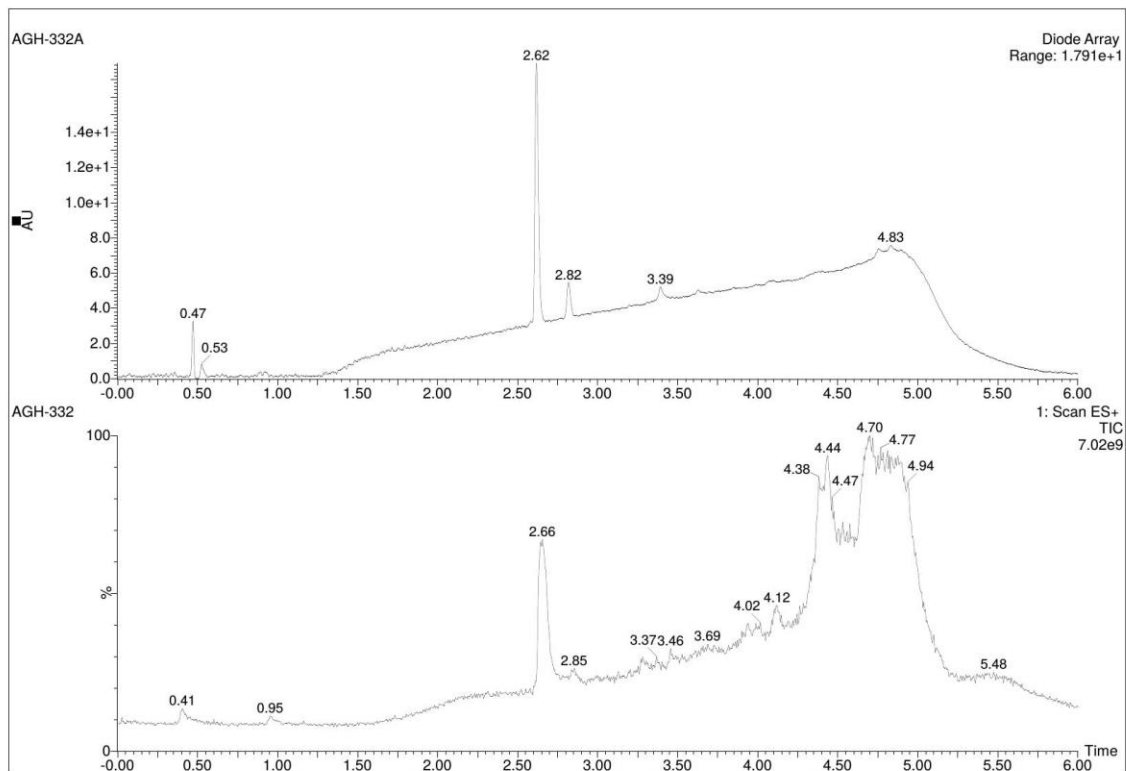




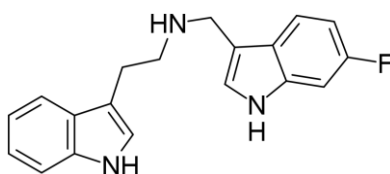
The product was obtained as a off-white solid. Yield: 67%.
 LCMS [M+1] = 414,89 (416,06 calculated).

^1H NMR (500 MHz DMSO- d_6) δ 11.03 (s, 1H), 10.76 (s, 1H), 7.98 (d, J = 1.7 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.36 – 7.27 (m, 3H), 7.25 – 7.17 (m, 2H), 7.11 (d, J = 2.4 Hz, 1H), 7.04 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 6.95 (ddd, J = 7.9, 6.9, 1.1 Hz, 1H), 3.86 (d, J = 0.8 Hz, 2H), 2.85 (d, J = 2.7 Hz, 4H).





[[6-fluoro-1*H*-indol-3-yl)methyl][2-(1*H*-indol-3-yl)ethyl]amine (13)

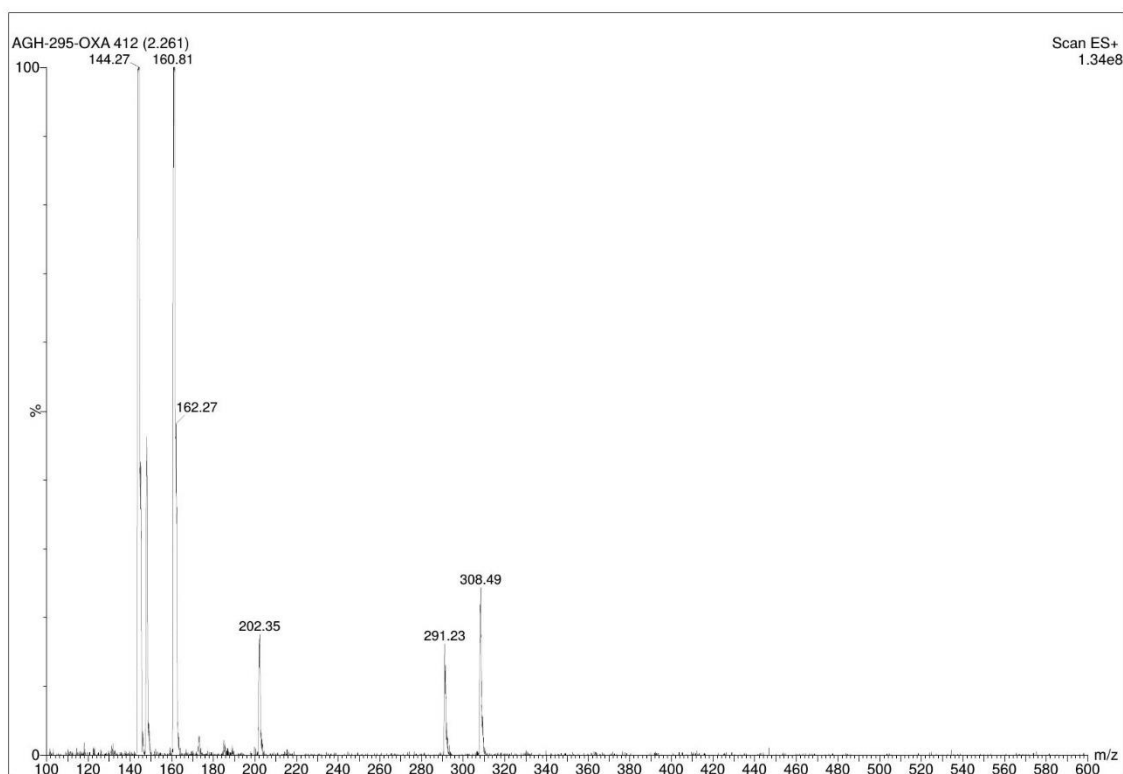


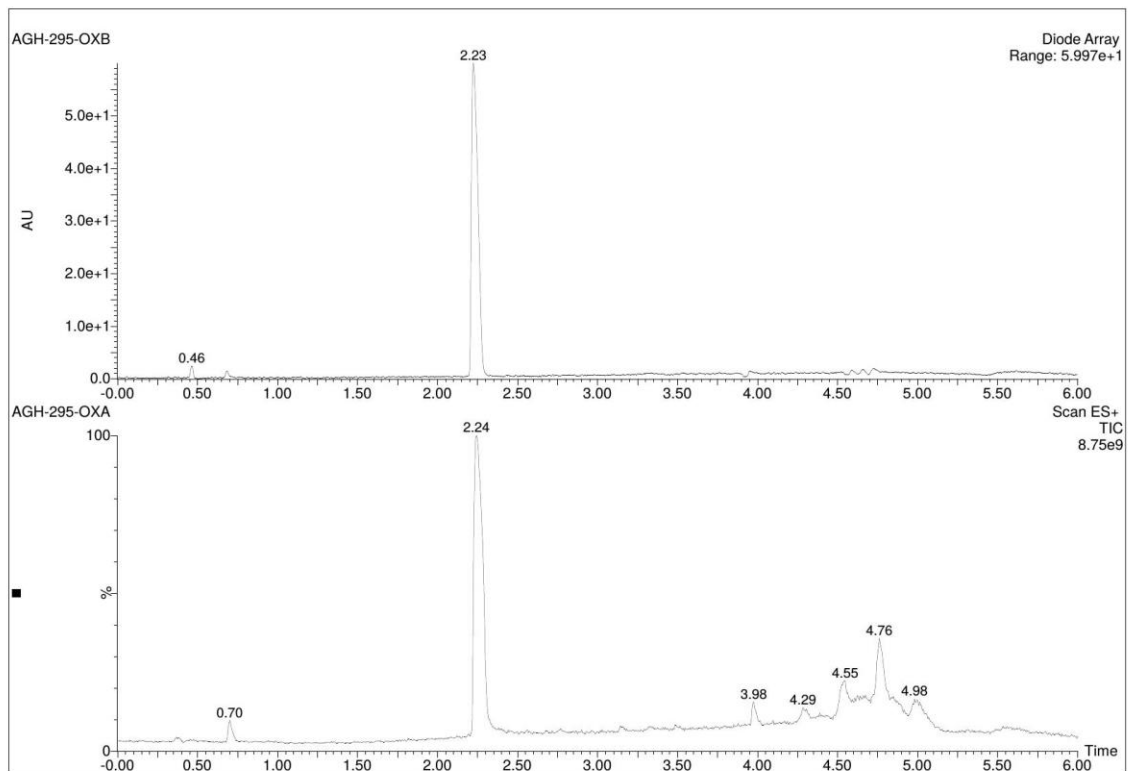
The product was obtained as a off-white solid. Yield: 40%.

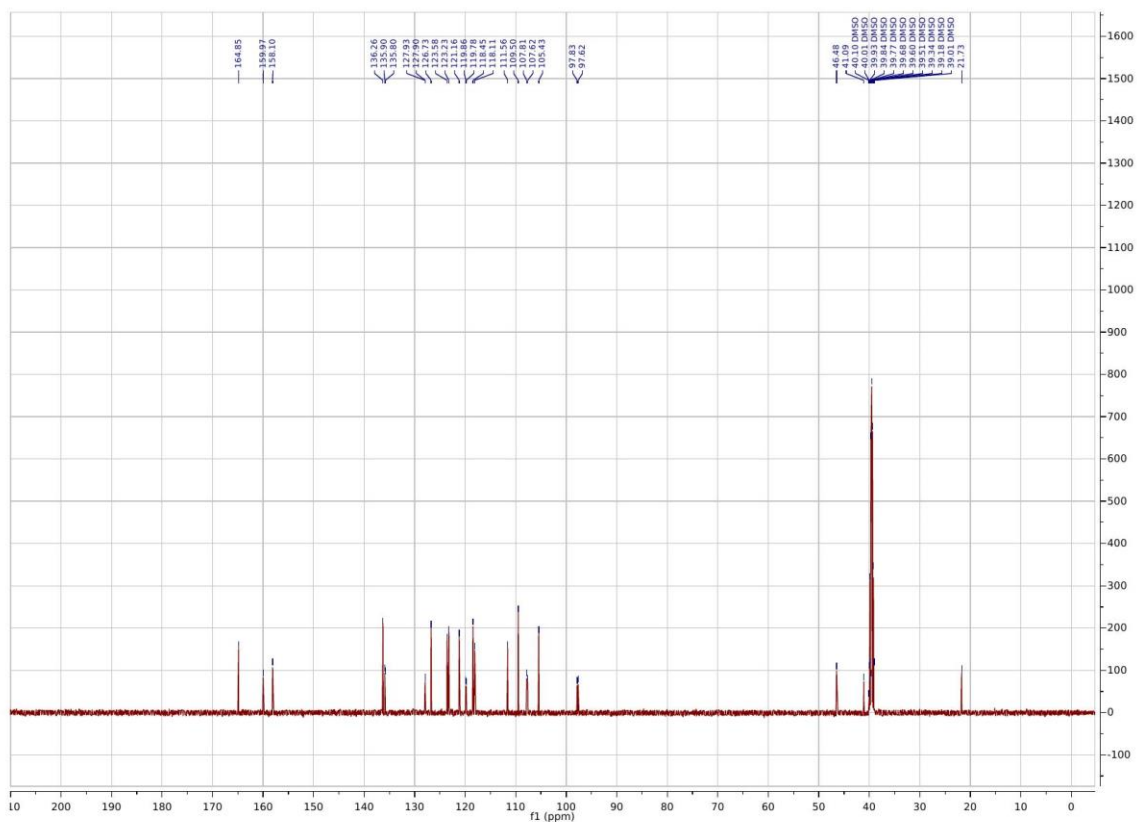
LCMS [M+1] = 308,49 (308,16 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.51 (d, $J = 2.5$ Hz, 1H), 10.98 (d, $J = 2.4$ Hz, 1H), 7.75 (dd, $J = 8.7, 5.4$ Hz, 1H), 7.55 (d, $J = 2.5$ Hz, 1H), 7.51 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.36 (dt, $J = 8.1, 0.9$ Hz, 1H), 7.22 (dd, $J = 10.0, 2.4$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.08 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 6.98 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1H), 6.94 (ddd, $J = 9.7, 8.7, 2.4$ Hz, 1H), 4.35 (s, 2H), 3.22 – 3.15 (m, 2H), 3.07 (dd, $J = 9.8, 6.4$ Hz, 2H).

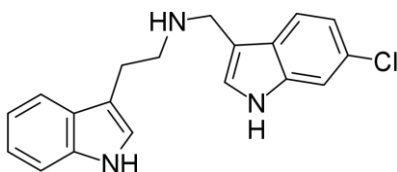
^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 164.85, 159.97, 158.10, 136.26, 135.90, 135.80, 127.93, 127.90, 126.73, 123.58, 123.23, 121.16, 119.86, 119.78, 118.45, 118.11, 111.56, 109.50, 107.81, 107.62, 105.43, 97.83, 97.62, 46.48, 41.09, 21.73.







[(6-chloro-1*H*-indol-3-yl)methyl][2-(1*H*-indol-3-yl)ethyl]amine (14)

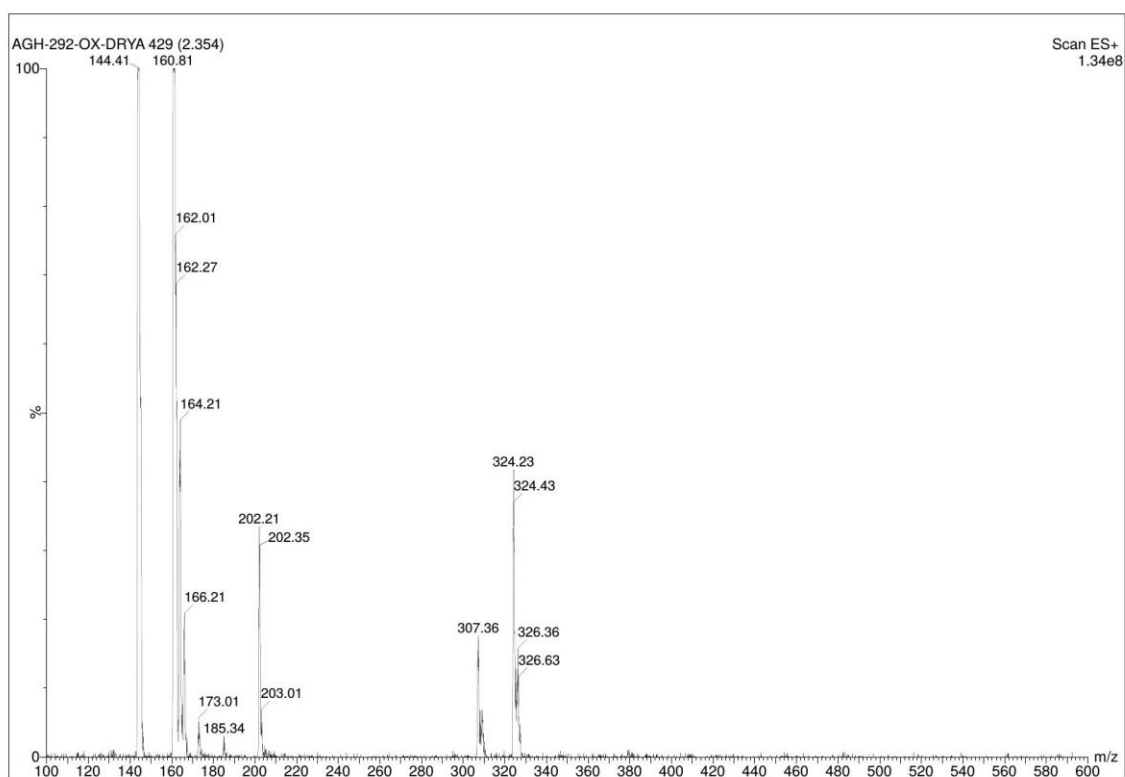


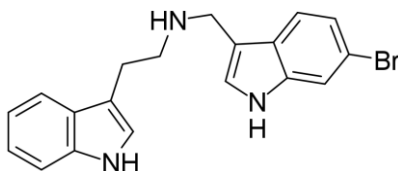
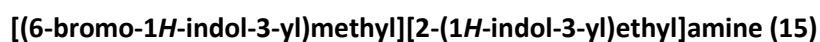
The product was obtained as a white solid. Yield: 55%.

LCMS [M+1] = 324,23 (324,13 calculated).

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.61 (d, $J = 2.5$ Hz, 1H), 10.98 (d, $J = 2.4$ Hz, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.59 (d, $J = 2.5$ Hz, 1H), 7.54 – 7.47 (m, 2H), 7.36 (dt, $J = 8.1, 0.9$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.12 – 7.05 (m, 2H), 6.98 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 4.36 (s, 2H), 3.22 – 3.14 (m, 2H), 3.07 (dd, $J = 9.8, 6.4$ Hz, 2H).

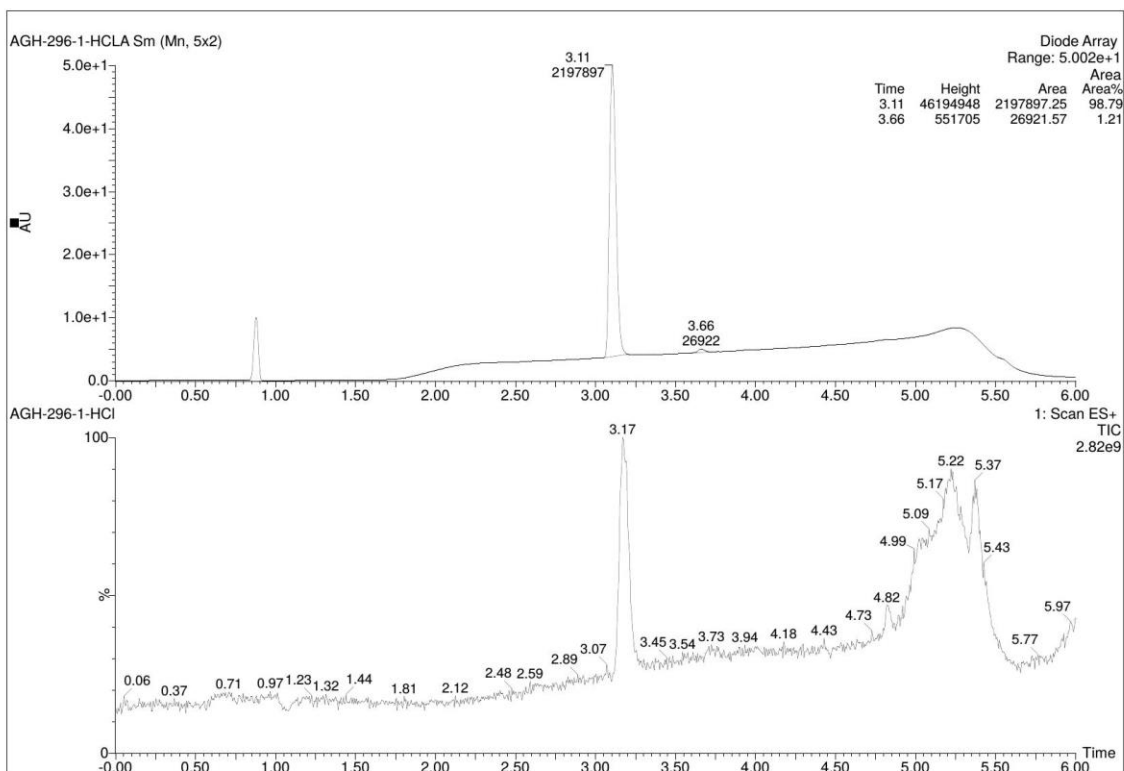
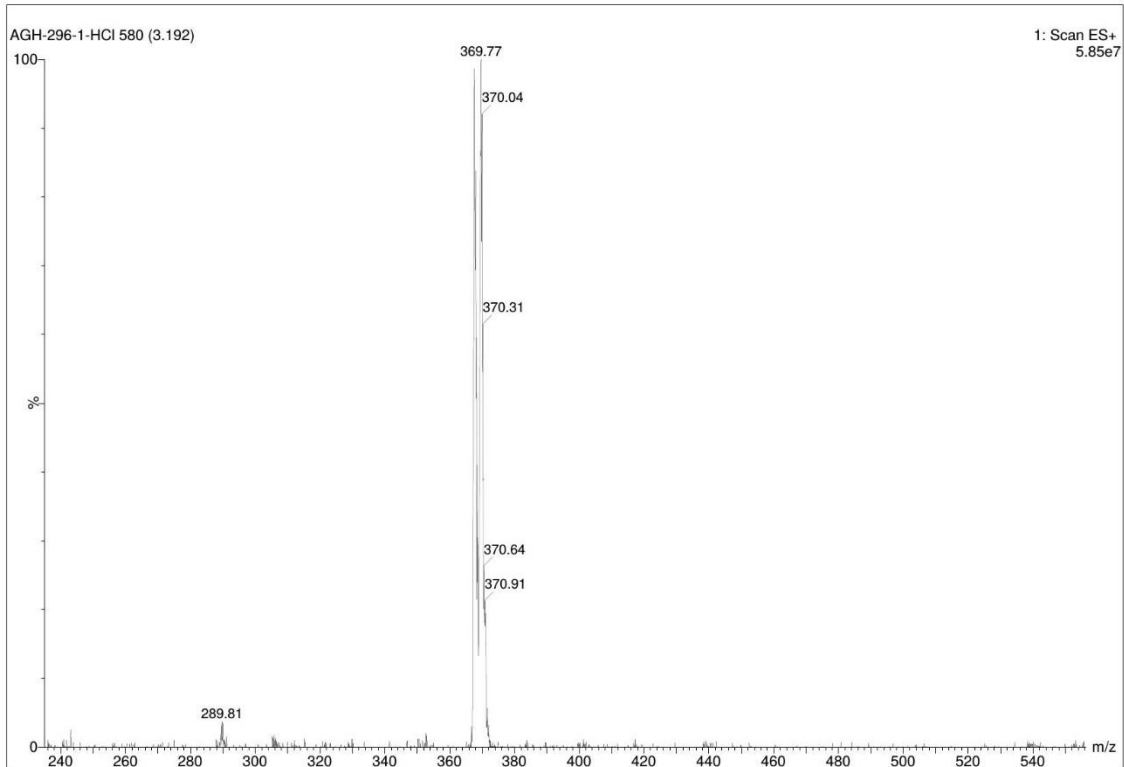
^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ 164.87, 136.36, 136.26, 128.43, 126.73, 126.34, 125.61, 123.23, 121.16, 120.15, 119.49, 118.45, 118.11, 111.56, 111.40, 109.49, 105.55, 46.49, 40.98, 21.74.

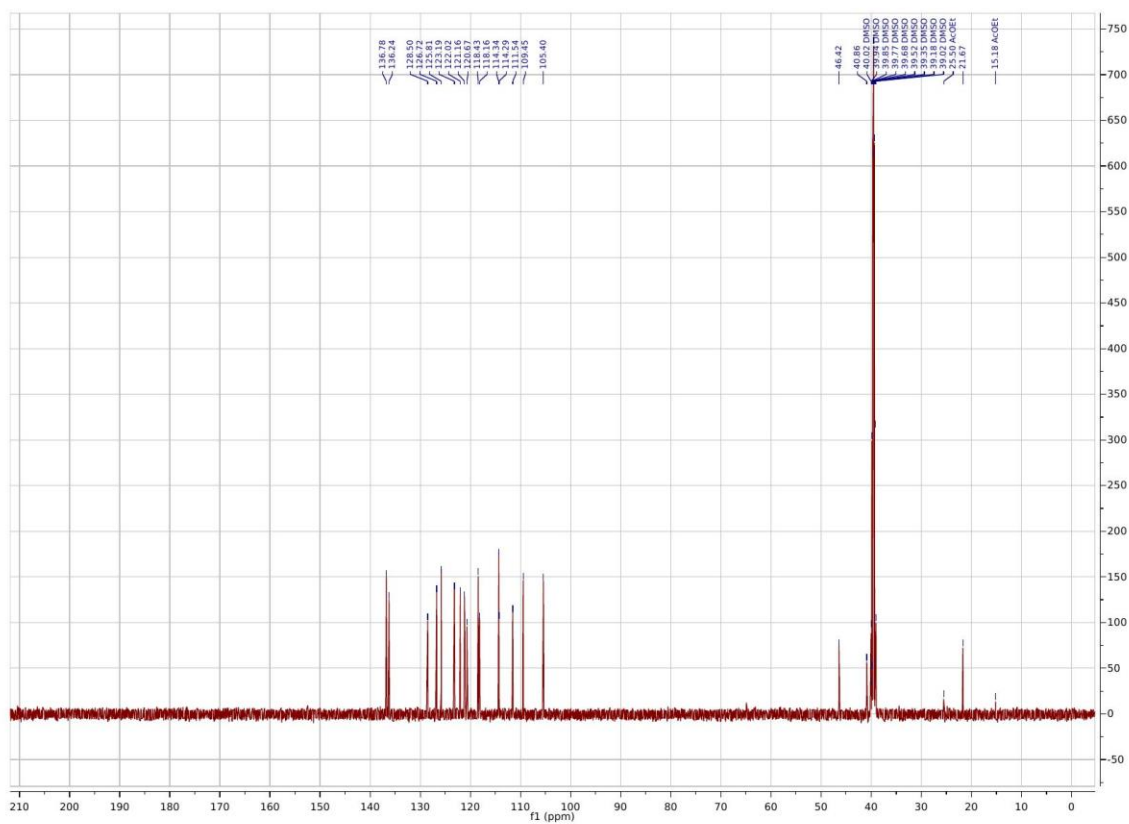
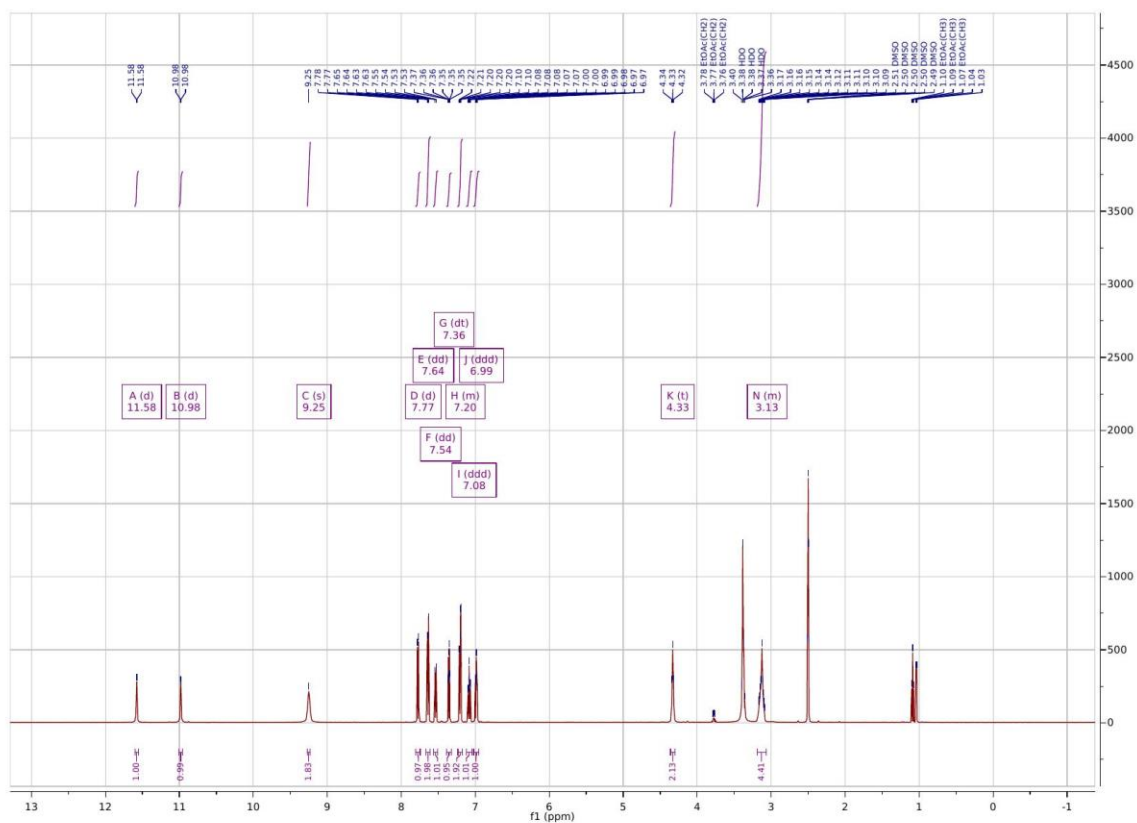




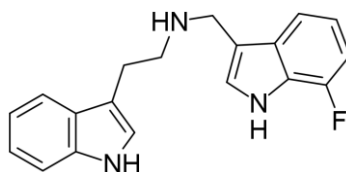
LCMS [M+1] = 367,77 (368,08 calculated).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 136.78, 136.24, 128.50, 126.72, 125.81, 123.19, 122.02, 121.16, 120.67, 118.43, 118.16, 114.34, 114.29, 111.54, 109.45, 105.40, 46.42, 40.86, 25.50, 21.67, 15.18.





[(7-fluoro-1H-indol-3-yl)methyl][2-(1H-indol-3-yl)ethyl]amine (16)

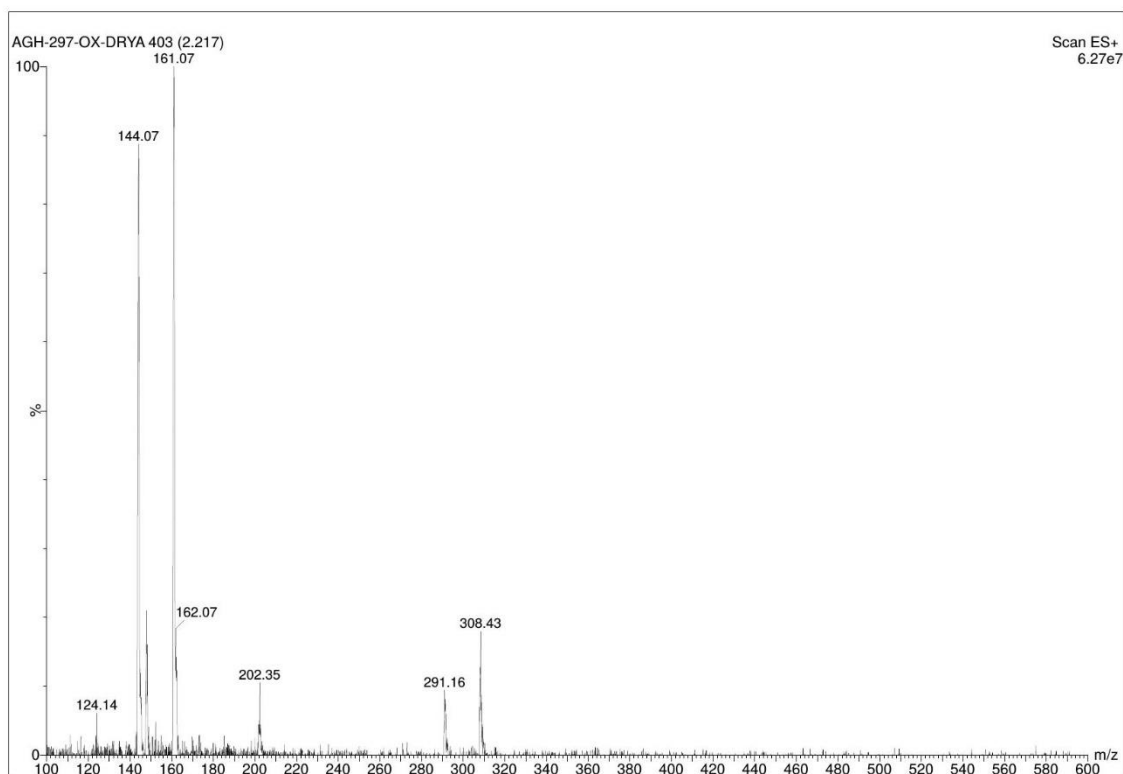


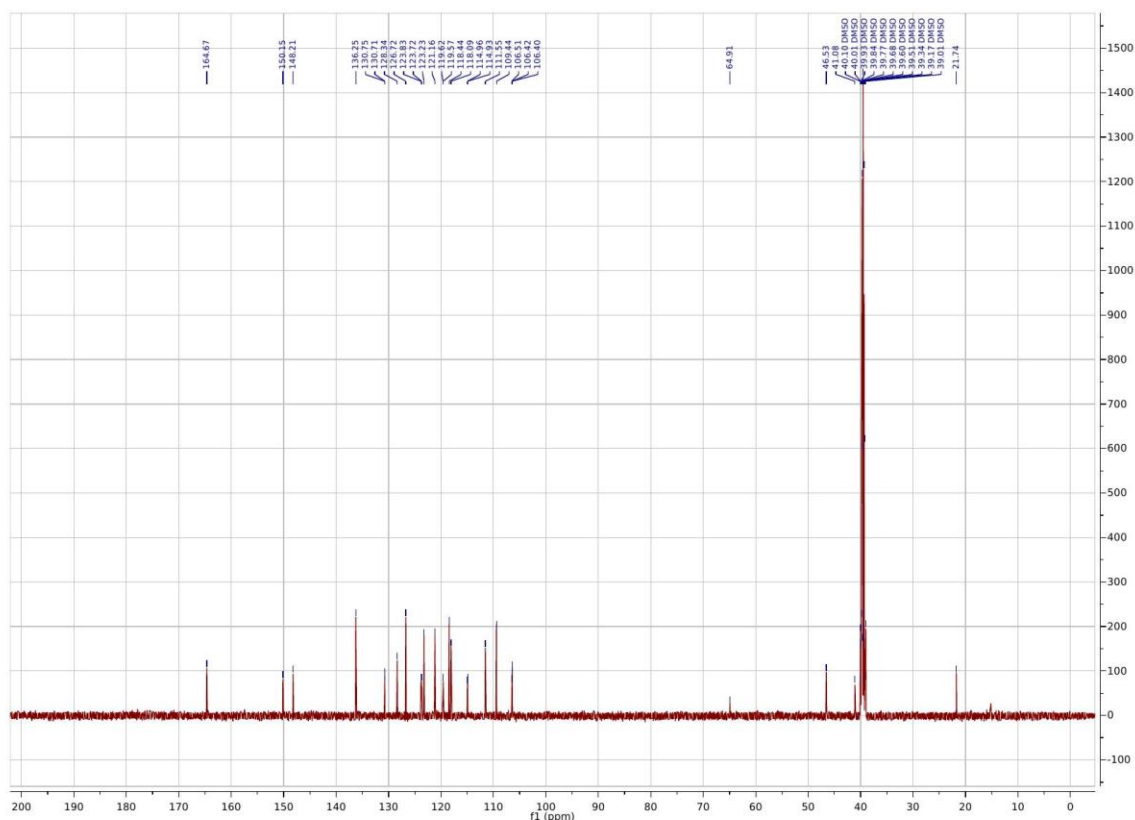
The product was obtained as a white solid. Yield: 39%.

LCMS [M+1] = 308,43 (308,16 calculated).

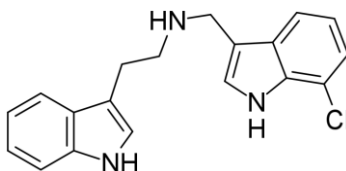
^1H NMR (500 MHz, DMSO- d_6) δ 11.90 (d, J = 2.4 Hz, 1H), 10.99 – 10.94 (m, 1H), 7.61 (d, J = 2.5 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.51 (dt, J = 7.9, 0.9 Hz, 1H), 7.36 (dt, J = 8.1, 0.9 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.11 – 7.02 (m, 2H), 7.02 – 6.94 (m, 2H), 4.37 (s, 2H), 3.19 (dd, J = 9.8, 6.4 Hz, 2H), 3.07 (dd, J = 9.8, 6.5 Hz, 2H).

^{13}C NMR (126 MHz, DMSO- d_6) δ 164.67, 150.15, 148.21, 136.25, 130.75, 130.71, 128.34, 126.72, 123.83, 123.72, 123.23, 121.16, 119.62, 119.57, 118.44, 118.09, 114.96, 114.93, 111.55, 109.44, 106.51, 106.42, 106.40, 46.53, 41.08, 21.74.





[(7-chloro-1*H*-indol-3-yl)methyl][2-(1*H*-indol-3-yl)ethyl]amine (17)

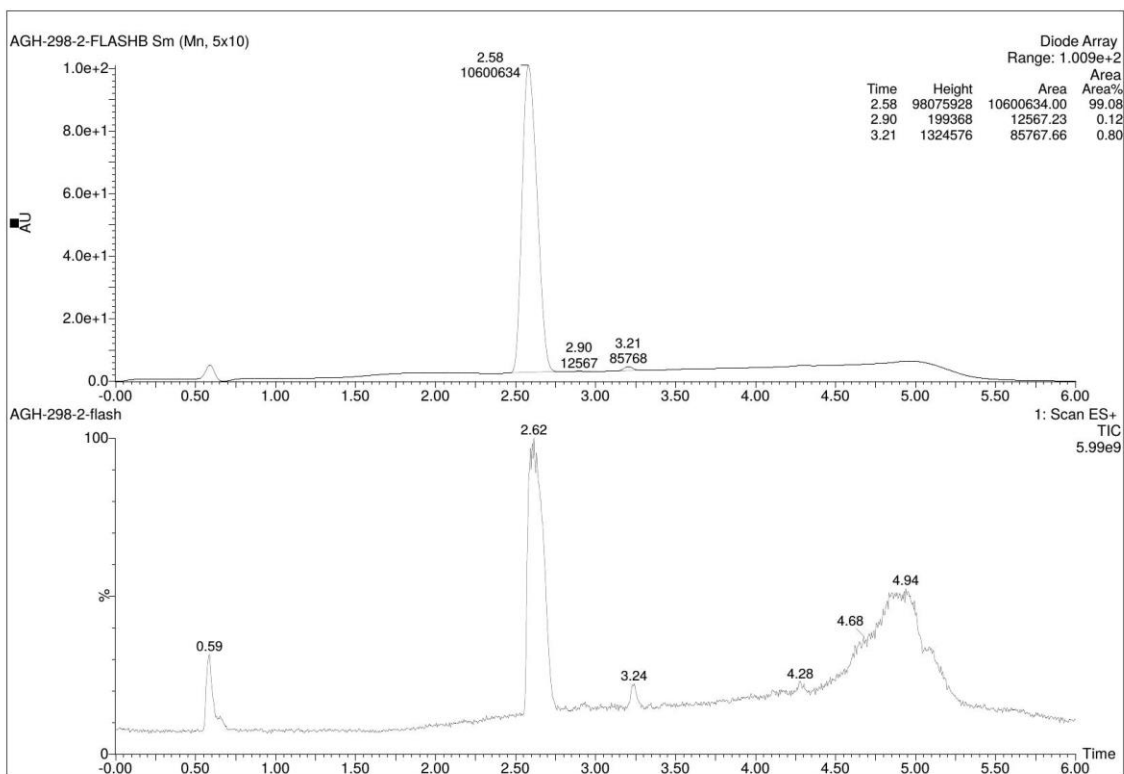
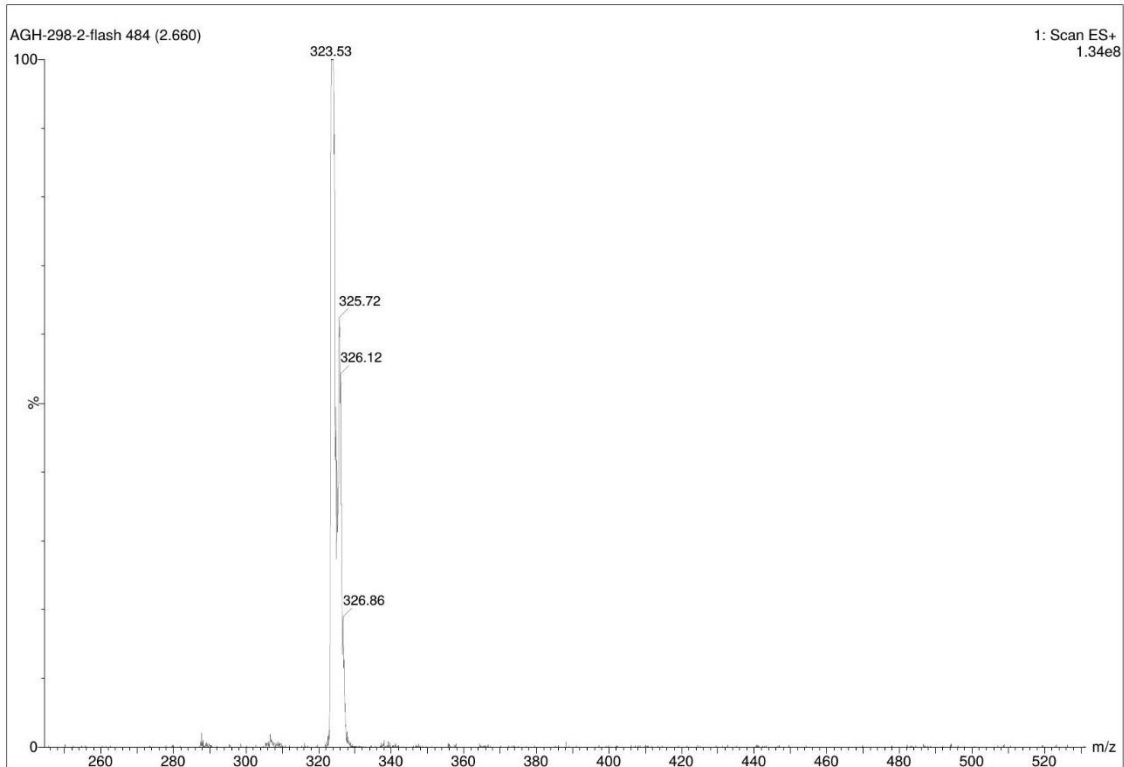


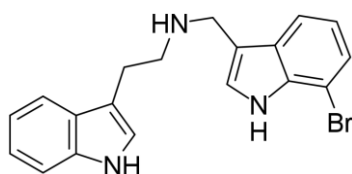
The product was obtained as a white solid. Yield: 55%.

LCMS [M+1] = 323,53 (324,13 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.77 (s, 1H), 10.99 (s, 1H), 7.75 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 2.5$ Hz, 1H), 7.51 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.36 (dt, $J = 8.0, 0.9$ Hz, 1H), 7.23 (dd, $J = 7.6, 0.9$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.12 – 7.04 (m, 2H), 6.98 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1H), 4.38 (s, 2H), 3.17 (s, 4H), 3.08 (dd, $J = 9.8, 6.4$ Hz, 2H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 164.93, 136.27, 132.76, 128.79, 128.52, 126.74, 123.23, 121.15, 120.25, 118.45, 118.11, 117.86, 116.07, 111.56, 109.52, 106.72, 48.62, 46.53, 41.02, 21.75.



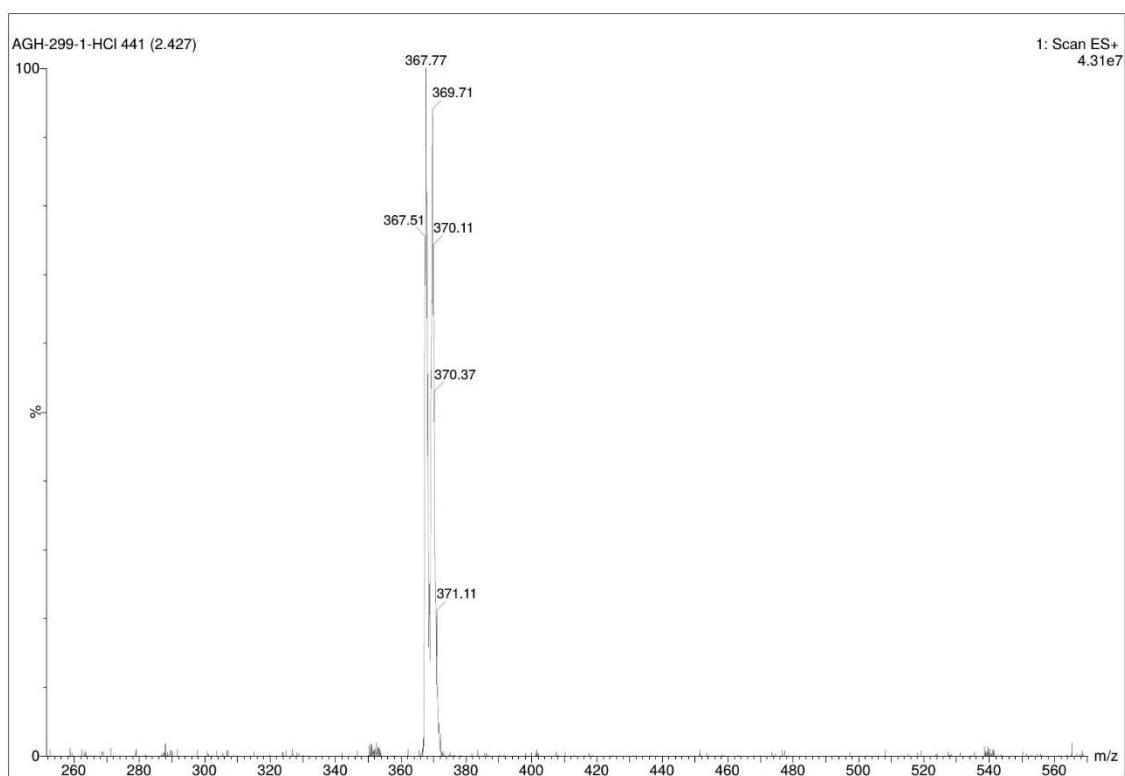


The product was obtained as a off-white solid. Yield: 50%.

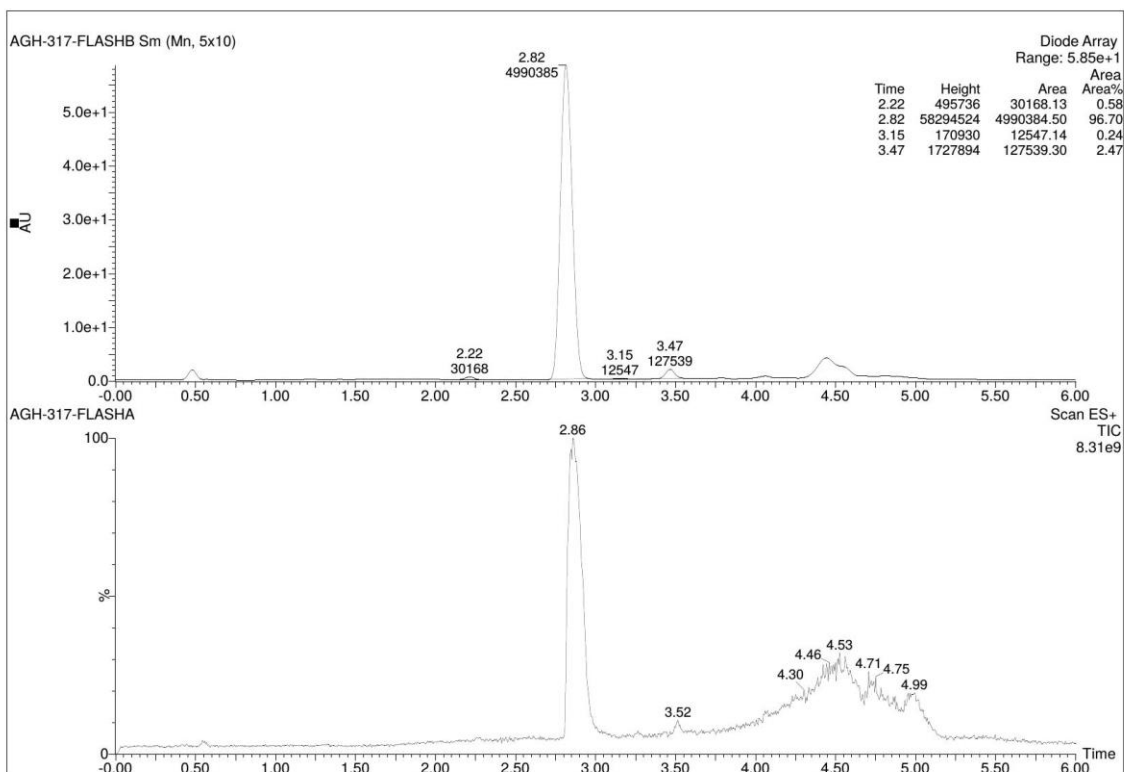
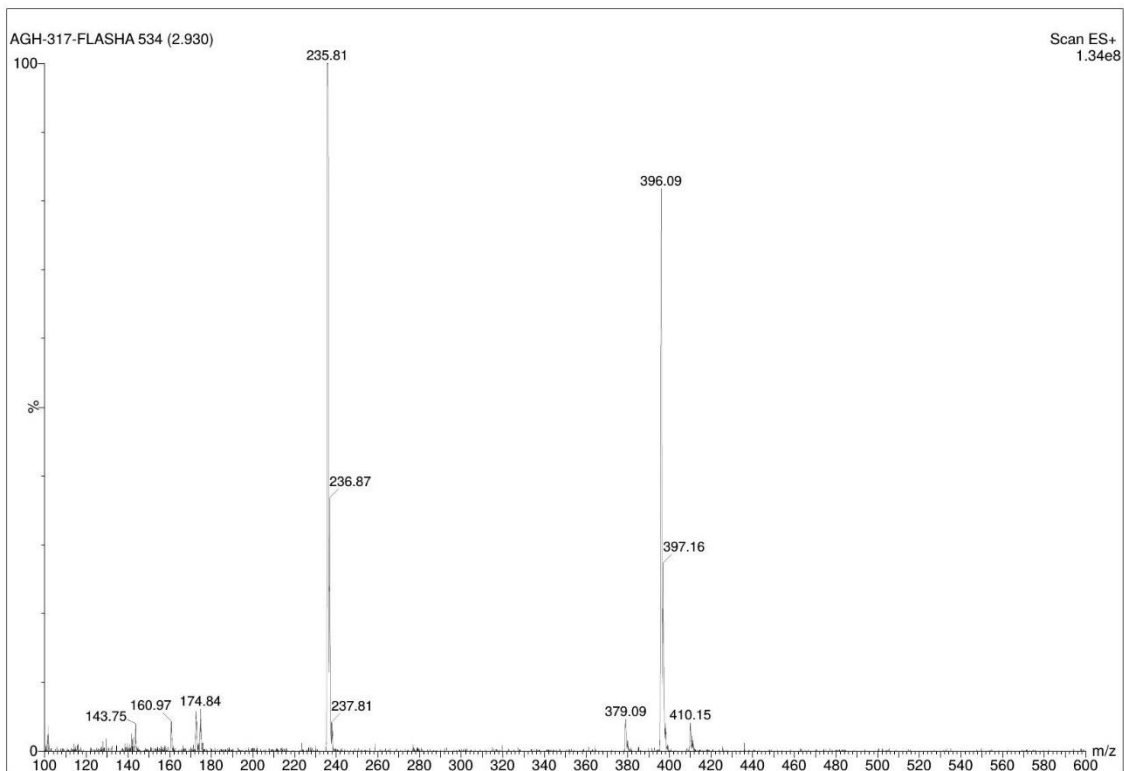
LCMS [M+1] = 367,77 (368,08 calculated).

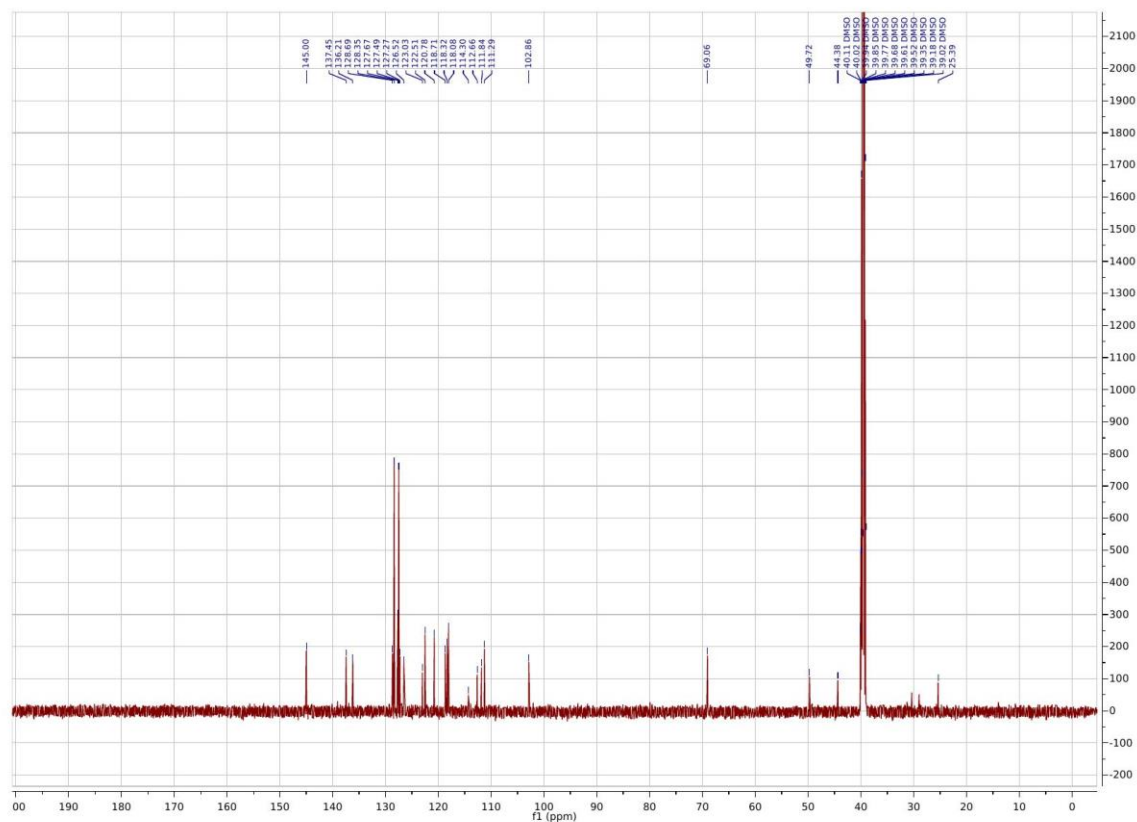
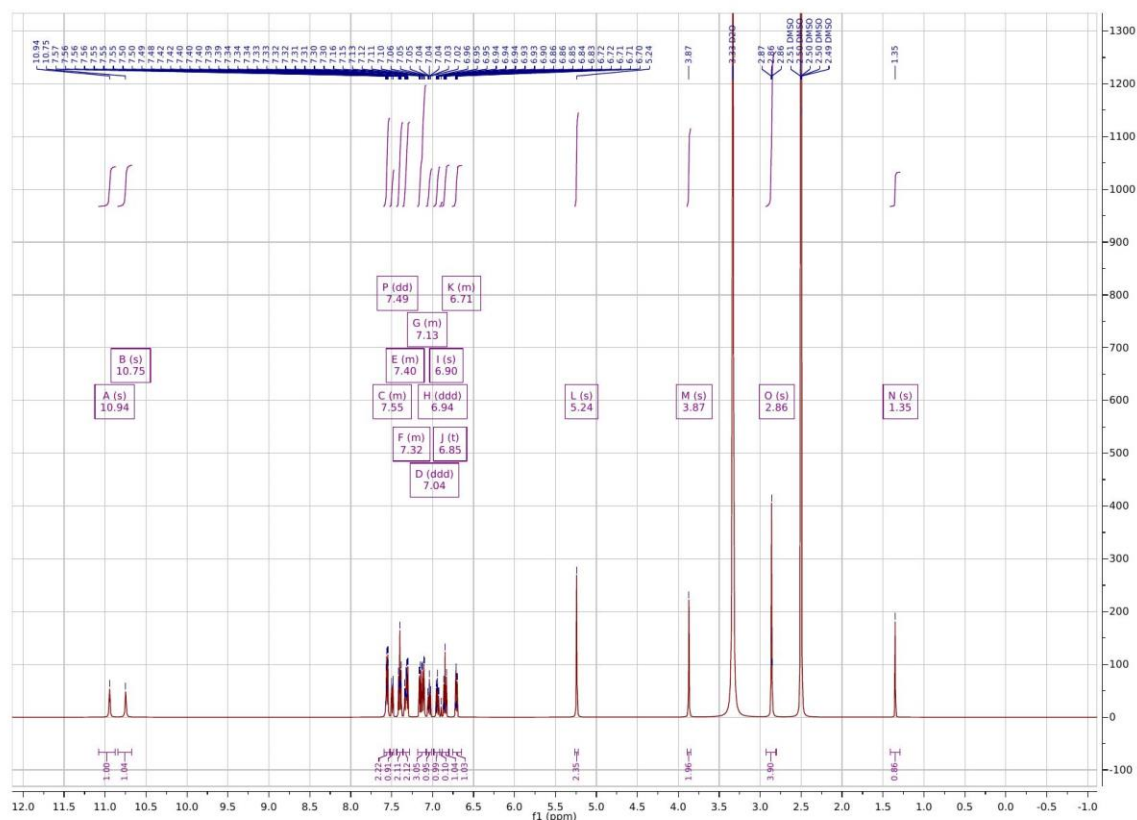
^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.60 (d, J = 3.0 Hz, 1H), 11.00 – 10.96 (m, 1H), 9.29 (s, 2H), 7.83 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.36 (ddd, J = 9.4, 7.4, 0.9 Hz, 2H), 7.20 (d, J = 2.4 Hz, 1H), 7.12 – 6.95 (m, 3H), 4.35 (t, J = 5.1 Hz, 2H), 3.14 (p, J = 8.6, 8.1 Hz, 4H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 136.24, 134.19, 128.73, 128.49, 126.73, 124.21, 123.20, 121.16, 120.65, 118.43, 118.16, 111.53, 109.44, 106.56, 104.30, 46.45, 40.98, 21.67.

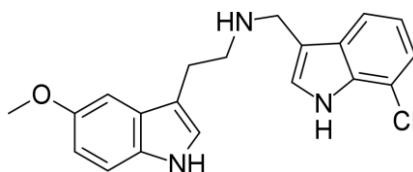


¹³C NMR (126 MHz, DMSO-*d*₆) δ 145.00, 137.45, 136.21, 128.69, 128.35, 127.67, 127.54, 127.49, 127.27, 126.52, 123.03, 122.51, 120.78, 118.71, 118.32, 118.08, 114.30, 112.66, 111.84, 111.29, 102.86, 69.06, 49.72, 44.38, 25.39.





[(7-chloro-1*H*-indol-3-yl)methyl][2-(5-methoxy-1*H*-indol-3-yl)ethyl]amine (20)

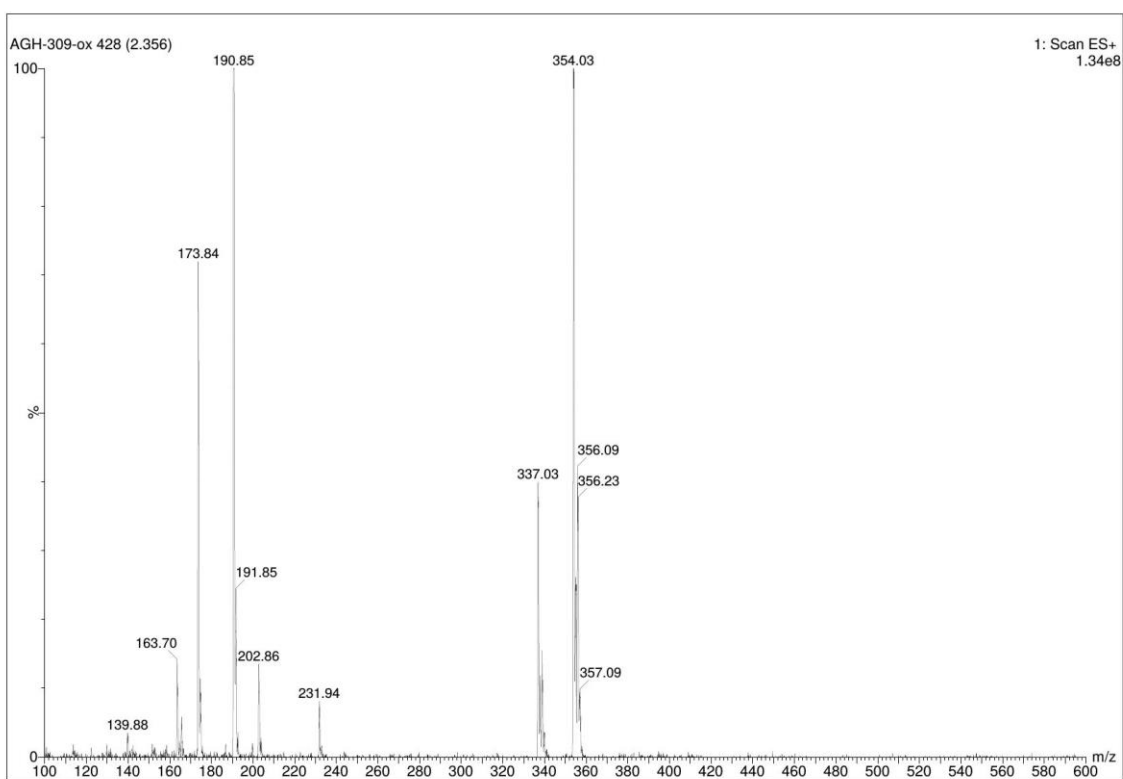


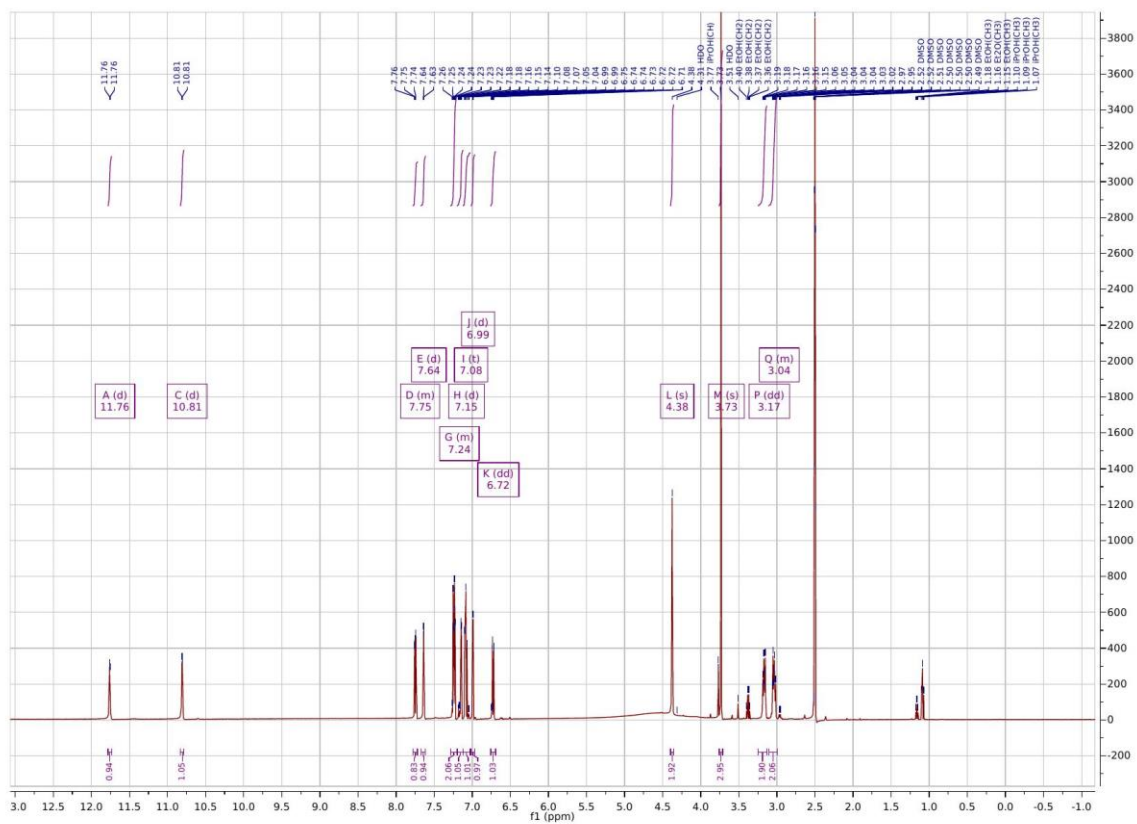
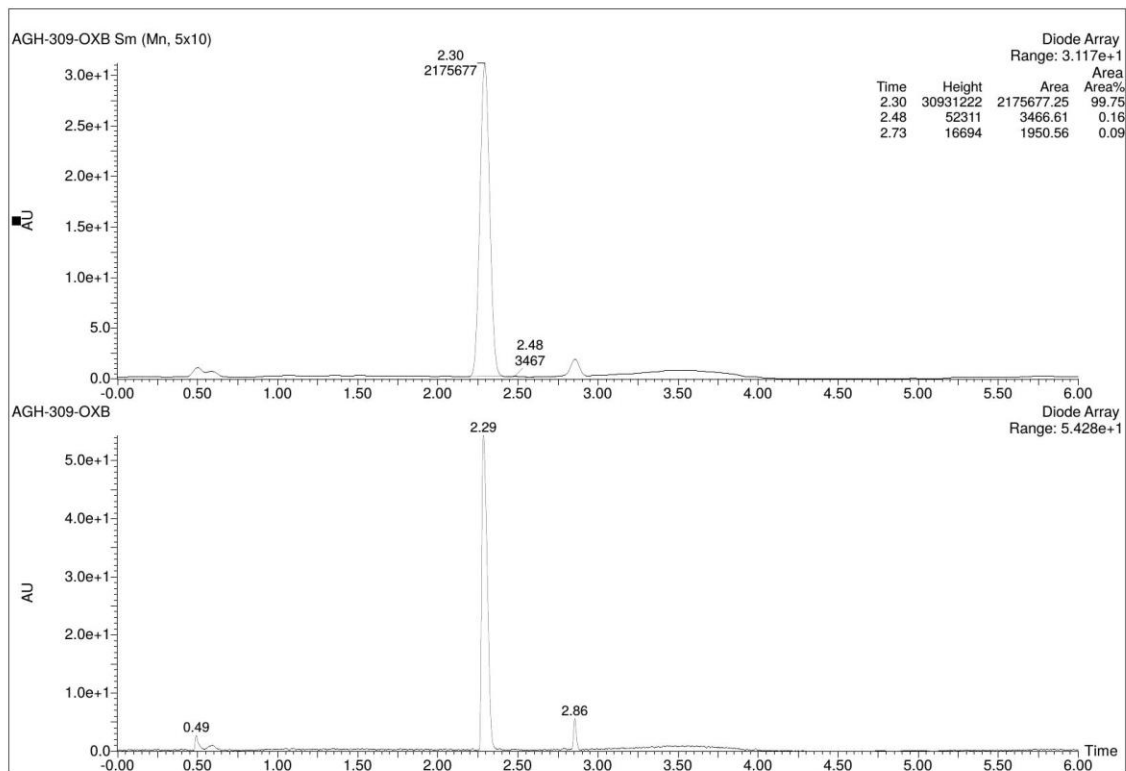
The product was obtained as a light brown solid. Yield: 37%.

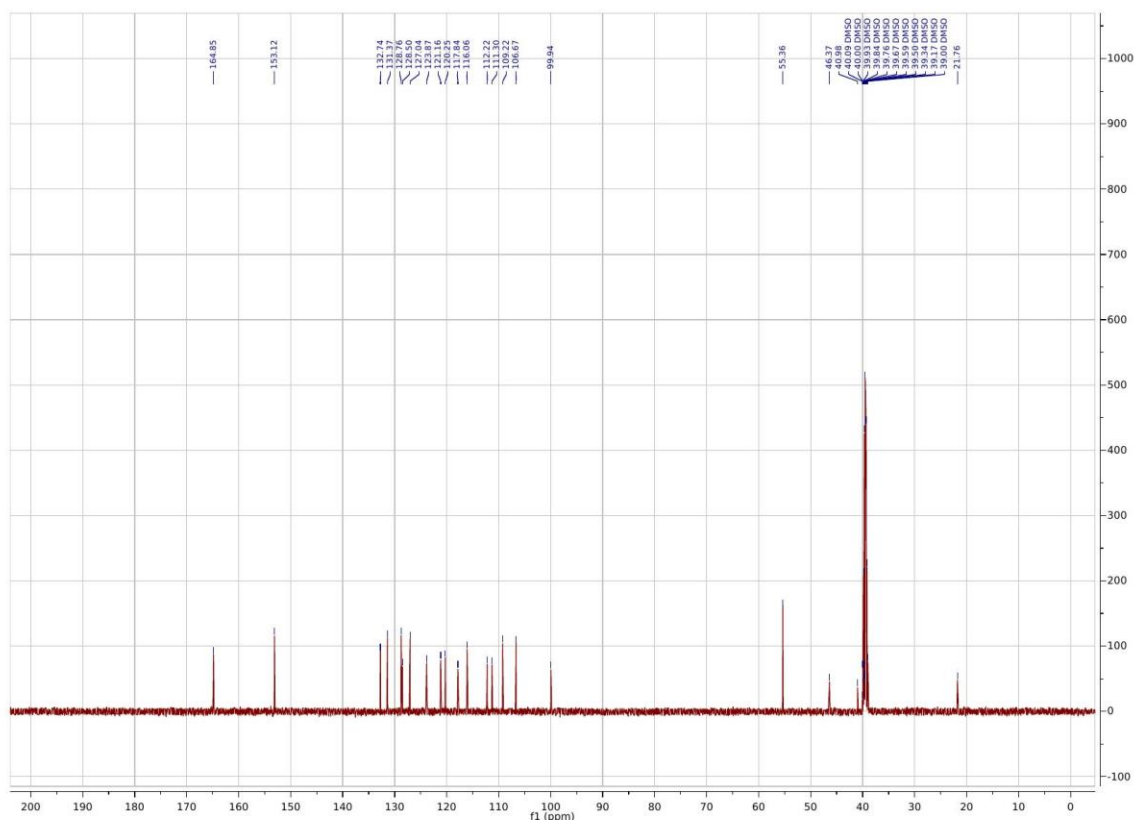
LCMS [M+1] = 354,03 (354,14 calculated).

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.76 (d, J = 2.6 Hz, 1H), 10.81 (d, J = 2.4 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.64 (d, J = 2.5 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.15 (d, J = 2.4 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.72 (dd, J = 8.7, 2.4 Hz, 1H), 4.38 (s, 2H), 3.73 (s, 3H), 3.17 (dd, J = 9.8, 6.4 Hz, 2H), 3.11 – 3.00 (m, 2H).

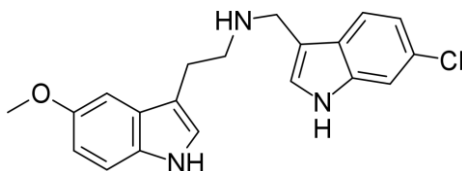
^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) δ 164.85, 153.12, 132.74, 131.37, 128.76, 128.50, 127.04, 123.87, 121.16, 120.25, 117.84, 116.06, 112.22, 111.30, 109.22, 106.67, 99.94, 55.36, 46.37, 40.98, 21.76.







[[6-chloro-1*H*-indol-3-yl)methyl][2-(5-methoxy-1*H*-indol-3-yl)ethyl]amine (21)

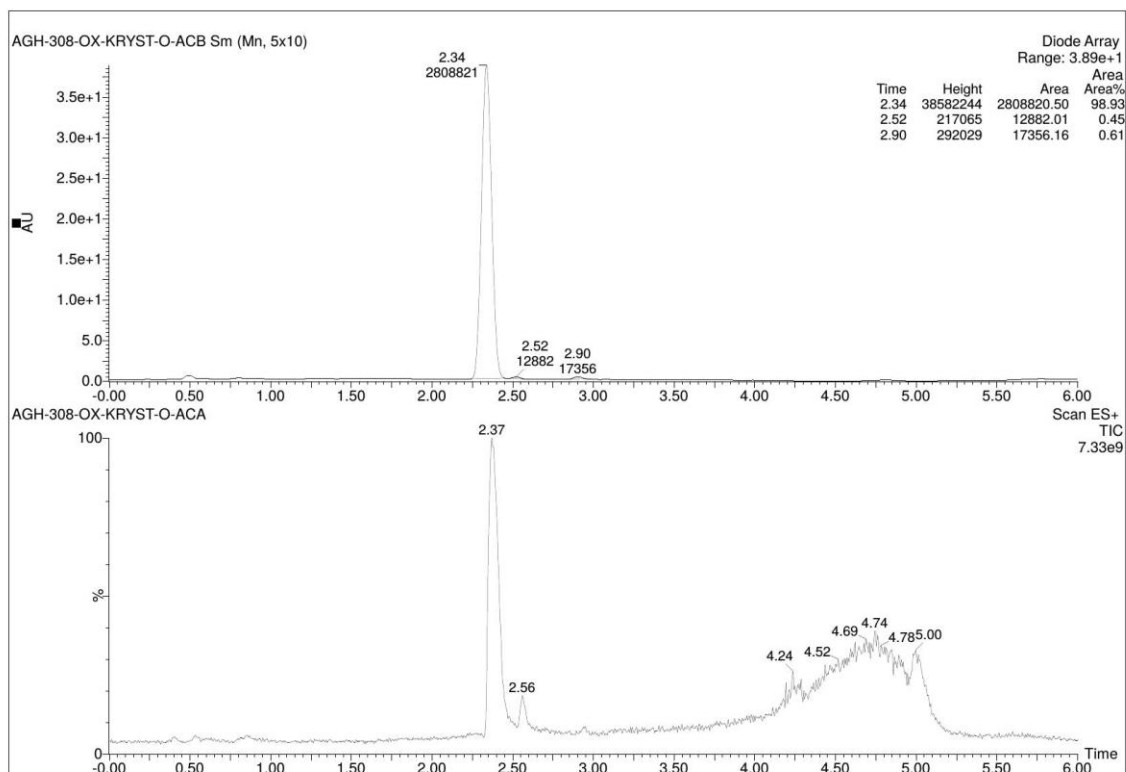
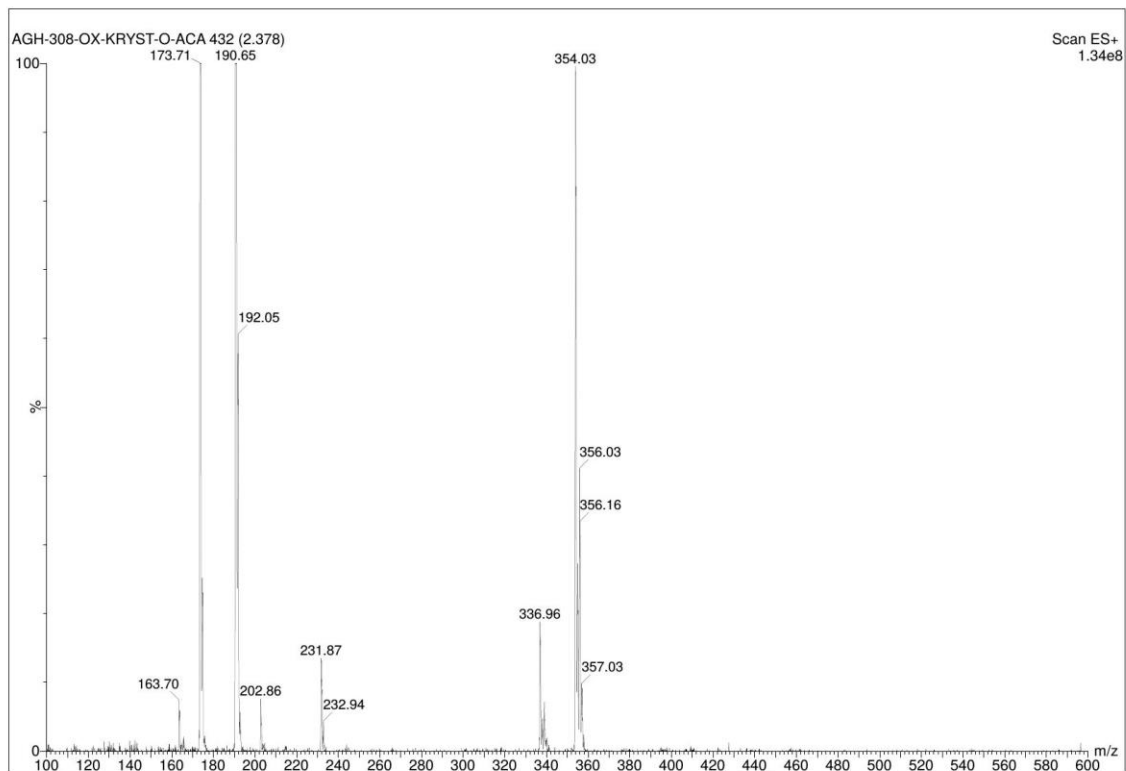


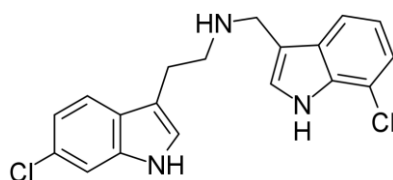
The product was obtained as a beige solid. Yield: 44%.

LCMS $[M+1] = 354,03$ (354,14 calculated).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.63 (d, $J = 2.5$ Hz, 1H), 10.82 (d, $J = 2.4$ Hz, 1H), 7.77 (d, $J = 8.5$ Hz, 1H), 7.59 (d, $J = 2.5$ Hz, 1H), 7.49 (d, $J = 1.9$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 2.4$ Hz, 1H), 7.08 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.73 (dd, $J = 8.7, 2.4$ Hz, 1H), 4.36 (s, 2H), 3.74 (s, 3H), 3.16 (dd, $J = 10.1, 6.2$ Hz, 2H), 3.04 (dd, $J = 9.9, 6.4$ Hz, 2H).

^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 165.00, 153.12, 136.36, 131.38, 128.41, 127.05, 126.32, 125.61, 123.85, 120.12, 119.47, 112.22, 111.39, 111.30, 109.24, 105.54, 99.94, 59.76, 55.35, 46.35, 40.91, 21.76.

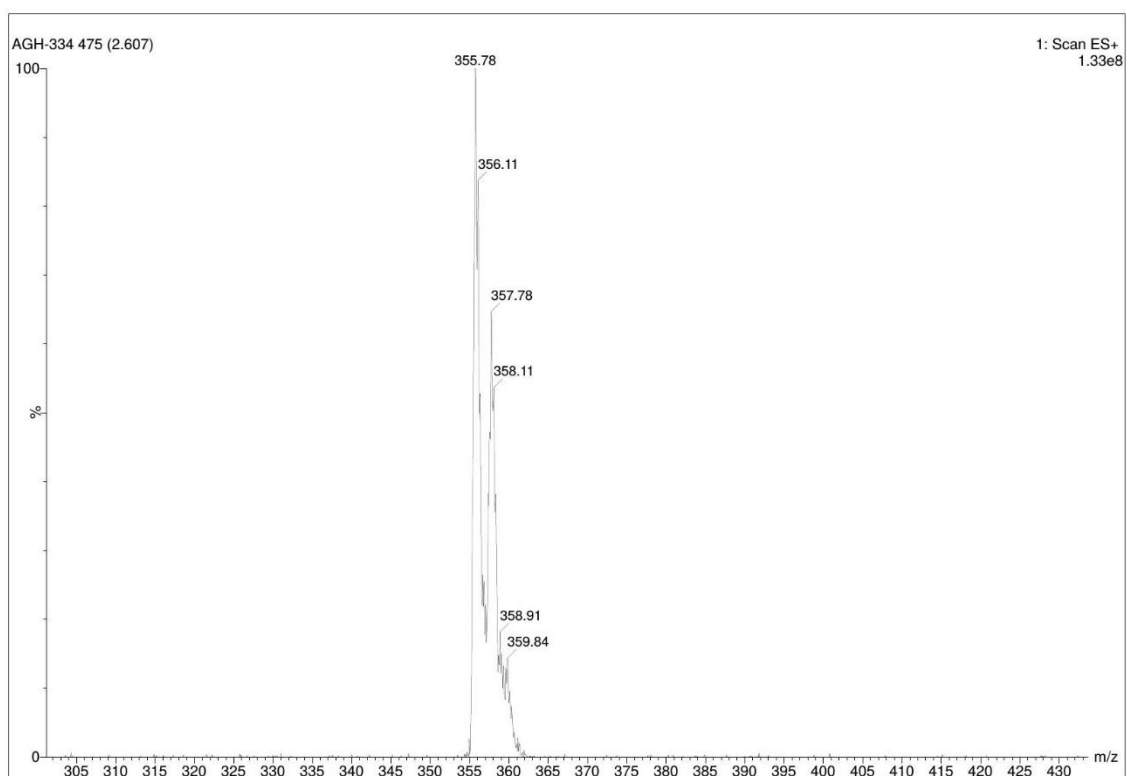


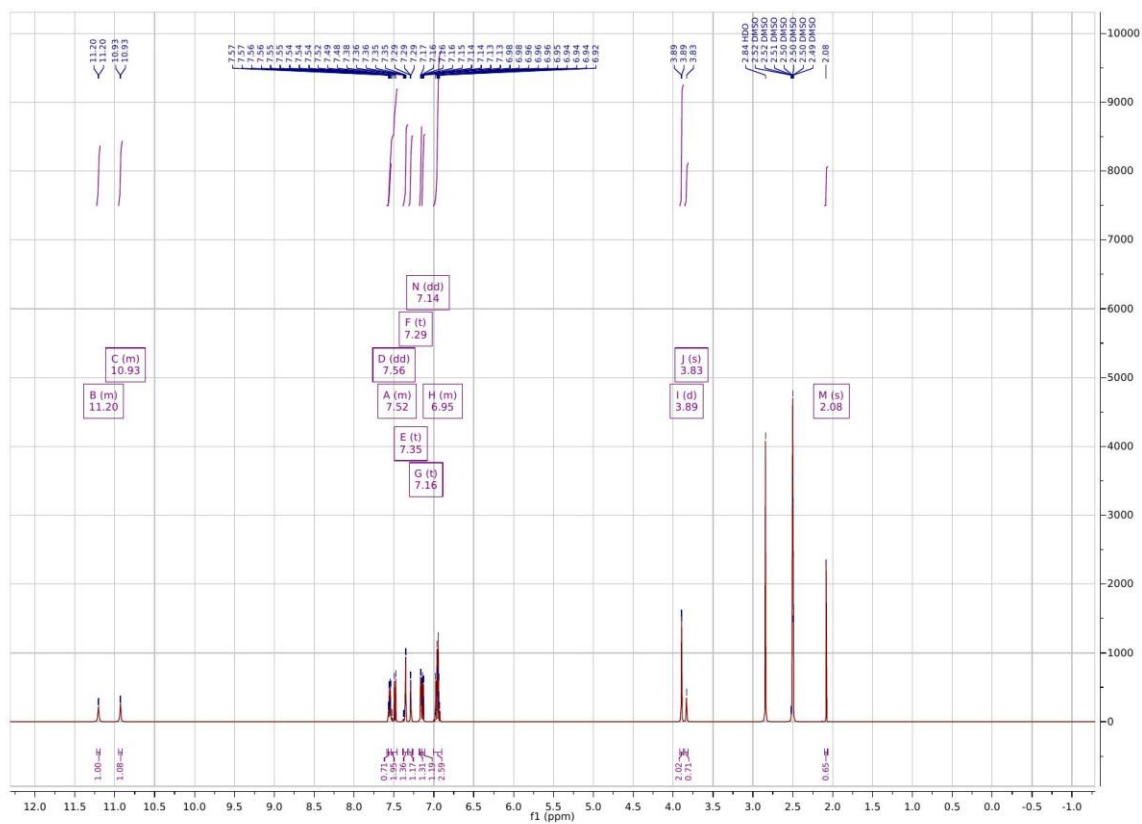
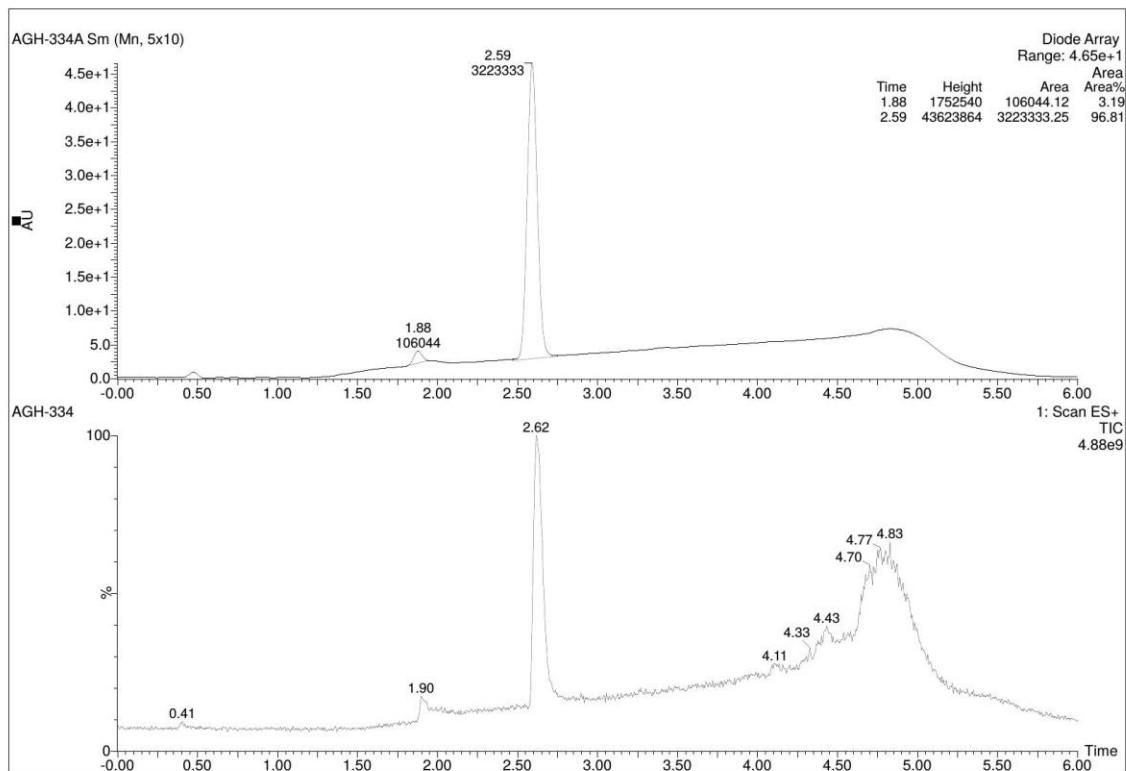


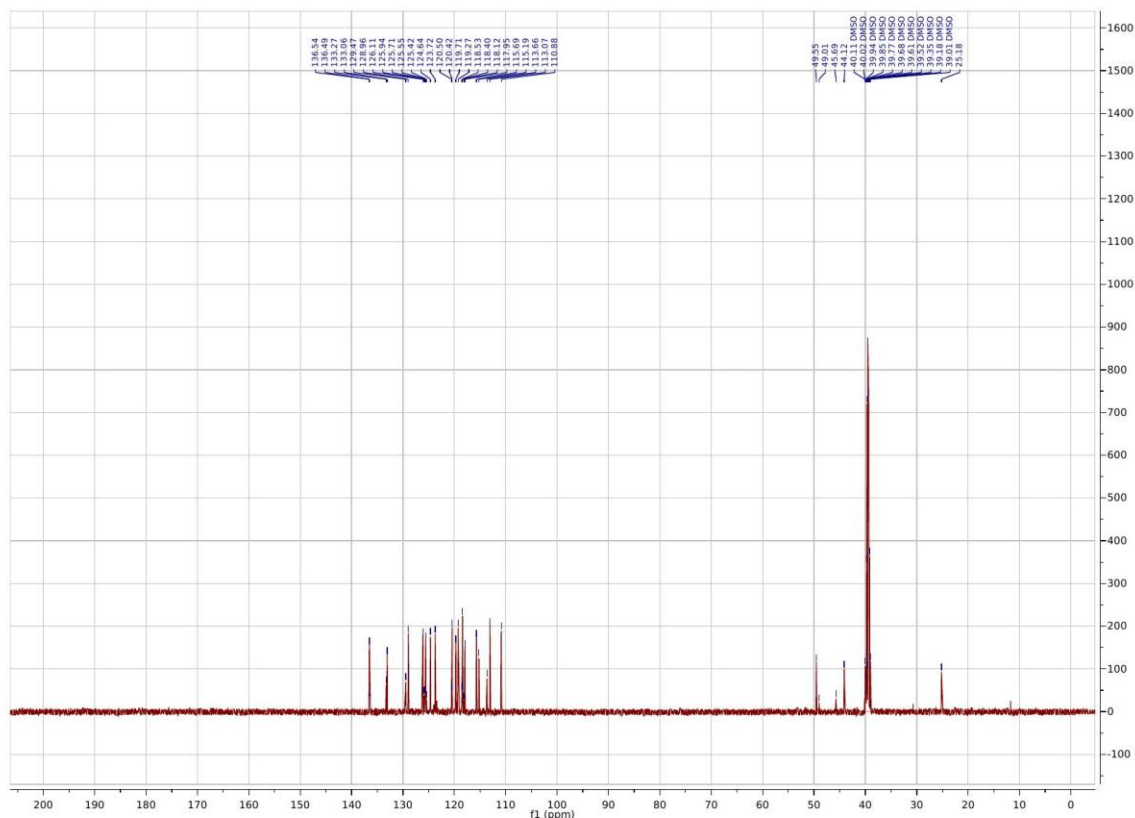
The product was obtained as a beige solid. Yield: 59%.

LCMS [M+1] = 357,78 (358,09 calculated).

^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 11.22 – 11.18 (m, 1H), 10.95 – 10.91 (m, 1H), 7.56 (dd, $J = 4.1, 0.9$ Hz, 1H), 7.57 – 7.46 (m, 2H), 7.35 (t, $J = 2.3$ Hz, 1H), 7.29 (t, $J = 1.9$ Hz, 1H), 7.16 (t, $J = 2.4$ Hz, 1H), 7.14 (dd, $J = 7.4, 1.0$ Hz, 1H), 7.00 – 6.90 (m, 3H), 3.89 (d, $J = 0.8$ Hz, 2H), 3.83 (s, 1H), 2.08 (s, 1H).







2. In vitro pharmacology

2.1 Radioligand binding assay

5-HT_{1A}/5-HT_{2A}/5-HT₆/5-HT₇/D₂ Radioligand Binding Assays. The membrane preparation and general assay procedures for the cloned receptors were adjusted to 96-microwell format as described in our former papers.⁵⁸⁻⁶¹ The cell pellets were thawed and homogenized in 10 volumes of assay buffer using an Ultra Turrax tissue homogenizer and were centrifuged twice at 35,000 g for 15 min at 4°C, with incubation for 15 min at 37°C in between the rounds of centrifugation. The composition of the assay buffers was as follows: for 5-HT_{1A}R: 50 mM Tris-HCl, 0.1 mM EDTA, 4 mM MgCl₂, 10 μM pargyline and 0.1% ascorbate; for 5-HT_{2A}R: 50 mM Tris-HCl, 0.1 mM EDTA, 4 mM MgCl₂ and 0.1% ascorbate; for 5-HT₆R: 50 mM Tris-HCl, 0.5 mM EDTA and 4 mM MgCl₂, and for 5-HT₇bR: 50 mM Tris-HCl, 4 mM MgCl₂, 10 μM pargyline and 0.1% ascorbate; for dopamine D₂LR: 50 mM Tris-HCl, 1 mM EDTA, 4 mM MgCl₂, 120 mM NaCl, 5 mM KCl, 1.5 mM CaCl₂ and 0.1% ascorbate.

All assays were incubated in a total volume of 200 μL in 96-well microtiter plates for 1 h at 37°C, except for 5-HT_{1A}R and 5-HT_{2A}R, which were incubated at room temperature and 27°C, respectively. The equilibration process was terminated by rapid filtration through Unifilter plates with a 96-well cell harvester and the radioactivity retained on the filters was quantified using a Microbeta plate reader (PerkinElmer, USA).

3 Metabolic stability

In silico AGH-292 (**14**)

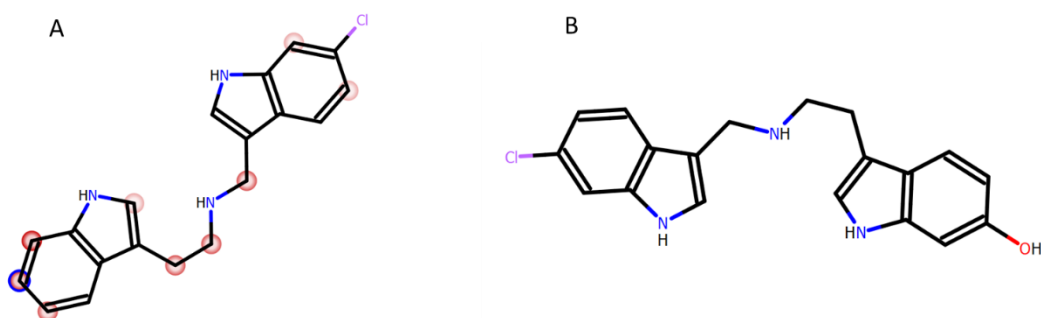


Figure S1. A: Prediction of the sites of metabolism by MetaSite 6.01. Blue circle marked on the functional group structures indicates the highest biotransformation probability. The fading red color shows decreasing of the metabolism probability. **B:** The most probable structure of **14** main metabolite.

In silico (**17**)

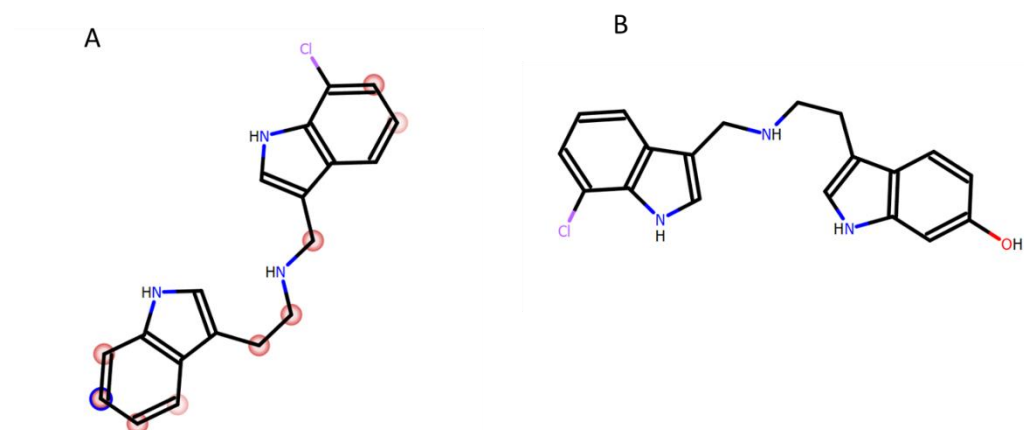


Figure S2. A: Prediction of the sites of metabolism by MetaSite 6.01. Blue circle marked on the functional group structures indicates the highest biotransformation probability. The fading red color shows decreasing of the metabolism probability. **B:** The most probable structure of **17** main metabolite.

In silico (**18**)

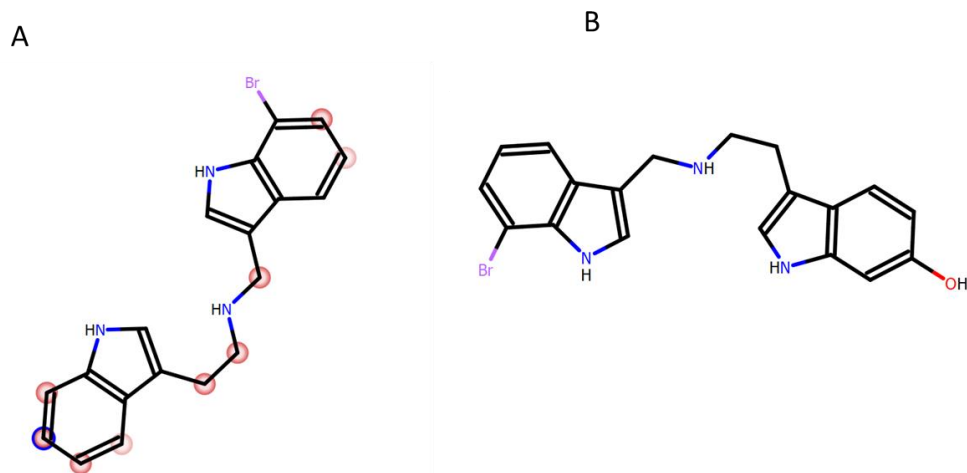


Figure S3. A: Prediction of the sites of metabolism by MetaSite 6.01. Blue circle marked on the functional group structures indicates the highest biotransformation probability. The fading red color shows decreasing of the metabolism probability. **B:** The most probable structure of **18** main metabolite.

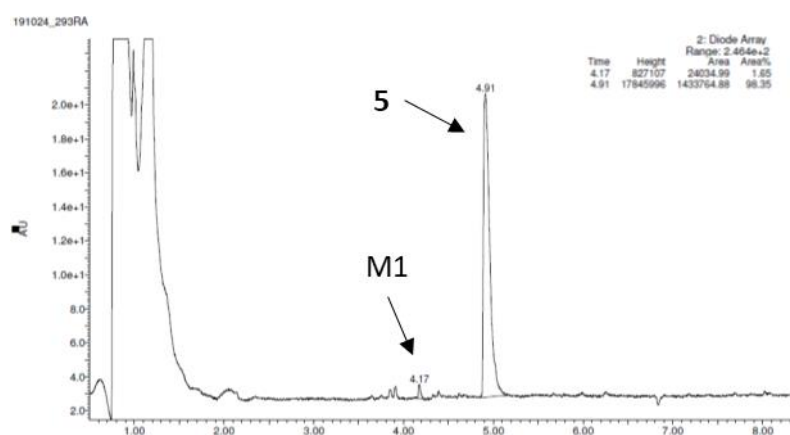


Figure S4. The UPLC spectra after 120 min reaction of **5** with mouse liver microsomes (MLMs).

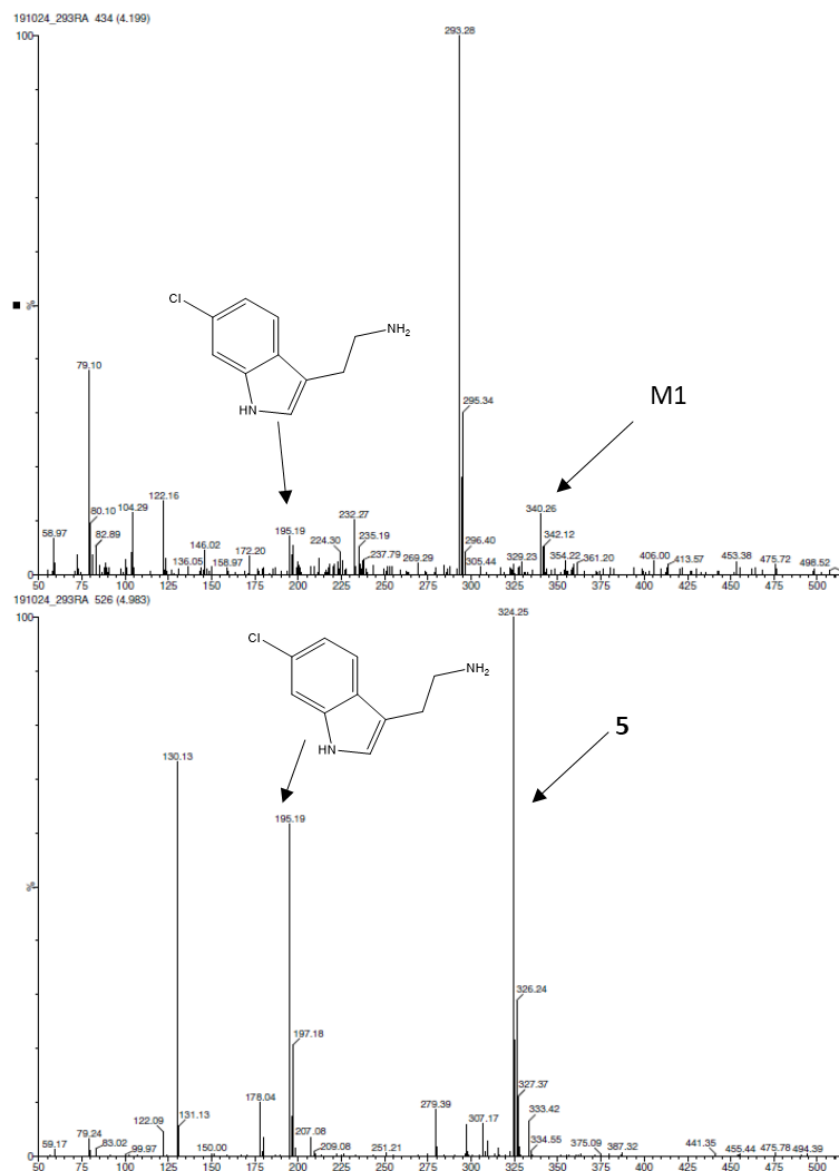


Figure S5. The MS spectra of **5** and its metabolite.

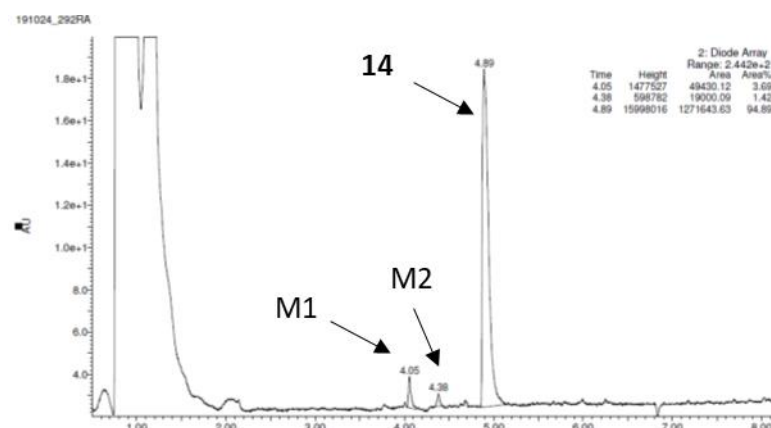


Figure S6. The UPLC spectra after 120 min reaction of **14** with mouse liver microsomes (MLMs).

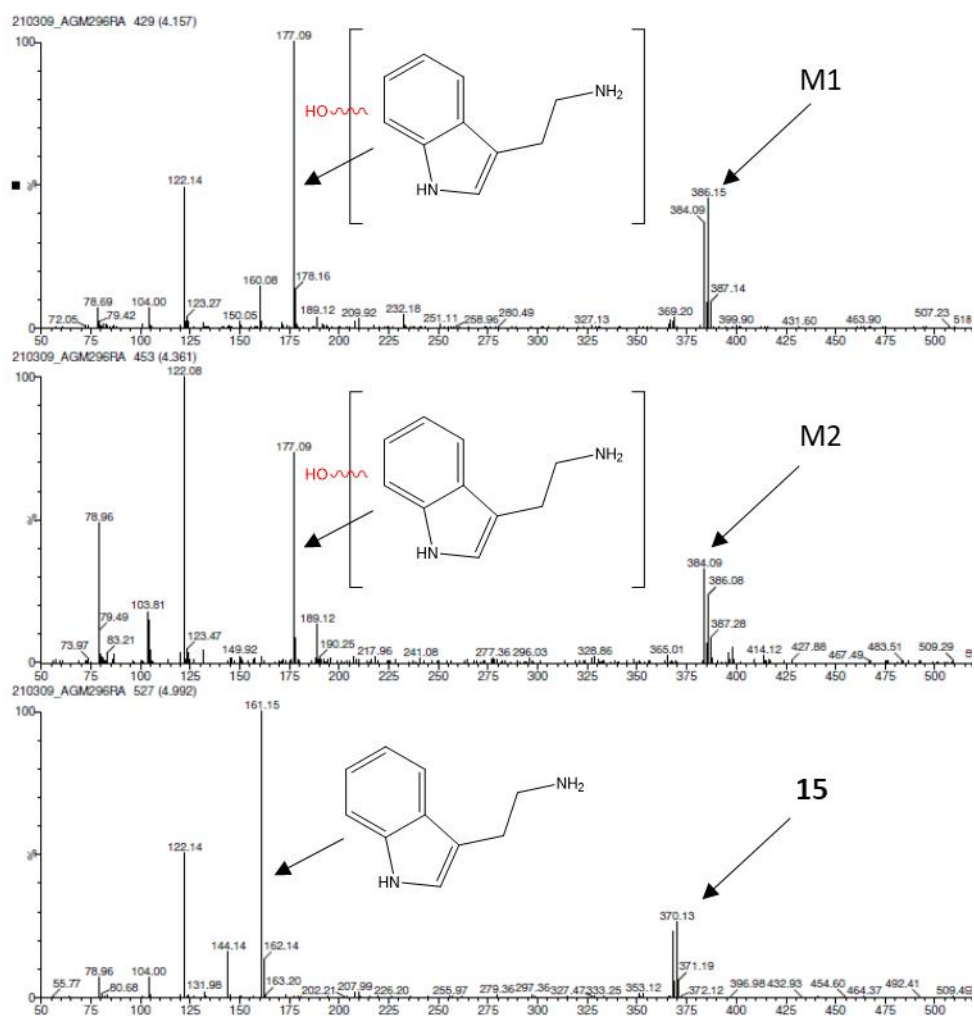


Figure S7. The MS spectra of **14** and its metabolites.

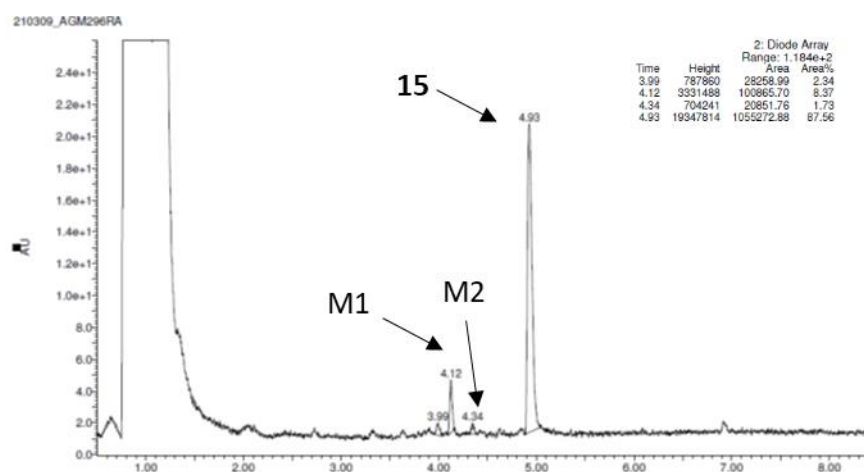


Figure S8. The UPLC spectra after 120 min reaction of **15** with mouse liver microsomes (MLMs).

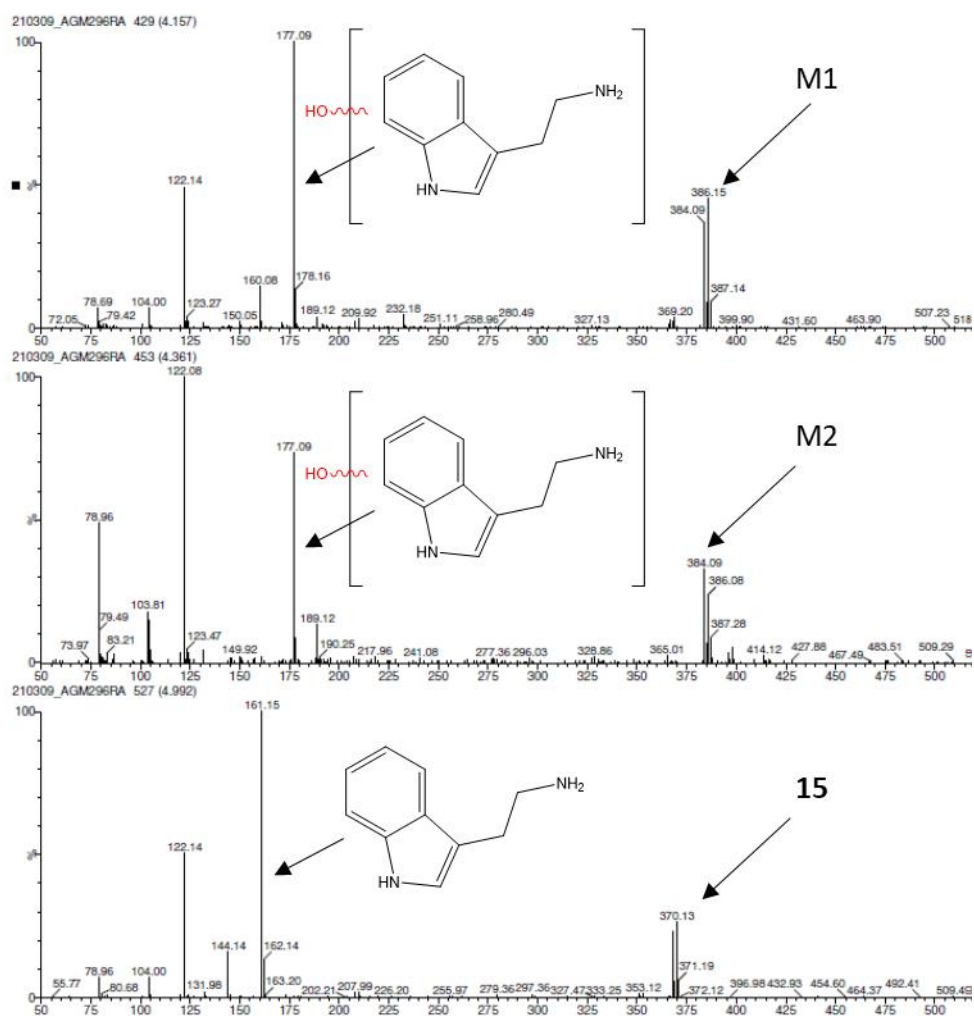


Figure S9. The MS spectra of **15** and its metabolites.

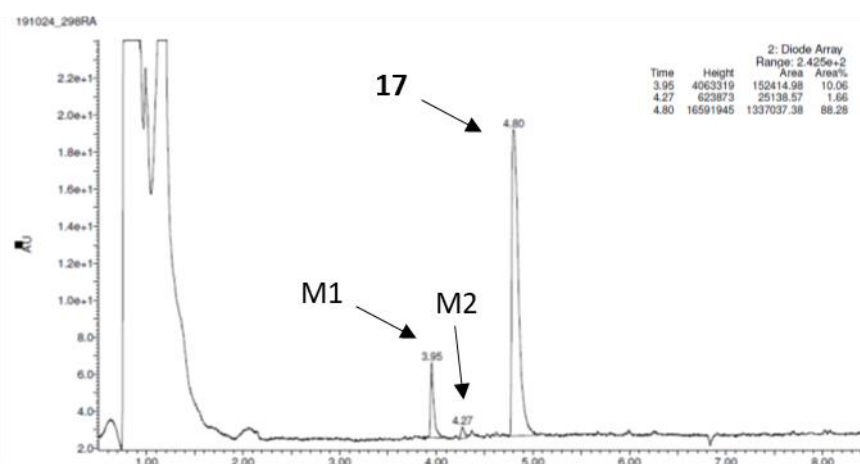


Figure S10. The UPLC spectra after 120 min reaction of **17** with mouse liver microsomes (MLMs).

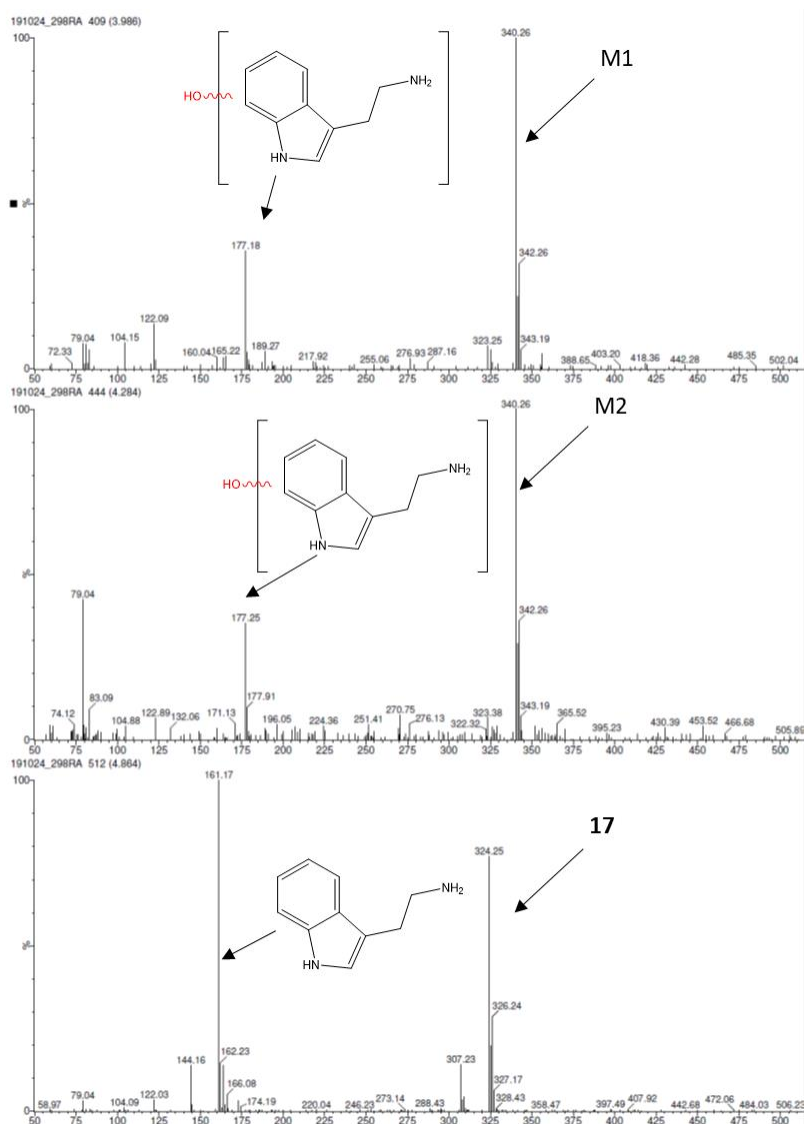


Figure S11. The MS spectra of **17** and its metabolites.

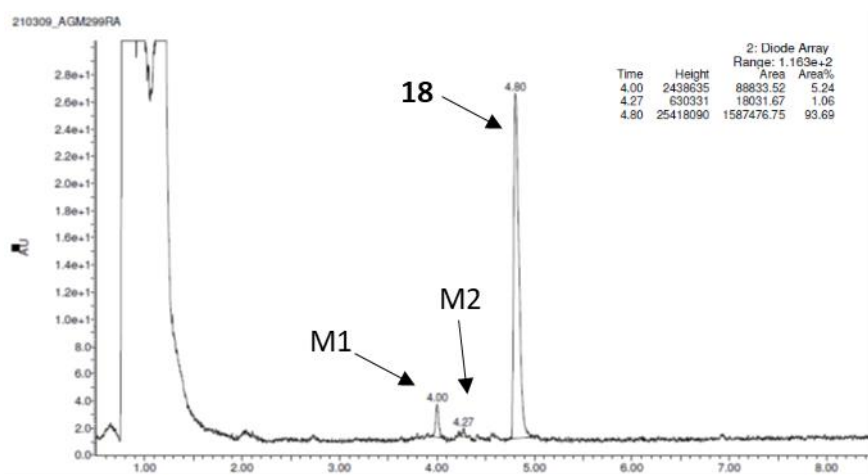


Figure S12. The UPLC spectra after 120 min reaction of **18** with mouse liver microsomes (MLMs).

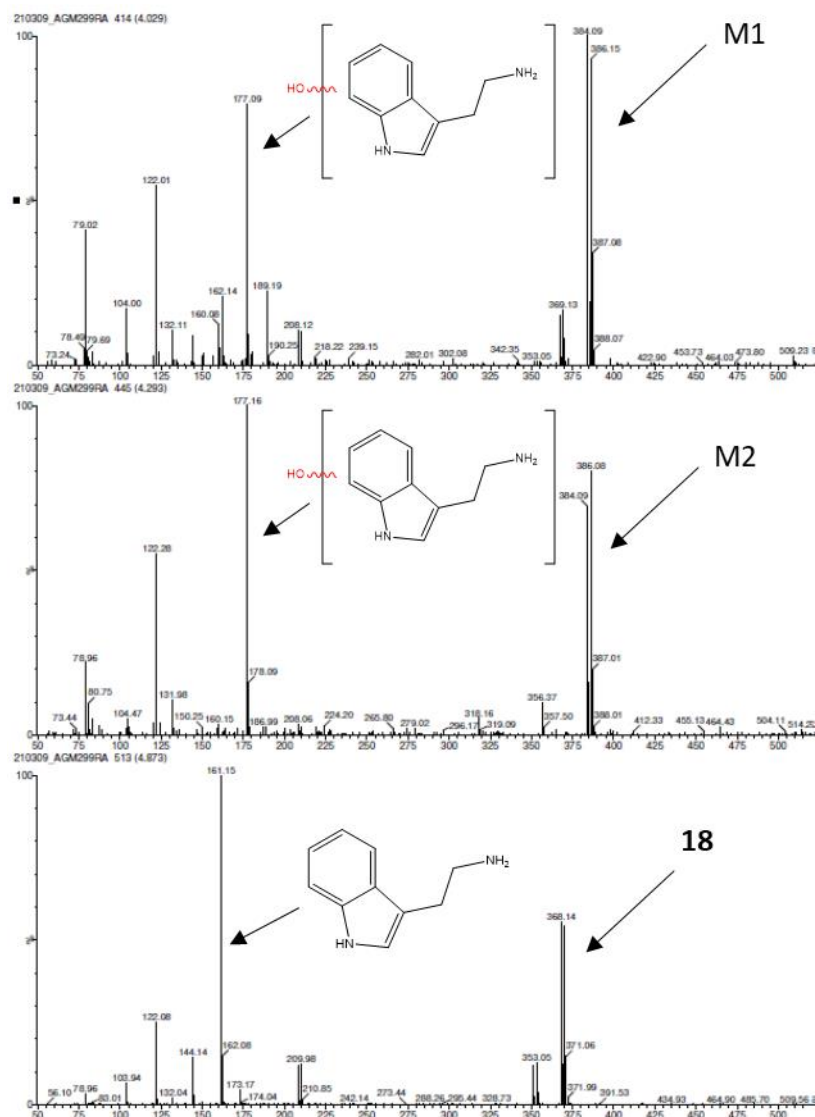


Figure S12. The MS spectra of **18** and its metabolites.