Supporting Information for

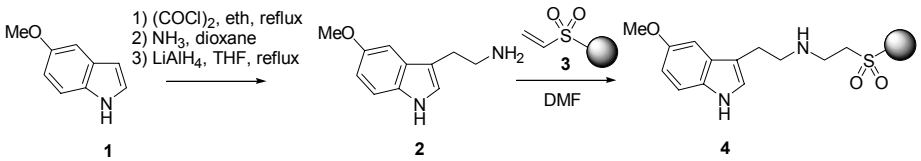
"A Versatile Linkage Strategy for Solid-Phase Synthesis of *N*,*N*-Dimethyltryptamines and β-Carbolines"

Tom Y. H. Wu and Peter G. Schultz*

The Scripps Research Institute, La Jolla, CA 92037, USA.

General. All reactions involving palladium and copper catalyst were carried out under an argon atmosphere and anhydrous conditions. Anhydrous tetrahydrofuran, ether, and dichloromethane were obtained by passing them through commercially available alumina columns. All other reagents, resins, and solvents were purchased at highest commercial quality and used without further purification. Purity of compounds was assessed by reverse-phase liquid chromatography mass spectrometer (4 minutes elution using 5% to 95% acetonitrile in water) with an UV detector at λ = 255 nm and an electrospray ionization source. NMR spectra were recorded on Bruker-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

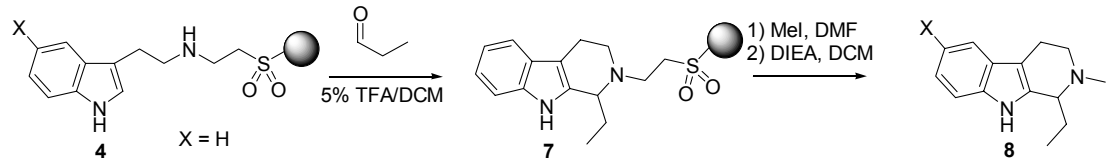
Preparation of 4.



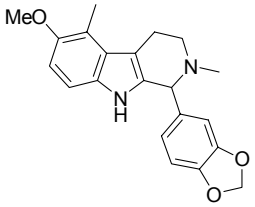
5-Methoxyindole **1** (1.0 g, 6.8 mmol) was suspended in ether (25 mL) and treated with oxalyl chloride (1.78 mL, 20.4 mmol) and stirred at reflux for 6h. The reaction was cooled to ambient temperature and the solids were filtered. The solids were treated with 0.5 M ammonia in dioxane (25 mL) and stirred at ambient temperature for 8h. The solids were filtered, suspended in THF and treated with lithium aluminum hydride (1.3 g, 34 mmol) followed by heating at reflux for 8h. The reaction was cooled to ambient temperature followed by slow addition of 1 mL 3N KOH, 2 mL H_2O, and then 3 mL 3N KOH sequentially. The reaction mixture was stirred at ambient temperature for 1h. The salts were filtered and the organic layer was removed. The aqueous layer was extracted with EtOAc and the combined organic layers were evaporated in *vacuo* (weight of crude = 1.44 g). Crude 5-methoxytryptamine (**2)** was dissolved in DMF (35 mL) and added to 1.8 g vinylsulfonylmethyl polystyrene resin **3** (2 mmol, 1.12 mmol/g) with stirring at ambient temperature for 16h. The resin was then washed with 10 mL of CH_2Cl_2, DMF,

H_2O, and MeOH. The washing procedure was repeated four times and the resin was dried overnight in *vacuo*.

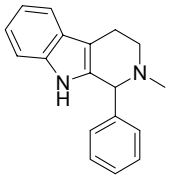
Preparation of 8 via Pictet-Spengler reaction on solid support.

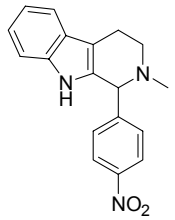
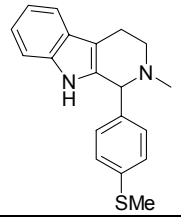
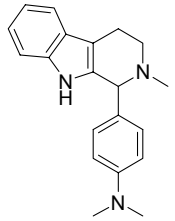
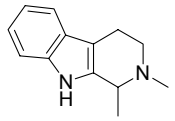
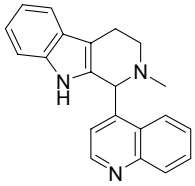
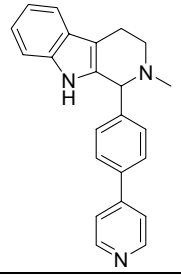
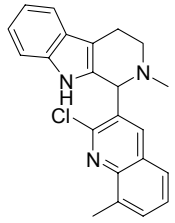
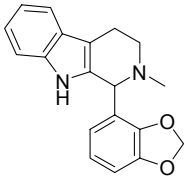


Resin-bound tryptamine **4** (150 mg, 0.150 mmol, ~1 mmol/g) was swelled in 5% TFA/DCM (2 mL), treated with propionaldehyde (107 μL, 1.5 mmol) and agitated at ambient temperature for 8h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was then suspended in DMF (2.0 mL), treated with MeI (96 μL 1.5 mmol) and agitated at ambient temperature for 12h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was again suspended in DCM (2.0 mL), treated with diisopropylethylamine (392 μL, 2.25 mmol) and agitated at ambient temperature for 24h. The resin was filtered and washed with 1 mL DCM twice. The filtrate and washings were concentrated in *vacuo* to give compound **8** (30.7 mg, 96%). LC-ESMS observed a single peak with $[M+H]^+$ 215.1 (calcd for $C_{14}H_{18}N_2$ 214.1). An analytical portion was purified by reverse-phase HPLC (C18 column) using 30 to 90% acetonitrile in water gradient for 8 minutes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.48 (d, 1H, *J* = 7.6Hz), 7.42 (d, 1H, *J* = 8.2Hz), 7.11-7.22 (m, 2H), 4.28-4.32 (m, 1H), 3.66-3.73 (m, 1H), 3.43-3.51 (m, 1H), 3.02-3.11 (m, 2H), 2.82 (s, 3H), 2.25-2.35 (m, 1H), 1.91-2.02 (m, 1H), 1.13 (t, 3H, *J* = 7.5Hz).

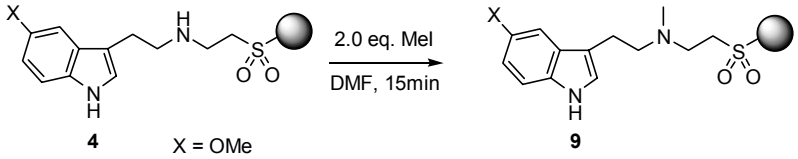


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 0.5H), 7.55 (s, 0.5H), 7.04 (d, 1H, *J* = 8.8Hz), 6.72-6.89 (m, 3H), 5.99 (s, 2H), 3.83 (s, 3H), 3.25-3.62 (m, 3.5H), 2.92-2.94 (m, 1.5H), 2.52-2.65 (m, 7H). LC-ESMS observed $[M+H]^+$ 351.2 (calcd for $C_{21}H_{22}N_2O_3$ 350.2).

Structure	Calcd for [M]	Observed $[M+H]^+$
	$C_{18}H_{18}N_2$ 262.15	263.2

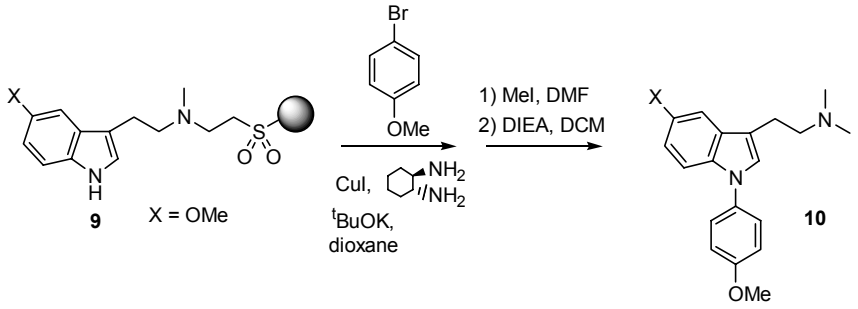
	$C_{18}H_{17}N_3O_2$ Exact Mass: 307.13	308.1
	$C_{19}H_{20}N_2S$ Exact Mass: 308.13	309.1
	$C_{20}H_{23}N_3$ Exact Mass: 305.19	306.2
	$C_{13}H_{16}N_2$ Exact Mass: 200.13	201.1
	$C_{21}H_{19}N_3$ Exact Mass: 313.16	314.2
	$C_{23}H_{21}N_3$ Exact Mass: 339.17	340.2
	$C_{22}H_{20}ClN_3$ Exact Mass: 361.13	362.1
	$C_{19}H_{18}N_2O_2$ Exact Mass: 306.14	307.1

Preparation of monomethylated resin-bound tryptamine 9.

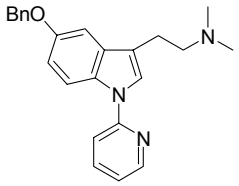


Resin-bound tryptamine **4** (500 mg, 0.5 mmol, ~1 mmol/g) was swelled in DMF (7.5 mL), treated with MeI (65 µL, 1 mmol) and agitated at ambient temperature for 15min. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times and the resin was dried overnight in *vacuo.*

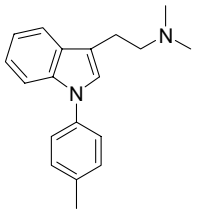
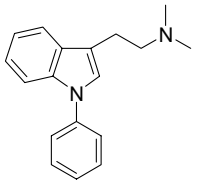
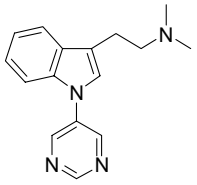
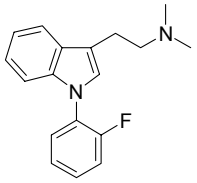
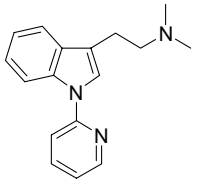
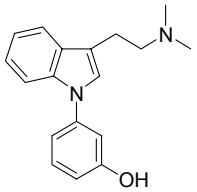
Preparation of 10 via Cu-mediated coupling on solid-support.

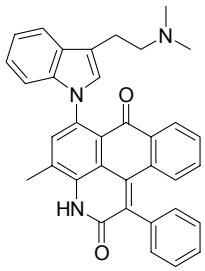
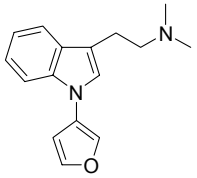
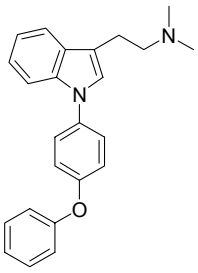
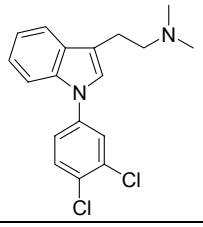
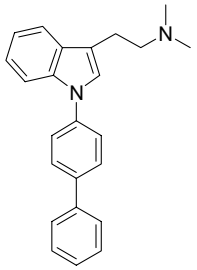
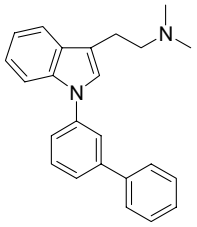
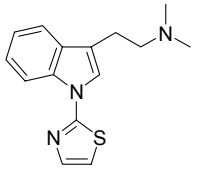


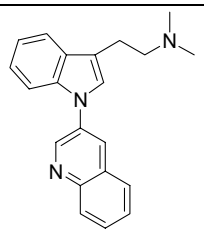
Resin-bound tryptamine **9** (150 mg, 0.15 mmol, ~1 mmol/g) was charged in a Schlenk flask with copper(I) iodide (29 mg, 0.15 mmol) and potassium *tert*-butoxide (168 mg, 1.5 mmol). The flask was evacuated and filled with argon gas. Dioxane (2 mL) and 1,2-*trans*-diaminocyclohexane (0.17 mL, 1.5 mmol) were then added via syringe and the solution was heated to 80°C for 24h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was then suspended in DMF (2.0 mL), treated with MeI (96µL 1.5mmol) and agitated at ambient temperature for 8h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was again suspended in DCM (2.0 mL), treated with diisopropylethylamine (392 µL, 2.25 mmol) and agitated at ambient temperature for 24h. The resin was filtered and washed with 1 mL DCM twice. The filtrate and washings were concentrated in *vacuo* to give **10** (36.0 mg, 74%). LC-ESMS observed a single peak with $[M+H]^+$ 325.2 (calcd for $C_{20}H_{24}N_2O_2$ 324.2). An analytical portion was purified by reverse-phase HPLC (C18 column) using 30 to 90% acetonitrile in water gradient for 8 minutes. ^{1}H NMR (500 MHz, $CDCl_3$*)* δ 7.30-7.32 (m, 3H), 7.11 (s, 1H), 7.09 (d, 1H, *J* = 2.2Hz), 7.00 (d, 2H, *J* = 9.2Hz), 6.85 (dd, 1H, *J* = 2.2Hz, 8.9Hz), 3.88 (s, 3H), 3.85 (s, 3H), 3.30-3.33 (m, 2H), 3.23-3.26 (m, 2H), 2.89 (s, 6H).



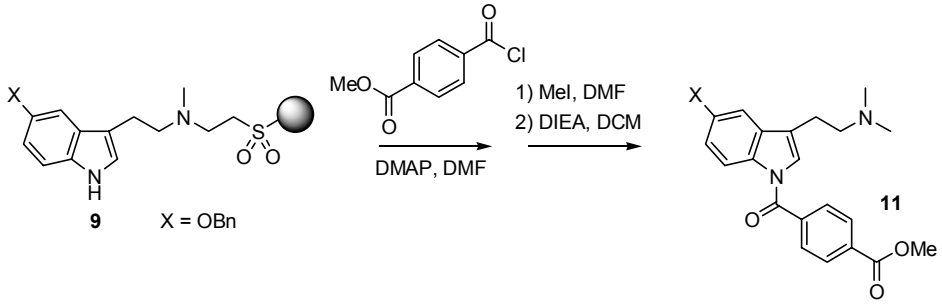
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, 1H, *J* = 4.8Hz), 8.12 (d, 1H, *J* = 9.2Hz), 7.80 (dt, 1H, *J* = 2.2Hz, 7.3Hz), 7.60 (s, 1H), 7.49 (d, 2H, *J* = 7.3Hz), 7.44 (d, 1H, *J* = 8.1Hz), 7.37 (t, 2H, *J* = 7.3Hz), 7.30 (t, 1H, *J* = 7.3Hz), 7.13-7.14 (m, 2H), 7.04 (dq, 1H, *J* = 2.2Hz, 8.8Hz), 5.17 (s, 2H), 3.20-3.35 (m, 4H), 2.85 (s, 6H). LC-ESMS observed $[M+H]^+$ 372.2 (calcd for $C_{24}H_{25}N_3$ 371.2).

Structure	Calcd for [M]	Observed $[M+H]^+$
	$C_{19}H_{22}N_2$ Exact Mass: 278.18	279.2
	$C_{18}H_{20}N_2$ Exact Mass: 264.16	265.2
	$C_{16}H_{18}N_4$ Exact Mass: 266.15	267.2
	$C_{18}H_{19}FN_2$ Exact Mass: 282.15	283.2
	$C_{17}H_{19}N_3$ Exact Mass: 265.16	266.2
	$C_{18}H_{20}N_2O$ Exact Mass: 280.16	281.2

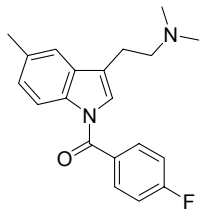
	$C_{35}H_{29}N_3O_2$ Exact Mass: 523.23	524.2
	$C_{16}H_{18}N_2O$ Exact Mass: 254.14	255.1
	$C_{24}H_{24}N_2O$ Exact Mass: 356.19	357.2
	$C_{18}H_{18}Cl_2N_2$ Exact Mass: 332.08	333.1
	$C_{24}H_{24}N_2$ Exact Mass: 340.19	341.2
	$C_{24}H_{24}N_2$ Exact Mass: 340.19	341.2
	$C_{15}H_{17}N_3S$ Exact Mass: 271.11	272.1

	$C_{21}H_{21}N_3$ Exact Mass: 315.17	316.2

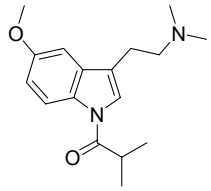
Preparation of 11 via acylation on solid-support with acid chloride.



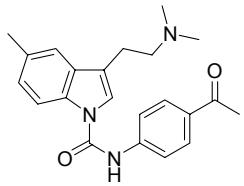
Resin-bound tryptamine **9** (150 mg, 0.15 mmol, ~1 mmol/g) was swelled in DMF (2 mL), treated with methyl 4-chlorocarbonylbenzoate (299 mg, 1.5 mmol) and 4-dimethylaminopyridine (183 mg, 1.5 mmol), and heated at 80°C for 12h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was then suspended in DMF (2.0 mL), treated with MeI (96μL 1.5mmol) and agitated at ambient temperature for 8h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was again suspended in DCM (2.0 mL), treated with diisopropylethylamine (392 μL, 2.25 mmol) and agitated at ambient temperature for 24h. The resin was filtered and washed with 1 mL DCM twice. The filtrate and washings were concentrated in *vacuo* to give **11** (15.3 mg, 22%). LC-ESMS observed a single peak with $[M+H]^+$ 457.2 (calcd for $C_{28}H_{28}N_2O_4$ 456.2). An analytical portion was purified by reverse-phase HPLC (C18 column) using 30 to 90% acetonitrile in water gradient for 8 minutes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 1H, J = 8.8Hz), 8.19 (d, 2H, J = 8.4Hz), 7.74 (d, 2H, J = 8.4Hz), 7.48 (d, 2H, J = 7.3Hz), 7.38 (t, 2H, J = 7.3Hz), 7.31 (t, 1H, J = 7.3Hz), 7.16 (d, 1H, J = 2.2Hz), 7.09 (dd, 1H, J = 2.2Hz, 8.8Hz), 7.05 (s, 1H), 5.18 (s, 2H), 3.97 (s, 3H), 33.11-3.20 (m, 4H), 2.84 (s, 6H).



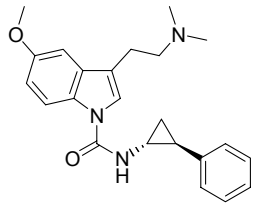
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1H, J = 8.5Hz), 8.05-8.09 (m, 1H), 7.72-7.74 (m, 2H), 7.11-7.21 (m, 4H), 3.13-3.29 (m, 4H), 2.88 (s, 6H), 2.47 (s, 3H). LC-ESMS observed $[M+H]^+$ 325.2 (calcd for $C_{20}H_{21}FN_2O$ 324.16).



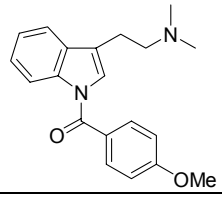
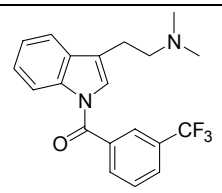
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, 1H, *J* = 9.1Hz), 7.41 (s, 1H), 6.96-7.00 (m, 2H), 3.87 (s, 3H), 3.16-3.31 (m, 5H), 2.88 (s, 6H), 1.32 (s, 3H), 1.31 (s, 3H). LC-ESMS observed $[M+H]^+$ 289.2 (calcd for $C_{17}H_{24}N_2O_2$ 288.18).

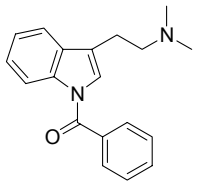
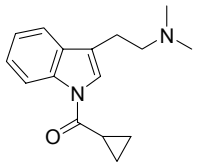
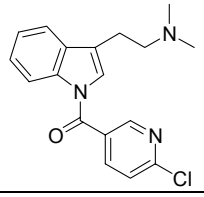
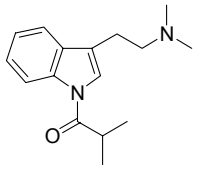
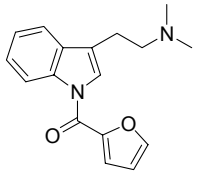
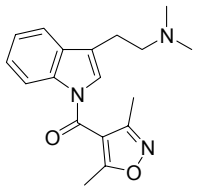
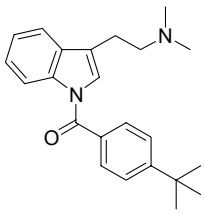
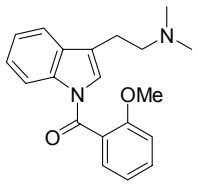


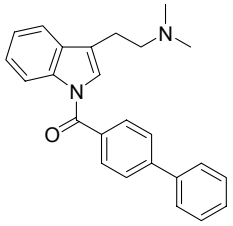
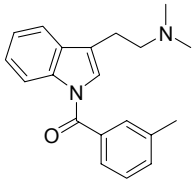
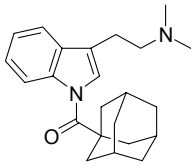
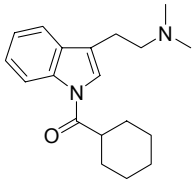
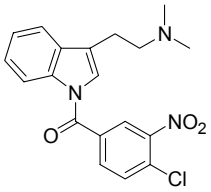
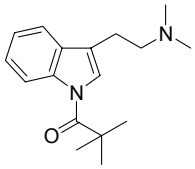
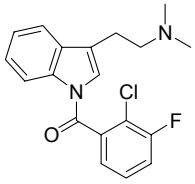
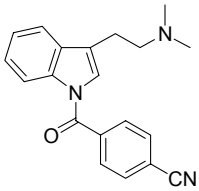
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.23 (s, 1H), 8.14 (d, 1H, *J* = 8.8Hz), 7.94 (d, 1H, J = 7.7Hz), 7.68-7.72 (m, 2H), 7.42 (t, 1H, *J* = 7.7Hz), 7.20 (s, 1H), 7.16 (d, 1H, 8.8Hz), 3.39 (t, 2H, *J* = 6.6Hz), 3.17 (t, 2H, *J* = 6.6Hz), 2.82 (s, 6H), 2.58 (s, 3H), 2.43 (s, 3H). LC-ESMS observed $[M+H]^+$ 364.2 (calcd for $C_{22}H_{25}N_3O_2$ 363.19).

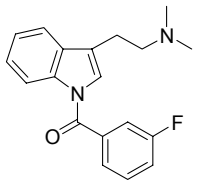
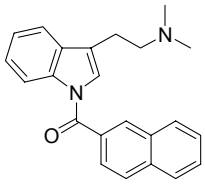
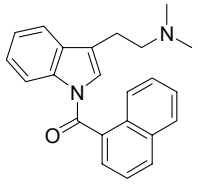
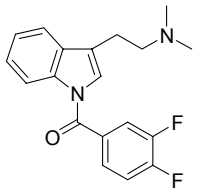
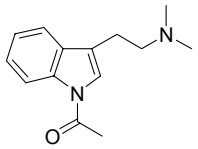
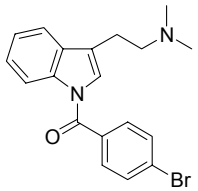
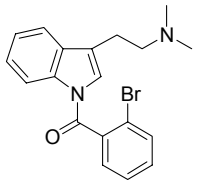
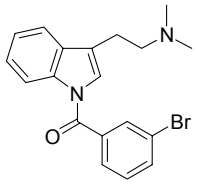
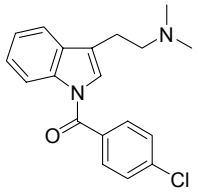


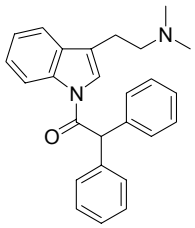
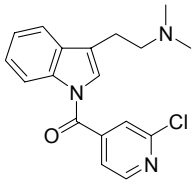
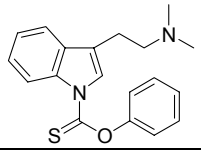
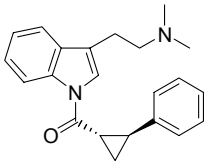
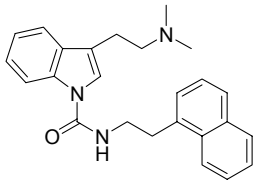
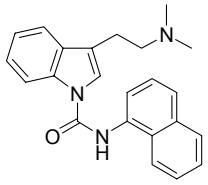
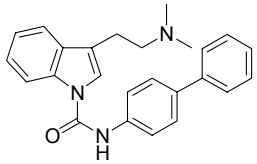
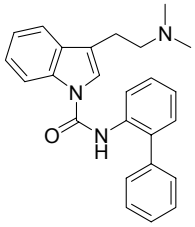
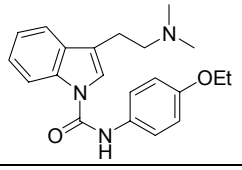
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 9.1Hz), 7.42 (s, 1H), 7.23-7.25 (m, 2H), 7.12-7.18 (m, 3H), 6.91 (dd, 1H, *J* = 2.7Hz, 9.1Hz), 6.86 (s, 1H), 3.81 (s, 3H), 3.25-3.29 (m, 2H), 3.02-3.05 (m, 3H), 2.92-2.96 (m, 1H), 2.78 (s, 6H), 2.16-2.21 (m, 1H), 1.24-1.34 (m, 2H). LC-ESMS observed $[M+H]^+$ 378.2 (calcd for $C_{23}H_{27}N_3O_2$ 377.21).

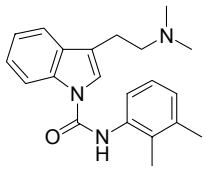
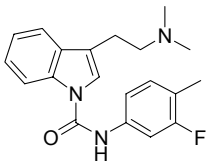
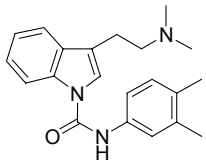
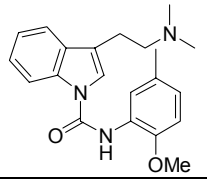
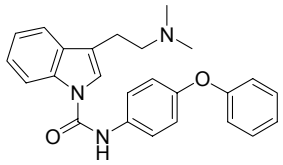
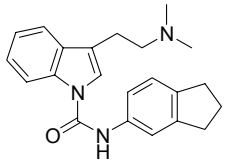
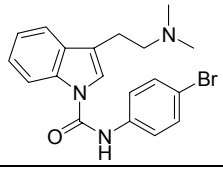
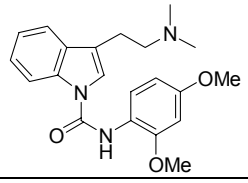
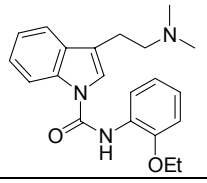
Structure	Calcd for [M]	Observed $[M+H]^+$
	$C_{20}H_{22}N_2O_2$ Exact Mass: 322.17	323.2
	$C_{20}H_{19}F_3N_2O$ Exact Mass: 360.14	361.1

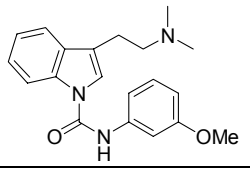
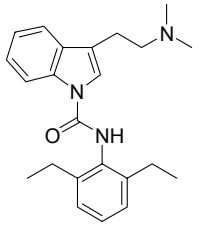
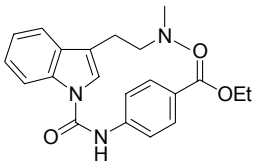
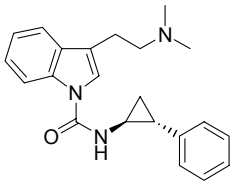
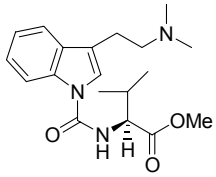
	$C_{19}H_{20}N_2O$ Exact Mass: 292.16	293.2
	$C_{16}H_{20}N_2O$ Exact Mass: 256.16	257.2
	$C_{18}H_{18}ClN_3O$ Exact Mass: 327.11	328.1
	$C_{16}H_{22}N_2O$ Exact Mass: 258.17	259.2
	$C_{17}H_{18}N_2O_2$ Exact Mass: 282.14	283.1
	$C_{18}H_{21}N_3O_2$ Exact Mass: 311.16	312.2
	$C_{23}H_{28}N_2O$ Exact Mass: 348.22	349.2
	$C_{20}H_{22}N_2O_2$ Exact Mass: 322.17	323.2

	$C_{25}H_{24}N_2O$ Exact Mass: 368.19	369.2
	$C_{20}H_{22}N_2O$ Exact Mass: 306.17	307.2
	$C_{23}H_{30}N_2O$ Exact Mass: 350.24	351.2
	$C_{19}H_{26}N_2O$ Exact Mass: 298.20	299.2
	$C_{19}H_{18}ClN_3O_3$ Exact Mass: 371.10	372.1
	$C_{17}H_{24}N_2O$ Exact Mass: 272.19	273.2
	$C_{19}H_{18}ClFN_2O$ Exact Mass: 344.11	345.1
	$C_{20}H_{19}N_3O$ Exact Mass: 317.15	318.2

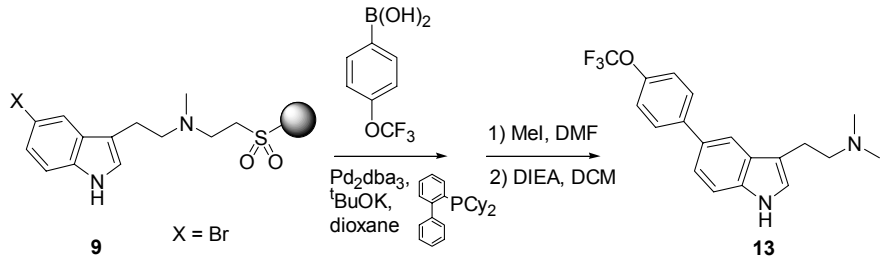
	$C_{19}H_{19}FN_2O$ Exact Mass: 310.15	311.2
	$C_{23}H_{22}N_2O$ Exact Mass: 342.17	343.2
	$C_{23}H_{22}N_2O$ Exact Mass: 342.17	343.2
	$C_{19}H_{18}F_2N_2O$ Exact Mass: 328.14	329.1
	$C_{14}H_{18}N_2O$ Exact Mass: 230.14	231.1
	$C_{19}H_{19}BrN_2O$ Exact Mass: 370.07	371.1
	$C_{19}H_{19}BrN_2O$ Exact Mass: 370.07	371.1
	$C_{19}H_{19}BrN_2O$ Exact Mass: 370.07	371.1
	$C_{19}H_{19}ClN_2O$ Exact Mass: 326.12	327.1

	$C_{26}H_{26}N_2O$ Exact Mass: 382.20	383.2
	$C_{18}H_{18}ClN_3O$ Exact Mass: 327.11	328.1
	$C_{19}H_{20}N_2OS$ Exact Mass: 324.13	325.1
	$C_{22}H_{24}N_2O$ Exact Mass: 332.19	333.2
	$C_{25}H_{27}N_3O$ Exact Mass: 385.22	386.2
	$C_{23}H_{23}N_3O$ Exact Mass: 357.18	358.2
	$C_{25}H_{25}N_3O$ Exact Mass: 383.20	384.2
	$C_{25}H_{25}N_3O$ Exact Mass: 383.20	384.2
	$C_{21}H_{25}N_3O_2$ Exact Mass: 351.19	352.2

	$C_{21}H_{25}N_3O$ Exact Mass: 335.20	336.2
	$C_{20}H_{22}FN_3O$ Exact Mass: 339.17	340.2
	$C_{21}H_{25}N_3O$ Exact Mass: 335.20	336.2
	$C_{21}H_{25}N_3O_2$ Exact Mass: 351.19	352.2
	$C_{25}H_{25}N_3O_2$ Exact Mass: 399.19	400.2
	$C_{22}H_{25}N_3O$ Exact Mass: 347.20	348.2
	$C_{19}H_{20}BrN_3O$ Exact Mass: 385.08	386.1
	$C_{21}H_{25}N_3O_3$ Exact Mass: 367.19	368.2
	$C_{21}H_{25}N_3O_2$ Exact Mass: 351.19	352.2

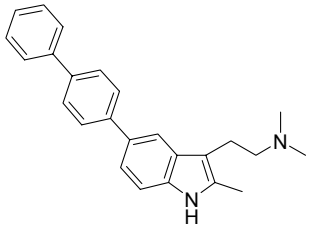
	$C_{20}H_{23}N_3O_2$ Exact Mass: 337.18	338.2
	$C_{23}H_{29}N_3O$ Exact Mass: 363.23	364.2
	$C_{22}H_{25}N_3O_3$ Exact Mass: 379.19	380.2
	$C_{22}H_{25}N_3O$ Exact Mass: 347.20	348.2
	$C_{19}H_{27}N_3O_3$ Exact Mass: 345.21	346.2

Preparation of 13 via Suzuki coupling on solid-support.

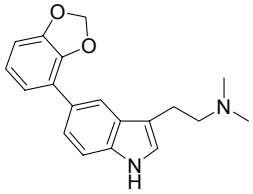
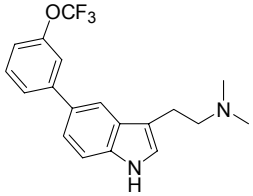
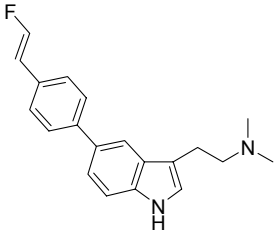
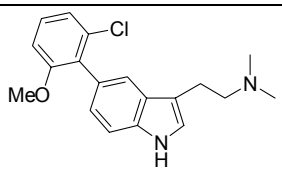
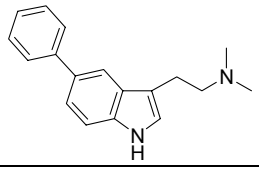


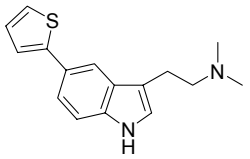
Resin-bound tryptamine **9** (150 mg, 0.15 mmol, ~1 mmol/g) was charged in a Schlenk flask with tris(dibenzylideneacetone) dipalladium(0) (21 mg, 0.023 mmol), 2-(dicyclo-hexylphosphino)biphenyl (32 mg, 0.09 mmol), 4-trifluoromethoxyphenylboronic acid (155 mg, 0.75 mmol), and potassium phosphate (318 mg, 1.5 mmol). The flask was evacuated and filled with argon gas. Dioxane (2 mL) was then added via syringe and the solution was heated to 80°C for 24h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin was then suspended in DMF (2.0 mL), treated with MeI (96μL 1.5mmol) and agitated at ambient temperature for 8h. The resin was then washed with 10 mL of CH_2Cl_2, DMF, H_2O, and MeOH four times. The resin

was again suspended in DCM (2.0 mL), treated with diisopropylethylamine (392 µL, 2.25 mmol) and agitated at ambient temperature for 24h. The resin was filtered and washed with 1 mL DCM twice. The filtrate and washings were concentrated in *vacuo* to give **13** (45.8 mg, 88%). LC-ESMS observed a single peak with $[M+H]^+$ 349.1 (calcd for $C_{19}H_{19}N_3O_2$ 348.1). An analytical portion was purified by reverse-phase HPLC (C18 column) using 30 to 90% acetonitrile in water gradient for 8 minutes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.73 (s, 1H), 7.65 (d, 2H, *J* = 8.4Hz), 7.39-7.44 (m, 2H), 7.27 (d, 2H, *J* = 8.4Hz), 7.09 (d, 1H), 3.25-3.26 (m, 4H), 2.84 (s, 6H).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.73 (d, 2H, *J* = 8.4Hz), 7.63-7.67 (m, 5H), 7.42-7.46 (m, 3H), 7.33-7.36 (m, 2H), 3.22 (s, 4H), 2.88 (s, 6H), 2.42 (s, 3H). LC-ESMS observed $[M+H]^+$ 355.2 (calcd for $C_{25}H_{26}N_2$ 354.21).

Structure	Calcd for [M]	Observed $[M+H]^+$
	$C_{19}H_{20}N_2O_2$ Exact Mass: 308.15	309.2
	$C_{19}H_{19}F_3N_2O$ Exact Mass: 348.14	349.1
	$C_{20}H_{21}FN_2$ Exact Mass: 308.17	309.2
	$C_{19}H_{21}ClN_2O$ Exact Mass: 328.13	329.1
	$C_{18}H_{20}N_2$ Exact Mass: 264.16	265.2

	$C_{16}H_{18}N_2S$ Exact Mass: 270.12	271.1