The Synthesis of Dopamine, Rotigotin, Ladostigil, Rasagiline Analogues 2-Amino-4,5,6-Trimethoxyindane, 1-Amino-5,6,7-Trimethoxyindane and Their Sulfamide Derivatives

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EXPERIMENTAL

All chemicals and solvents are commercially available and they were used after distillation or treatment with drying agents. Column Chromatography (CC): silica gel (SiO₂, 60-mesh; Merck). M.p.: BUCHI 530 a capillary melting-point apparatus; uncorrected. IR spectra: Perkin-Elmer spectrophotometer; solutions in 0.1 mm cells. ¹H- and ¹³C-NMR spectra: Varian 400 (400 and 100 MHz, resp.) and Bruker 400 (400 and 100 MHz, resp.) spectrometer; δ in ppm rel. to Me₄Si as internal standard, J in Hz. Elemental analysis (EA): Leco CHNS-932 apparatus. PLC: 1 mm of silica gel (SiO₂, 60 PF; Merck); preparative thin-layer chromatography; on glass plates.

5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-one (8)

Compound **8** was prepared as described in the literature.^[1] ¹H- and ¹³C-NMR data of this compound has been reported previously.^[2]

Methyl 5,6,7-trimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (9)

Into a 250-mL round-bottom flask was placed 5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-one (**8**) (6 g, 27.02 mmol) in THF (100 mL). Then 3 equiv. (1.95 g, 81.00 mmol) NaH and DMC (5.7 mL, 67.50 mmol) in THF (10 mL) were added to the mixture. The reaction mixture was refluxed for 24 h. The mixture was cooled to room temperature and it was acidified with glacial AcOH (2 mL). Aqueous solution of Na₂CO₃ (10 mL) was added to the mixture and then it was extracted with EtOAc (3x10 mL). The combined organic phases were washed with water (10 mL) and dried over Na₂SO₄. Evaporation of the solvent and column chromatography of the residue on silica gel (50 g) with 30% EtOAc-Hexane gave ester **9** (7.45 g, 98%). Yellowish solid. Mp 88-90 °C; IR (CH₂Cl₂, cm⁻¹): 2941, 2067, 1737, 1692, 1588, 1482, 1325, 1253, 1138; ¹H-NMR (400 MHz, CDCl₃): 6.67 (s, 1H, Ar-H); 4.00 (s, 3H, OCH₃); 3.92 (s, 3H, OCH₃); 3.81 (s, 3H, OCH₃); 3.75 (s, 3H, OCH₃); 3.67 (dd, J=8.4, 4.0 Hz, 1H); 3.40 (A of AB, dd, J=17.2, 4.0 Hz, 1H); 3.15 (B of AB, dd, J=17.2, 8.4 Hz, 1H). ¹³C-NMR (100 MHz, CDCl₃): 195.6 (CO); 170.2 (CO); 160.7 (C); 152.4 (C); 151.9 (C); 141.2 (C); 121.2 (C); 103.8 (CH); 62.2 (OCH₃); 61.6 (OCH₃); 56.6 (OCH₃); 54.1 (OCH₃); 52.9 (CH); 30.2 (CH₂). Anal. Calcd for C₁₄H₁₆O₆: C 59.99, H 5.75; found: C 60.09, H 5.68.

Methyl 4,5,6-trimethoxy-2,3-dihydro-1H-indene-2-carboxylate (**10**)

To a stirred solution of ester **9** (7.0 g, 24.98 mmol) in TFA (38 mL) was added Et₃SiH (16.0 mL, 100.45 mmol) under N₂ gas. Then the mixture was refluxed for 4 h, TFA was evaporated in vacuo. The saturated solution of Na₂CO₃ was added to the residue up to pH=8. The mixture was extracted with EtOAc (3x50 mL). A dilute solution of HCl was added to the combined organic layers up to pH=5. Drying of the organic layer over Na₂SO₄ column chromatography of the residue on silica gel (40 g) with 5% EtOAc-Hexane yielded carboxylate **10** (4.2 g, 63%). Yellowish oil. IR (CH₂Cl₂, cm⁻¹): 2941, 2840, 1734, 1588, 1465, 1339, 1250, 1116; ¹H-NMR (400 MHz, CDCl₃): 6.47 (*s*, 1H, Ar-H); 3.81 (*s*, 3H, OCH₃); 3.744 (*s*, 3H, OCH₃); 3.74 (*s*, 3H, OCH₃); 3.64 (*s*, 3H, OCH₃); 3.26-3.22 (*m*, 1H, CH-CO); 3.16-3.05 (*m*, 4H, 2CH₂). ¹³C-NMR (100 MHz, CDCl₃): 175.7 (CO); 153.4 (C); 149.7 (C); 140.5 (C); 137.3 (C); 125.9 (C); 103.5 (CH); 61.1 (OCH₃); 60.5 (OCH₃); 56.3 (OCH₃); 52.0 (OCH₃); 43.6 (CH); 36.6 (CH₂); 33.5 (CH₂). Anal. Calcd for C₁₄H₁₈O₅: C 63.15, H 6.81; found: C 63.21, H 6.68.

4,5,6-trimethoxy-2,3-dihydro-1H-indene-2-carboxylic acid (**11**)

A saturated solution of NaOH in H₂O-MeOH (20 mL) was added to a stirred solution of carboxylate **10** (4.2 g, 15.77 mmol) in MeOH (60 mL). The reaction mixture was stirred for 24 h at room temperature. After the most of MeOH was evaporated in vacuo, H₂O (30 mL) and CH₂Cl₂ (30 mL) were added to the residue. The organic layer was thrown and H₂O phase was acidified with conc. HCl up to pH=1. Then H₂O layer was extracted with CH₂Cl₂ (3x50 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was evaporated in vacuo. Carboxylic acid **11** (3.7 g, 93%) was synthesized as a white solid. Mp 112-114 °C (lit.^[3] Mp 110-111 °C). IR (CH₂Cl₂, cm⁻¹): 3456, 2941, 2840, 1706, 1465, 1339, 1253, 1111. ¹H-NMR (400 MHz, CDCl₃): 9.89 (*br. s*, 1H, OH); 6.54 (*s*, 1H, Ar-H); 3.89 (*s*, 3H, OCH₃); 3.830 (*s*, 3H, OCH₃); 3.826 (*s*, 3H, OCH₃); 3.39-3.27 (*m*, 1H, CH-CO); 3.24-3.13 (*m*, 4H, 2CH₂). ¹³C-NMR (100 MHz, CDCl₃): 181.6 (CO); 153.5 (C); 149.8 (C); 140.6 (C); 137.2 (C); 125.8 (C); 103.5 (CH); 61.3 (OCH₃); 60.7 (OCH₃); 56.4 (OCH₃); 43.6 (CH); 36.6 (CH₂). 33.4 (CH₂). Anal. Calcd for C₁₃H₁₆O₅: C 61.90, H 6.39; found: C 61.58, H 6.23.

Benzyl (4,5,6-trimethoxy-2,3-dihydro-1H-inden-2-yl)carbamate (**12**)

NEt₃ (2.39 mL, 17.24 mmol) and DPPA (3.71 mL, 17.23 mmol) were added to a solution of carboxylic acid **11** (3.6 g, 14.27 mmol) in benzene (40 mL). The reaction mixture was stirred at refluxed temperature for 4 h. BnOH (4.46 mL, 43.07 mmol) was added to the reaction mixture and it was stirred for 30 h. After benzene was evaporated in vacuo, column chromatography of the residue on silica gel (50 g) with 20% EtOAc-Hexane afforded carbamate **12** (4.1 g, 80%). Colorless oil. IR (CH₂Cl₂, cm⁻¹): 3352, 2935, 1703, 1553, 1332, 1190; ¹H-NMR (400 MHz, CDCl₃): 7.31-7.26 (*m*, 5H, Ar-H); 6.49 (*s*, 1H, Ar-H); 5.44 (*d*, *J*=7.2 Hz, 1H, NH); 5.05 (*s*, 2H, CH₂); 4.56-4.40 (*m*, 1H, CH-N); 3.83 (*s*, 3H, OCH₃); 3.79 (*s*, 3H, OCH₃); 3.77 (*s*, 3H, OCH₃); 3.24-3.14 (*m*, 2H, CH₂); 2.78-2.70 (*m*, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃): 156.3 (CO); 153.4 (C); 150.1 (C); 140.6 (C); 136.8 (C); 136.7 (C); 128.7 (2CH); 128.3 (3CH); 125.1 (C); 104.1 (CH); 66.8 (OCH₂); 61.2 (OCH₃); 60.6 (OCH₃); 56.4 (OCH₃); 52.6 (CH-N); 40.7 (CH₂); 37.4 (CH₂). Anal. Calcd for C₂₀H₂₃NO₅: C 67.21, H 6.49, N 3.92; found: C 67.13, H 6.65, N 3.88.

5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-ol (15)

Into a 100-mL round-bottom flask was placed 5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-one **8** (1.0 g, 4.50 mmol) in MeOH (30 mL). Then NaBH₄ (0.171 g, 4.52 mmol) was added to the reaction mixture and the mixture was allowed to stir for 4 h at room temperature. Methanol in the mixture was evaporated and then H₂O (30 mL) was added to the residue. Organic layer was extracted with CH₂Cl₂ (3x10 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was evaporated. Alcohol **15** (1.00 g, 99% yield) was synthesized as an orange oil. IR (CH₂Cl₂, cm⁻¹): 3423, 2935, 2840, 1588, 1462, 1412, 1334, 1233, 1113; ¹H-NMR (400 MHz, CDCl₃): 6.53 (*s*, 1H, Ar-H); 5.40-5.38 (*m*, 1H, CH-O); 3.99 (*s*, 3H, OCH₃); 3.83 (*s*, 3H, OCH₃); 3.82 (*s*, 3H, OCH₃); 3.07-3.01 (*m*, 1H, CH₂); 2.77-2.69 (*m*, 1H, CH₂); 2.48 (*br. s*, 1H, OH); 2.44-2.35 (*m*, 1H, CH₂); 2.03-1.95 (*m*, 1H, CH₂). ¹³C-NMR (100 MHz, CDCl₃): 154.9 (C); 150.2 (C); 140.2 (C); 139.8 (C); 129.4 (C); 103.5 (CH); 74.7 (CH-O); 61.19 (OCH₃); 61.15 (OCH₃); 56.3 (OCH₃); 35.0 (CH₂); 30.8 (CH₂). Anal. Calcd for C₁₂H₁₆O₄: C 64.27, H 7.19; found: C 64.21, H 7.23.

1-azido-5,6,7-trimethoxy-2,3-dihydro-1H-indene (16)

Into a 100-mL double-necked flask was placed 5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-ol **15** (0.8 g, 3.57 mmol) in THF (30 mL). DBU (0.64 mL, 2.59 mmol) was added to the mixture under N₂ gas and then DPPA (0.92 mL, 4.25 mmol) was added to the mixture at 0 °C. The reaction mixture was allowed to stir for 24 h at room temperature under N₂. THF was evaporated and then H₂O (40 mL) was added to the residue. The organic layer was extracted with EtOAc (3x30 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was evaporated. Column chromatography of the residue on silica gel (100 g) with 10% EtOAc-Hexane yielded azide **16** (0.6 g, 67%). Orange oil. IR (CH₂Cl₂, cm⁻¹): 2935, 2834, 2095, 1633, 1465, 1412, 1337, 1116; ¹H-NMR (400 MHz, CDCl₃): 6.55 (*s*, 1H, Ar-H); 5.01-4.99 (*m*, 1H, CH-N); 4.00 (*s*, 3H, OCH₃); 3.82 (*s*, 6H, 2OCH₃); 3.07-2.99 (*m*, 1H, CH₂); 2.79-2.72 (*m*, 1H, CH₂); 2.34-2.27 (*m*, 1H, CH₂); 2.13-2.06 (*m*, 1H, CH₂). ¹³C-NMR (100 MHz, CDCl₃): 155.5 (C); 150.6 (C); 140.4 (C); 130.3 (C); 125.4 (C); 103.3 (CH); 64.8 (CH-N); 61.2 (OCH₃); 61.1 (OCH₃); 56.3 (OCH₃); 33.2 (CH₂); 31.4 (CH₂). Anal. Calcd for C₁₂H₁₅N₃O₃: C 57.82, H 6.07, N 16.86; found: C 57.75, H 6.11, N 16.90.

General Procedure for the synthesis of Sulfamoyl carbamates (Benzyl N-(4,5,6-trimethoxy-2,3-dihydro-1H-inden-2-yl) sulfamoyl carbamate (19))

BnOH (0.73 g, 6.75 mmol) was added to a solution of CSI (0.77 g, 4.50 mmol) in CH₂Cl₂ (10 mL) at 0 °C. A solution of amine **14** (1.00 g, 4.48 mmol) in CH₂Cl₂ (30 mL) and NEt₃ (0.5 g, 4.94 mmol) were added to the solution of CSI drop wise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. It was allowed to warm up to room temperature and stirred for 3 h. A solution of 0.1 N HCl (50 mL) was added to the cooling reaction mixture at 0 °C. After organic layer was separated, H₂O layer was extracted with CH₂Cl₂ (2x30 mL). Combined organic phases were dried over Na₂SO₄ and the solvent was evaporated. Column chromatography on silica gel (50 g) with 25% EtOAc-Hexane was applied to the residue to give carbamate **19** (1.55 g, 79%). White solid. Mp 163-165 °C; IR (CH₂Cl₂, cm⁻¹): 3462, 2929, 2672, 2044, 1739, 1465, 1339, 1160, 1113; ¹H-NMR (400 MHz, CDCl₃): 7.36-7.35 (*m*, 5H, Ar-H); 6.47 (*s*, 1H, Ar-H); 5.55 (*d*, *J*=7.6 Hz, 1H, NH); 5.20 (*s*, 2H, CH₂Ph); 4.76 (*br. s*,

1H, NH); 4.23-4.15 (*m*, 1H, CH-N); 3.85 (*s*, 3H, OCH₃); 3.82 (*s*, 6H, 2OCH₃); 3.22 (*dd*, *J*=15.9, 7.3 Hz, 1H, CH₂); 3.13 (*dd*, *J*=15.9, 7.3 Hz, 1H, CH₂); 2.83-2.76 (*m*, 2H, CH₂). ¹³C-NMR (100 MHz, CDCl₃): 153.5 (C); 151.4 (C); 149.8 (CO); 140.7 (C); 135.3 (C); 134.7 (C); 128.9 (CH); 128.8 (2CH); 128.5 (2CH); 124.0 (C); 103.8 (CH); 68.6 (OCH₂); 61.1 (OCH₃); 60.5 (OCH₃); 56.3 (OCH₃); 55.5 (CH-N); 40.1 (CH₂); 36.7 (CH₂). Anal. calc. for C₂₀H₂₄N₂O₇S: C 55.03, H 5.54, N 6.42, S 7.35; found: C 55.10, H 5.50, N 6.48, S 7.31.

Benzyl N-(5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-yl)sulfamoyl carbamate (20)

Sulfamoyl carbamate **20** was synthesized with a yield of 77% according to the general procedure described above for **19**. White solid. Mp 126-128 °C; IR (CH₂Cl₂, cm⁻¹): 3352, 3213, 2962, 1724, 1557, 1405, 1358, 1296, 1183; ¹H NMR (400 MHz, DMSO-d₆): 11.35 (*br. s*, 1H, NH); 8.22 (*d*, *J*=7.6 Hz, 1H, NH); 7.43-7.35 (*m*, 5H, Ar-H); 6.58 (*s*, 1H, Ar-H); 5.18 (*s*, 2H, CH₂); 4.06-3.97 (*m*, 1H, CH-N); 3.74 (*s*, 6H, 2OCH₃); 3.68 (*s*, 3H, OCH₃); 3.09 (*dd*, *J*=15.7, 7.8 Hz, 1H, CH₂); 2.99 (*dd*, *J*=15.7, 7.8 Hz, 1H, CH₂); 2.77-2.69 (*m*, 2H, CH₂). ¹³C NMR (100 MHz, DMSO-d₆): 152.7 (C); 151.6 (C); 149.1 (CO); 139.8 (C); 136.0 (C); 135.9 (C); 128.4 (2CH); 128.2 (CH); 128.0 (2CH); 124.1 (C); 104.0 (CH); 66.6 (OCH₂); 60.4 (CH-N); 60.0 (OCH₃); 56.0 (OCH₃); 54.2 (OCH₃); 38.9 (CH₂); 35.7 (CH₂). Anal. Calcd for C₂₀H₂₄N₂O₇S: C 55.03, H 5.54, N 6.42, S 7.35; found: C 55.07, H 5.52, N 6.59, S 7.1.

General procedure for the synthesis of sulfamides (N-(4,5,6-trimethoxy-2,3-dihydro-1H-inden-2-yl) sulfamide (21))

Pd-C (50 mg) was added to a stirred solution of carbamate **19** (0.50 g, 1.15 mmol) in MeOH (30 mL). The mixture was hydrogenated for 4 h at room temperature. The catalyst was removed by filtration. The evaporation of the solvent, crystallization of the resulting mixture from MeOH-Et₂O gave sulfamide **21** (0.26 g, 75% yield). White solid. Mp 125-127 °C; IR (CH₂Cl₂, cm⁻¹): 3302, 2948, 1742, 1551, 1474, 1359, 1187; ¹H-NMR (400 MHz, DMSO-d₆): 6.87 (*d*, *J*=7.2 Hz, 1H, NH); 6.65 (*s*, 1H, Ar-H); 6.59 (*br. s*, 2H, NH₂); 4.06-3.97 (*m*, 1H, CH-N); 3.77 (*s*, 3H, OCH₃); 3.74 (*s*, 3H, OCH₃); 3.68 (*s*, 3H, OCH₃); 3.16 (*dd*, *J*=15.7, 7.7 Hz, 1H, CH₂); 3.10 (*dd*, *J*=15.8, 7.7 Hz, 1H, CH₂); 2.83-2.73 (*m*, 2H, CH₂). ¹³C-NMR (100 MHz, DMSO-d₆): 152.6 (C); 149.1 (C); 139.8 (C); 136.5 (C); 124.7 (C); 104.1 (CH); 60.4 (OCH₃); 59.9 (OCH₃); 55.9 (OCH₃); 53.9 (CH-N); 39.7 (CH₂); 36.5 (CH₂). Anal. calc. for C₁₂H₁₈N₂O₅S: C 47.67, H 6.00, N 9.27, S 10.61; found: C 47.73, H 6.08, N 9.32, S 10.58.

N-(5,6,7-trimethoxy-2,3-dihydro-1H-inden-1-yl) Sulfamide (22)

Sulfamide **22** was synthesized with a yield of 72% by the procedure described above for sulfamide **21**. Yellow solid. Mp 136-138 °C; IR (CH₂Cl₂, cm⁻¹): 3436, 2939, 2853, 1634, 1465, 1338, 1151, 1116, 1062; ¹H-NMR (400 MHz, Acetone-d₆): 6.68 (*s*, 1H, Ar-H); 5.95 (*s*, 2H, NH₂); 5.73 (*d*, *J*=6.4 Hz, 1H, NH); 5.02 (*ddd*, *J*=10.0, 6.4, 3.2 Hz, 1H, CH-N); 3.96 (*s*, 1H, OCH₃); 3.84 (*s*, 3H, OCH₃); 3.77 (*s*, 3H, OCH₃); 3.08-3.00 (*m*, 1H, CH₂); 2.73 (*ddd*, *J*=15.7, 8.3, 4.1 Hz, 1H, CH₂); 2.41-2.25 (*m*, 2H, CH₂); ¹³C-NMR (100 MHz, Acetone-d₆): 155.8 (C); 151.0 (C); 141.5 (C); 140.9 (C); 127.6 (C); 104.7 (CH); 61.3 (CH-N); 60.9

(OCH₃); 58.0 (OCH₃); 56.4 (OCH₃); 34.8 (CH₂); 31.3 (CH₂). Anal. Calcd for C₁₂H₁₈N₂O₅S: C 47.67, H 6.00, N 9.27, S 10.61; found: C 47.53, H 5.86, N 9.24, S 10.66.

¹H and ¹³C-NMR spectra of synthesized compounds

INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	2657.220	6.647	21.8	40	750.167	1.877	4.5
2	1899.458	4.751	7.5				
3	1883.592	4.737	10.1				
4	1880.460	4.724	9.8				
5	1876.728	4.685	11.6				
6	1870.863	4.680	7.1				
7	1868.664	4.674	6.5				
8	1856.566	4.644	487.2				
9	1840.436	4.604	30.1				
10	1514.528	3.789	66.7				
11	1512.995	3.784	70.2				
12	1486.388	3.748	6.5				
13	1482.899	3.734	3.9				
14	1468.133	3.723	3.7				
15	1467.970	3.672	75.4				
16	1466.137	3.668	75.2				
17	1456.972	3.645	72.7				
18	1455.139	3.640	75.2				
19	1440.475	3.603	8.1				
20	1436.442	3.593	6.1				
21	1185.892	2.916	4.6				
22	1157.827	2.886	6.4				
23	1149.385	2.875	7.0				
24	1142.429	2.858	5.5				
25	1103.936	2.761	4.3				
26	1086.971	2.744	6.2				
27	1088.906	2.724	6.8				
28	1080.474	2.703	4.9				
29	1073.508	2.685	4.2				
30	976.726	2.443	4.5				
31	969.028	2.424	6.2				
32	965.728	2.416	4.6				
33	962.785	2.408	6.6				
34	954.730	2.388	5.4				
35	770.330	1.927	4.3				
36	767.031	1.919	4.7				
37	763.365	1.910	5.8				
38	756.766	1.893	5.9				
39	753.100	1.884	4.8				

B52.060317. 417ENMR

D2O

INDEX	FREQUENCY	PPM	HEIGHT
1	15802.666	155.219	13.8
2	15012.139	149.344	9.4
3	14223.228	141.486	21.2
4	13977.555	139.052	10.6
5	12303.615	122.399	16.8
6	10495.393	104.411	47.9
7	6155.601	61.238	32.6
8	6145.743	61.139	31.9
9	5649.817	56.206	40.4
10	5468.385	54.202	45.2
11	3055.744	30.399	58.4
12	3036.959	30.232	56.0

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