Synthesis of 6,7-Dimethoxy-1-[(halophenoxy)-methyl]-1,2,3,4-tetrahydroisoquinolines

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Some 6,7-dimethoxy-1-[(halophenoxy)methyl]-1,2,3,4-tetrahydroisoquinolines were synthesized from *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-chloroacetamide *via* three steps in good yield.

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In the previous paper [1], we reported the pharmacological characterization of effects of verapamil and 1-(4'-methoxybenzyl)-6,7-dihydroxy-3,4-dihydroisoquinoline on isolated guinea pig and rat terachesalis. In connection with our research program for the study on the pharmacological characterization of novel isoquinoline derivatives, we required some isoquinolines containing a multihalophenoxymethyl moiety at the C-1 position.

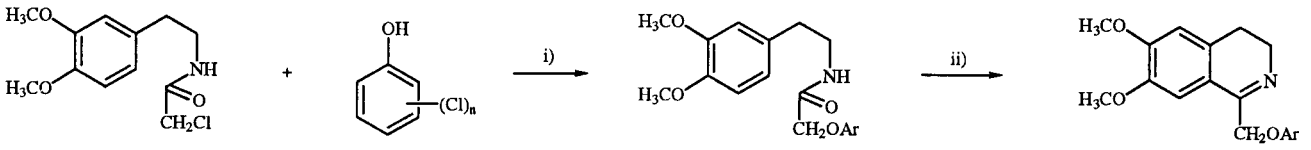
In this paper, we would like to report the synthesis of 6,7-dimethoxy-1-[(halophenoxy)methyl]-1,2,3,4-tetrahydroisoquinolines. *N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-chloroacetamide (**1**) was prepared from 2-(3,4-dimethoxyphenyl)ethylamine according to Cho's method [2].

Reaction of **1** with halophenols **2** in the presence of potassium carbonate gave the corresponding amide **3** in good yield. The structures of **3** were established by ir, ^{1}H nmr and elemental analyses. The infrared spectra of **3** detected the absorption bends of NH, carbonyl and C-O bonds. The ^{1}H nmr spectra also show the proton signals of two OCH_3, two CH_2 as triplets, one OCH_2 as singlet and NH (δ 7.92-8.20 ppm as triplet) involving the aromatic protons.

The Bischler-Napieralski cyclization [3] of **3** with phosphorus oxychloride gave the corresponding 3,4-dihydroisoquinoline derivatives **4** in good yield. The infrared spectra of compounds **4** did not show the absorption bands of amide carbonyl and NH groups. The ^{1}H nmr spectra of compounds **4** revealed the proton signals of two OCH_3 (δ 3.74-3.92 ppm as singlets for C-6, δ 3.80-3.93 ppm as singlet for C-7), two CH_2 of C-3 and C-4 positions (δ 3.52-3.79 ppm as triplet for C-3, δ 2.55-2.71 ppm as triplet for C-4) and one OCH_2 of side chain at C-1 position (δ 4.97-5.25 ppm as singlet) involving aromatic protons in the δ 6.66-7.55 ppm range.

Reduction of **4** with sodium borohydride in methanol afforded the corresponding 1,2,3,4-tetrahydroisoquinolines **5** in good yield, respectively. The infrared spectra of compounds **5** showed the absorption bands of NH in the 3326-3480 cm^{-1} range. The ^{1}H nmr spectra of **5** also showed proton signals of two OCH_3 (δ 3.70-3.86 ppm as a singlet for C-6, δ 3.71-3.88 ppm as a singlet for C-7), one NH of N-2 position (δ 2.00-2.74 ppm as broad singlet) one methine at the C-1 position (δ 4.30-4.45 ppm as multiplet) and two CH_2 (δ 4.06-4.35 ppm as a multiplet

Scheme I



i) K_2CO_3, CH_3CN, reflux. ii) $POCl_3$, Toluene, reflux.
iii) $NaBH_4$, Methanol.

2-5	a	b	c	d	e	f
(Cl)n	2-Cl	3-Cl	4-Cl	2,3-Cl_2	2,4-Cl_2	2,5-Cl_2
2-5	**g**	**h**	**i**	**j**	**k**	
(Cl)n	2,6-Cl_2	3,4-Cl_2	3,5-Cl_2	2,4,6-Cl_3	2,4,5-Cl_3	

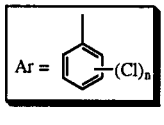


Table 1

Yields, Melting Points and IR Spectral Data of **3**

Compound No.	Yield (%)	mp [a]	IR (Potassium Bromide) (cm^{-1})
3a	90	76-77 (DH)	3438, 3086, 3026, 2956, 2850, 1694, 1600, 1502, 1498, 1366, 1302, 1264, 1240, 1156, 1076, 1036, 852, 818, 760, 714
3b	93	84-85 (D)	3372, 3092, 3036, 2962, 2868, 1674, 1608, 1560, 1528, 1492, 1460, 1378, 1320, 1246, 1148, 1044, 1026, 908, 860, 784, 618
3c	94	100-101 (D)	3350, 3110, 3026, 1962, 2854, 1670, 1606, 1560, 1528, 1504, 1460, 1292, 1252, 1170, 1154, 1056, 1030, 860, 836, 816
3d	88	89-90 (DH)	3440, 3094, 3012, 2948, 2848, 1678, 1590, 1554, 1522, 1470, 1437, 1302, 1268, 1240, 1160, 1308, 1076, 1050, 1028, 900, 804, 778
3e	92	92-93 (D)	3432, 3102, 3016, 2950, 2926, 2848, 1694, 1550, 1532, 1498, 1454, 1306, 1260, 1156, 1106, 1072, 1040, 820, 804, 766
3f	81	110-111 (DH)	3383, 3102, 3026, 2998, 2954, 2866, 1670, 1600, 1562, 1528, 1454, 1378, 1282, 1250, 1174, 1152, 1114, 1080, 1046, 816, 650, 614
3g	94	77-78 (DH)	3320, 3100, 3024, 2956, 2852, 1678, 1576, 1530, 1466, 1442, 1264, 1242, 1148, 1032, 856, 816, 780, 608
3h	92	130-131 (DH)	3312, 3108, 3028, 2960, 2862, 1672, 1606, 1570, 1528, 1482, 1274, 1238, 1150, 1040, 826, 654
3i	91	141-143 (DH)	3284, 3104, 3022, 2948, 2850, 1670, 1592, 1580, 1520, 1448, 1425, 1260, 1238, 1158, 1100, 1028, 830, 806, 604
3j	89	141-143 (A)	3410, 3078, 3028, 2950, 1680, 1550, 1526, 1464, 1444, 1276, 1240, 1148, 1036, 900, 802, 778
3k	73	97-98 (DH)	3332, 3084, 3002, 2942, 2828, 1660, 1588, 1550, 1518, 1470, 1440, 1354, 1300, 1252, 1228, 1134, 1074, 1020

[a] Recrystallization solvent; A = Acetone, D = Diethyl ether, DH = Diethyl ether/ *n*-hexane (1:1, v/v).

Table 2

Yields, Melting Points and IR Spectral Data of **4**

Compound No.	Yield (%)	mp [a]	IR (Potassium Bromide) (cm^{-1})
4a	93	105-106 (DH)	3082, 3026, 2950, 2858, 1620, 1610, 1600, 1584, 1528, 1498, 1472, 1378, 1306, 1280, 1262, 1240, 1220, 1162, 1064, 1044, 866, 756
4b	89	91-92 (DH)	3080, 3036, 2954, 2850, 1608, 1532, 1493, 1464, 1378, 1280, 1220, 1160, 1056, 886, 853, 770
4c	89	113-114 (DH)	3032, 2982, 2866, 1640, 1614, 1580, 1504, 1370, 1340, 1302, 1240, 1220, 1164, 1098, 1060, 870, 835, 640
4d	80	103-104 (D)	3040, 2952, 2854, 1616, 1582, 1550, 1470, 1378, 1306, 1280, 1222, 1164, 1066, 1048, 860, 820, 774
4e	90	116-117 (D)	3012, 2944, 2844, 1612, 1602, 1570, 1518, 1482, 1360, 1294, 1270, 1230, 1208, 1150, 1048, 860, 808
4f	92	106-107 (D)	3120, 3062, 2972, 2948, 2870, 1622, 1592, 1532, 1498, 1474, 1274, 1222, 1076, 1034, 916, 820
4g	89	103-104 (D)	3102, 3034, 2950, 2882, 2850, 1620, 1584, 1530, 1458, 1290, 1264, 1228, 1170, 1074, 982, 784
4h	90	135-136 (DH)	3114, 3032, 2972, 2864, 1638, 1604, 1582, 1528, 1490, 1466, 1380, 1340, 1306, 1286, 1228, 1168, 1140, 1070, 1032, 864, 820, 642
4i	86	127-128 (D)	3102, 3034, 2950, 2882, 2850, 1620, 1584, 1530, 1458, 1290, 1264, 1228, 1170, 1074, 982, 784
4j	87	132-133 (E)	3084, 3008, 2932, 2840, 1618, 1602, 1570, 1542, 1516, 1450, 1420, 1382, 1352, 1260, 1200, 1124, 1080, 1030, 852, 806
4k	85	129-130 (D)	3100, 3012, 2950, 2924, 2846, 1618, 1588, 1522, 1490, 1474, 1468, 1360, 1272, 1256, 1238, 1220, 1020, 1080, 1040, 1018, 998, 878, 860

[a] Recrystallization solvent; D = Diethyl ether, DH = Diethyl ether/ *n*-hexane (1:1, v/v), E = Ethanol.

for OCH_2 at the α-position; δ 2.61-2.89 ppm as a multiplet for CH_2 at the C-4). Whereas, the proton signals for methylene at the C-3 position were detected two multiplets in the δ 2.81-3.12 ppm range for an axial proton and at δ 3.05-3.37 ppm range for the equatorial proton. According to Grethe, *et al.* [4], the axial proton signal at the C-3 position in tetrahydroisoquinoline resonate further up-field than at the equatorial proton in the ^1H nmr spectra. The proton signals of an α-methylene group show as a multiplet because it may be the diastereomeric protons.

Further research including the pharmacological action are under way in our laboratory.

Table 3

Yields, Melting Points and IR Spectral Data of **5**

Compound No.	Yield (%)	mp [a]	IR (Potassium Bromide) (cm^{-1})
5a	90	129-130 (DH)	3400, 3038, 2982, 2950, 2906, 1618, 1596, 1526, 1486, 1458, 1330, 1256, 1224, 1120, 1062, 1040, 1020, 998, 818, 798, 750
5b	91	73-74 (DH)	3480, 3070, 3028, 3006, 2974, 2884, 1594, 1520, 1472, 1320, 1260, 1240, 1222, 1110, 1016, 992, 770
5c	87	94-95 (DH)	3368, 3072, 3008, 2932, 1588, 1570, 1514, 1328, 1258, 1220, 1110, 1004, 852, 820, 805
5d	88	121-122 (D)	3372, 3100, 3034, 2970, 2932, 2864, 1622, 1596, 1526, 1474, 1372, 1278, 1250, 1230, 1130, 1054, 1012, 786
5e	90	105-106 (D)	3380, 3102, 3028, 2980, 2830, 1622, 1532, 1500, 1446, 1340, 1306,1280, 1238, 1120, 1024, 864, 810, 740
5f	89	119-120 (D)	3350, 3100, 3012, 2952, 2922, 2850, 1620, 1592, 1520, 1480, 1460, 1402, 1264, 1226, 1120, 1000, 804, 750
5g	84	93-94 (DH)	3350, 3004, 2918, 2836, 1614, 1520, 1444, 1324, 1258, 1222, 1118, 980, 850, 782, 742
5h	95	105-106 (DH)	3368, 3120, 3038, 2950, 2864, 1626, 1608, 1536, 1492, 1460, 1306, 1280, 1244, 1132, 1036, 1020, 870, 832, 816, 764
5i	95	95-96 (D)	3326, 3106, 3040, 2972, 2930, 2868, 2934, 1600, 1584, 1536, 1460, 1440, 1278, 1340, 1318, 1268, 1240, 1128, 1046, 1018, 956, 850, 812, 758, 722
5j	86	117-118 (DH)	3350, 3112, 3022, 2956, 2924, 2848, 1620, 1594, 1522, 1476, 1360, 1258, 1120, 1080, 1040, 1018, 1000, 882, 864, 788, 764
5k	93	143-144 (D)	3350, 3112, 3016, 2956, 2922, 2850, 1620, 1594, 1524, 1492, 1476, 1453, 1362, 1258, 1220, 1118, 1080, 1040, 1020, 1000, 882, 864, 790, 764

[a] Recrystallization solvent; D = Diethyl ether, DH = Diethyl ether/-*n*-hexane (1:1, v/v).

Table 4

^{1}H NMR Spectral Data of **3**

Compound No.	Solvent [a]	^{1}H NMR (ppm) [b] 2-NH (t)	3"-OMe (s) [c]	4"-OMe (s) [c]	1'-CH_2 (t)	2'-CH_2 (t)	OCH_2- (s)	Ar-H (m)
3a	D	8.05	3.85	3.86	3.61-3.67	2.80-2.85	4.50	6.73-7.38
3b	D	8.10	3.84	3.86	3.35-3.62	2.76-2.81	4.44	6.62-7.29
3c	D	8.10	3.82	3.84	3.54-3.61	2.76-2.81	4.41	6.16-7.24
3d	D	7.94	3.72	3.73	3.35-3.39	2.64-2.69	4.63	6.72-7.28
3e	D	8.00	3.71	3.72	3.30-3.40	2.26-2.70	4.59	6.68-7.58
3f	D	7.92	3.72	3.73	3.37-3.39	2.67-2.71	4.65	6.70-7.49
3g	C	8.20	3.71	3.73	3.33-3.36	2.65-2.71	4.56	6.67-7.19
3h	D	8.16	3.71	3.72	3.31-3.53	2.64-2.69	4.52	6.67-7.55
3i	D	8.20	3.71	3.73	3.33-3.36	2.66-2.71	4.56	6.67-7.19
3j	D	8.10	3.71	3.73	3.37-3.43	2.70-2.81	4.39	6.70-7.90
3k	C	8.10	3.86	3.86	3.52-3.70	2.67-2.82	4.46	6.74-7.47

[a] D = Dimethyl-d_6 sulfoxide, C = Deuteriochloroform; [b] Abbreviations used: s = singlet, t = triplet, m = multiplet and Ar = aromatic. The proton signals of all NH were exchangeable with deuterium oxide; [c] Assignment may be interchanged.

Table 5

^{1}H NMR Spectral Data of **4**

Compound No.	Solvent [a]	^{1}H NMR (ppm) [b] 6-OMe (s) [c]	7-OMe (s) [c]	3-CH_2 (t)	4-CH_2 (t)	OCH_2- (s)	Ar-H (m)
4a	C	3.82	3.90	3.72-3.77	2.62-2.67	5.14	6.66-7.44
4b	C	3.86	3.93	3.73-3.79	2.66-2.71	5.05	6.71-7.28
4c	C	3.86	3.93	3.73-3.79	2.65-2.70	5.05	6.71-7.28
4d	D	3.75	3.80	3.57-3.61	2.56-2.59	5.24	6.95-7.31
4e	D	3.75	3.80	3.58-3.61	2.55-2.59	5.22	6.88-7.55
4f	D	3.75	3.80	3.56-3.62	2.56-2.60	5.25	6.86-7.44
4g	D	3.78	3.82	3.55-3.59	2.59-2.63	4.97	6.91-7.51
4h	D	3.78	3.80	3.52-3.60	2.55-2.60	5.14	6.90-7.53
4i	D	3.74	3.81	3.56-3.60	2.56-2.60	5.17	6.90-7.15
4j	C	3.92	3.93	3.70-3.75	2.66-2.71	4.97	6.71-7.46
4k	C	3.92	3.93	3.70-3.75	2.66-2.71	4.97	6.71-7.46

[a] D = Dimethyl-d_6 sulfoxide, C = Deuteriochloroform; [b] Abbreviations used: s = singlet, t = triplet, m = multiplet and Ar = aromatic; [c] Assignment may be interchanged.

Table 6

^{1}H NMR Spectral Data of **5**

Compound No.	Solvent [a]	^{1}H NMR (ppm) [b] 1-CH (m)	2-NH (bs)	3-CH_2	4-CH_2 (m)	6-OMe (*s*) [c]	7-OMe (*s*) [c]	α-CH_2 (m)	Ar-H
5a	C	4.42-4.45	2.35	3.02-3.07 (m, 1H_a), 3.19-3.25 (m, 1H_e)	2.72-2.84	3.85	3.86	4.14-4.25	6.63 (*s*, 1H), 6.76 (*s*, 1H), 6.89-7.38 (m, 4H)
5b	C	4.35-4.40	2.71	3.01-3.09 (m, 1H_a), 3.19-3.27 (m, 1H_e)	2.75-2.86	3.86	3.88	4.10-4.17	6.64 (*s*, 1H), 6.68 (*s*, 1H), 6.83-7.28 (m, 4H)
5c	C	4.35-4.39	2.60	3.01-3.09 (m, 1H_a), 3.19-3.27 (m, 1H_e)	2.74-2.85	3.86	3.88	4.09-4.16	6.64 (*s*, H), 6.68 (*s*, H), 6.86-6.91 (m, 2H), 7.22-7.28 (m, 2H)
5d	C	4.30-4.38	2.54	2.81-2.88 (m, 1H_a), 3.05-3.15 (m, 1H_e)	2.61-2.64	3.70	3.71	4.10-4.26	6.68 (*s*, 1H), 6.95 (*s*, 1H), 7.20-7.34 (m, 3H)
5e	C	4.41-4.45	2.53	3.00-3.09 (m, 1H_a), 3.18-3.26 (m, 1H_e)	2.76-2.80	3.85	3.86	4.09-4.23	6.63 (*s*, 1H), 6.73 (*s*, 1H), 6.85-7.37 (m, 3H)
5f	C	4.30-4.35	2.54	2.84-2.88 (m, 1H_a), 3.08-3.11 (m, 1H_e)	2.61-2.64	3.86	3.86	4.10-4.23	6.68 (*s*, 1H), 6.95 (*s*, 1H), 7.01-7.48 (m, 3H)
5g	C	4.42-4.45	2.74	3.04-3.12 (m, 1H_a), 3.29-3.37 (m, 1H_e)	2.77-2.89	3.84	3.85	4.17-4.35	6.62 (*s*, 1H), 6 68 (*s*, 1H), 7.00-7.32 (m, 3H)
5h	C	4.33-4.37	2.38	3.00-3.07 (m, 1H_a), 3.16-3.24 (m, 1H_e)	2.71-2.79	3.85	3.86	4.07-4.15	6.63 (*s*, 1H), 6.65 (*s*, 1H), 6.77-7.34 (m, 3H)
5i	C	4.32-4.37	2.38	2.83-3.07 (m, 1H_a), 3.15-3.24 (m, 1H_e)	2.71-2.79	3.85	3.86	4.06-4.13	6.63 (*s*, 1H), 6.64 (*s*, 1H), 6.84-6.96 (m, 3H)
5j	C	4.39-4.43	2.00	3.03-3.11 (m, 1H_a), 3.27-3.35 (m, 1H_e)	2.64-2.80	3.84	3.85	4.07-4.32	6.61 (*s*, 1H), 6.65 (*s*, 1H), 7.32 (*s*, 2H)
5k	C	4.40-4.44	2.36	3.00-3.08 (m, 1H_a), 3.16-3.24 (m, 1H_e)	2.75-2.78	3.85	3.85	4.09-4.21	6.63 (*s*, 1H), 6.72 (*s*, 1H), 7.02 (*s*, 1H), 7.44 (*s*, 1H)

[a] D = Dimethyl-d_6 sulfoxide, C = Deuteriochloroform; [b] Abbreviations used: *s* = singlet, d = doublet, t = triplet, m = multiplet, H_a = axial hydrogen, H_e = equatorial hydrogen and Ar = aromatic. Coupling constant in Hz unit. All NH proton signals were exchangeable with deuterium oxide; [c] Assignment may be interchanged.

Table 7

Elemental Analytical Data of Compound **3**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N
3a	$C_{18}H_{20}NO_4Cl$	61.80	5.76	4.00
		61.84	5.89	4.11
3b	$C_{18}H_{20}NO_4C1$	61.80	5.76	4.00
		61.98	5.88	4.09
3c	$C_{18}H_{20}NO_4Cl$	61.80	5.76	4.00
		62.00	5.87	4.23
3d	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.43	5.01	3.78
3e	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.53	5.13	3.89
3f	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.47	5.09	3.77
3g	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.33	5.21	3.89
3h	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.35	5.02	3.69
3i	$C_{18}H_{19}NO_4Cl_2$	56.26	4.98	3.65
		56.33	4.99	3.87
3j	$C_{18}H_{18}NO_4Cl_3$	51.64	4.33	3.35
		51.76	4.57	3.25
3k	$C_{18}H_{18}NO_4Cl_3$	51.64	4.33	3.35
		51.80	4.56	3.42

Table 8

Elemental Analytical Data of Compound **4**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N
4a	$C_{18}H_{18}NO_3Cl$	65.16	5.47	4.22
		65.24	5.54	4.40
4b	$Cl_8H_{18}NO_3Cl$	65.16	5.47	4.22
		65.33	5.65	4.35
4c	$C_{18}H_{18}NO_3Cl$	65.16	5.47	4.22
		65.17	5.55	4.34
4d	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.11	4.79	4.00
4e	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.32	4.88	3.98
4f	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.14	4.75	3.96
4g	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.22	4.87	3.89
4h	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.31	4.70	4.03
4i	$C_{18}H_{17}NO_3Cl_2$	59.03	4.68	3.82
		59.10	4.90	4.01
4j	$C_{18}H_{16}NO_3Cl_3$	53.96	4.02	3.50
		54.03	4.15	3.67
4k	$C_{18}H_{16}NO_3Cl_3$	53.96	4.02	3.50
		54.12	4.22	3.78

Table 9

Elemental Analytical Data of Compound **5**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N
5a	$C_{18}H_{20}NO_3Cl$	64.77	6.04	4.20
		64.79	6.15	4.33
5b	$C_{18}H_{20}NO_3Cl$	64.77	6.04	4.20
		64.80	6.23	4.35
5c	$C_{18}H_{20}NO_3Cl$	64.77	6.04	4.20
		64.98	6.18	4.42
5d	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		58.88	5.35	3.90
6e	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		58.94	5.42	3.97
5f	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		58.98	5.33	3.90
5g	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		59.00	5.30	3.93
5h	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		58.91	5.29	3.99
5i	$C_{18}H_{19}NO_3Cl_2$	58.71	5.20	3.80
		58.94	5.38	3.97
5j	$C_{18}H_{18}NO_3Cl_3$	53.69	4.51	3.48
		53.89	4.66	3.75
5k	$C_{18}H_{18}NO_3Cl_3$	53.69	4.51	3.48
		53.90	4.78	3.63

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed with a Perkin Elmer 240C. Margnetic resonance spectra were obtained on a Varian Unity Plus 300 spectrometer with chemical shift values reported in δ unit (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Open-bed chromatography was carried out silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(halophenoxy)acetamides **3**.

A mixture of **1** (39 mmoles), phenol derivatives **2** (40 mmoles), potassium carbonate (41 mmoles) and acetonitrile (80 ml) was refluxed for 6 hours. After cooling to room temperature, the mixture was filtered and washed with acetonitrile (10 ml x 2). The combined filtrate was evaporated under reduced pressure. The residue was triturated in water/diethyl ether (1:1, v/v; 100 ml) with stirring. The resulting crystals were filtered and washed with diethyl ether (10 ml x 2). The crude product was recrystallized to give compounds **3**.

6,7-Dimethoxy-1-[(halophenoxy)methyl]-3,4-dihydroisoquinolines **4**.

A solution of **3** (20 mmoles), phosphorus oxychloride (22 mmoles) and dry toluene (80 ml) was refluxed for 4 hours. The mixture was evaporated under reduced pressure. Ammonia water (28%) was added to the residue. After stirring for 10 minutes, the mix-

ture was filtered and washed with *n*-hexane (10 ml x 2). The resulting residue was applied to the top of an open-bed silica gel column (3 x 10 cm). The column was eluted with methylene chloride/ethyl acetate (10:3, v/v). Fractions containing the product were combined and evaporated under reduced pressure. The crude product was recrystallized to afford compounds **4**.

6,7-Dimethoxy-1-[(halophenoxy)methyl]-1,2,3,4-tetrahydroisoquinolines **5**.

A mixture of **4** (11 mmoles), sodium borohydride (12 mmoles) and methanol (50 ml) was stirred for 8 hours at room temperature. After evaporating the solvent, water (50 ml) and methylene chloride (50 ml) was added to the residue with stirring. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was recrystallized to give **5**.

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