

Supporting Information

Revisiting Ullmann-ether Reaction: A Concise and Amenable Synthesis of Novel Dibenzoepino[4,5-*d*]pyrazoles by Intramolecular Etheration of 4,5-(*o,o'*-Halohydroxy)arylpyrazoles

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Synthetic Procedures

Experimental procedures for the synthesis of precursors and key intermediates and spectrometric data.

Pg. S2-S3: protected salicylaldehyde derivatives (**7**)

Pg. S4-S7: α -aminonitriles (**8**), arylmethyl alcohols (**9**) and arylmethyl bromides (**10**)

Pg. S7-S9: synthesis of deoxybenzoins (**4a-f**) *via* α -aminonitriles

Pg. S9-S12: synthesis of deoxybenzoins (**4g-k**) *via* Friedel-Crafts acylation and ester derivatives (**13**)

Pg. S12-S15: enamino ketones (**3**) and isoflavones (**14**)

Pg. S15-S17: *O*-protected 4,5-diarylpyrazoles (**15-16**)

Pg. S17-S20: *o,o'*-Halohydroxy-4,5-diarylpyrazoles (**2** and **17**)

Pg. S20-S21: attempts at synthesis of arylboronic acids

Pharmacological Procedures

Pg. S22: Table S1. Radiolabeled binding assay screening results

Pg. S23-S34:

Experimental pharmacological procedures for measuring binding affinities at 5-HT_{1A}, 5-HT_{2A}, 5-HT₃, serotonin transporter, all muscarinic receptors, D₁, D₂, dopamine transporter, α_1 , α_2 , noradrenaline transporter and H₁ receptors (in this order).

Pg. S34-S35: references

Experimental Section

Instrumentation, General Procedures and Materials. Preparative HPLC was performed on a WATER 600A chromatograph coupled to a refraction index detector R401 using a HIBAR LiChrosorb column (purchased from Merck). 2-Iodo-benzaldehyde **7g**, 4,5-dimethoxy-2-iodobenzaldehyde **7h**, 2-(*N,N*-dimethylamino)-2-(2-iodophenyl)acetonitrile **8g**, 2-(*N,N*-dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)acetonitrile **8h** and 2-iodobenzyl bromide were prepared according to the procedure previously reported by us.¹ Reactions carried out as referred in the text “in screw-capped tubes”, were performed in ace pressure tubes purchased from Aldrich Co. Trimethylborate and triisopropylborate were triply distilled from sodium just prior to use. *o*-Tolyl benzenesulfonate was prepared by sulfonylation of commercial *o*-cresol as described below. This product is now commercially available in small quantities from Ambinter, ChemDiv, Inc., Contact Service Co. and Summit Pharmaceuticals Int. Corp.

Synthesis of protected salicylaldehyde derivatives (7).

2,4-Dichloro-6-formylphenyl benzenesulfonate (7b). Typical procedure. Benzenesulfonyl chloride (99%, 8.5 mL, 66.2 mmol) was added to a stirred solution of 3,5-dichlorosalicylaldehyde (9.8 g, 51.3 mmol) in anhydrous pyridine (16 mL) under atmosphere of Ar at ambient temperature. The reaction mixture was heated at 80°C for 2 h, and after cooling to ambient temperature, was quenched with 1.4 M HCl (250 mL) and extracted with DCM (3 x 50 mL). The organic layer was successively washed with 1.5 M NaOH (3 x 10 mL), 1.4 M HCl (3 x 10 mL) and H₂O (3 x 10 mL), dried (anh. Na₂SO₄), filtered off and the solvent was evaporated under reduced pressure. The crude product was crystallized from Et₂O to afford the sulfonate **7b** (17.0 g, 74%) as a white powder: mp 98-100°C (Et₂O); *Rf* 0.45 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 7.58-7.64 (3H, m), 7.76 (1H, dddd, *J* = 7.6, 7.6, 1.2, 1.2 Hz), 7.81 (1H, d, *J* = 2.3 Hz), 7.92-7.95 (2H, dd, *J* = 7.5, 2.3 Hz); ¹³C NMR (CDCl₃) δ 127.0, 128.7, 129.6, 130.4, 132.5, 133.8, 134.4, 145.6, 185.4; FTIR (neat film, cm⁻¹): 1700, 1388, 1192; EIMS (*m/z*, %) 332 (M+1, 1), 330 (M-1, 1), 141 (39), 77 (100). Anal. Calcd for C₁₃H₈Cl₂O₄S: C, 47.15; H, 2.43. Found: C, 47.31; H, 2.32.

When the same procedure applied to commercial salicylaldehyde while substituting benzenesulfonyl chloride for tosyl chloride as reagent, **2-formylphenyl tosylate (7a)** was obtained: 90%, as a white powder; mp 61-62°C (Et₂O); *Rf* 0.35 (60% DCM/hexanes); ¹H NMR (CDCl₃) δ 2.45 (3H, s), 7.20 (1H, dd, *J* = 8.2, 1.2 Hz), 7.33 (2H, d, *J* = 7.9 Hz), 7.41 (1H, d, *J* = 7.5, 1.2 Hz), 7.58 (1H, ddd, *J* = 8.3, 7.5, 1.5 Hz), 7.70 (2H, d, *J* = 7.9 Hz), 7.86 (1H, dd, *J* = 7.6, 1.5 Hz), 9.98 (1H, s); ¹³C NMR (CDCl₃) δ 21.4, 123.4, 127.3, 128.3, 129.0, 129.9, 130.8, 135.1, 146.1, 150.8, 187.0; FTIR (neat film, cm⁻¹): 1698, 1378, 1175; EIMS (*m/z*, %) 276 (M⁺, 2), 155 (43), 139 (12), 121 (44), 91 (100). Anal. Calcd for C₁₄H₁₂O₄S: C, 60.86; H, 4.38. Found: C, 60.99; H, 4.29.

By using the same procedure and starting from the appropriate commercial material, the following products were obtained:

4-Chloro-2-formylphenyl benzenesulfonate (7c): 79%, as colorless needles; mp 87-88°C (Et₂O); *Rf* 0.56 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 7.11 (1H, d, *J* = 8.7 Hz), 7.47 (1H, d, *J* = 2.8 Hz), 7.51-7.60 (2H, m), 7.72 (1H, dddd, *J* = 7.2, 7.2, 1.2, 1.2 Hz), 7.75-7.85 (3H, m), 9.90 (1H, s); ¹³C NMR (CDCl₃) δ 125.2, 128.3, 129.5, 130.1, 133.6, 134.9, 135.2, 149.0, 185.7; FTIR (neat film, cm⁻¹): 1694, 1384, 1167; EIMS (*m/z*, %) 298 (M+2, 2), 296 (M⁺, 7), 155 (14), 141 (52), 125 (11), 77 (100). Anal. Calcd for C₁₃H₉ClO₄S: C, 52.62; H, 3.06. Found: C, 52.81; H, 2.91.

2-Formyl-5-nitrophenyl benzenesulfonate (7d): 61%, as a white powder; mp 127-128°C (Et₂O); *Rf* 0.43 (40% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 7.43 (1H, d, *J* = 9.2 Hz), 7.62 (1H, dd, *J* = 7.5, 7.5 Hz), 7.87 (2H, dd, *J* = 7.5, 7.5 Hz), 7.88 (2H, d, *J* = 7.6 Hz), 8.43 (1H, dd, *J* = 9.1, 2.7 Hz), 8.71 (1H, d, *J* = 2.7 Hz), 9.99 (1H, s); ¹³C NMR (CDCl₃) δ 124.3, 125.0, 128.4, 129.6, 129.9, 133.6, 135.6, 146.3, 154.4, 185.0; FTIR (neat film, cm⁻¹): 1700, 1534, 1386, 1351, 1188; EIMS (*m/z*, %) 166 (22), 137 (24), 120 (20), 77 (100). Anal. Calcd for C₁₃H₉NO₆S: C, 50.82; H, 2.95, N; 4.56. Found: C, 50.69; H, 2.69, N, 4.77.

1-Formyl-naphthalen-2-yl benzenesulfonate (7e): 87%, as colorless prismatic crystals; mp 88-90°C (Et₂O); *Rf* 0.42 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 7.29 (1H, d, *J* = 9.1 Hz), 7.52-7.77 (6H, m), 7.84 (2H, d, *J* = 9.1 Hz), 8.08 (1H, dd, *J* = 8.3, 2.0 Hz), 9.12 (1H, d, *J* = 8.3 Hz), 10.4 (1H, s); ¹³C NMR (CDCl₃) δ 121.1, 122.8, 125.6, 127.1, 128.3, 129.5, 129.8, 131.9, 133.9, 135.0, 136.5, 152.8, 189.6; FTIR (neat film, cm⁻¹): 1688, 1381, 1184; EIMS (*m/z*, %) 312 (M⁺, 28), 170 (89), 154 (20), 143 (22), 115 (96), 77 (100). Anal. Calcd for C₁₇H₁₂O₄S: C, 65.37; H, 3.87. Found: C, 65.49; H, 3.69

***o*-Tolyl benzenesulfonate:** 91%, as white flakes; mp 34-36°C (Et₂O); *Rf* 0.45 (10% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.06 (3H, s), 6.99 (1H, d, *J* = 5.6 Hz), 7.12-7.15 (3H, m), 7.53 (2H, dd, *J* = 7.5, 7.5 Hz), 7.68 (1H, dd, *J* = 7.5, 7.5 Hz), 7.87 (2H, d, *J* = 7.2 Hz); ¹³C NMR (CDCl₃) δ 16.1, 122.2, 126.8, 127.0, 128.2, 129.6, 131.4, 134.1, 135.2, 135.9, 148.1; FTIR (neat film, cm⁻¹): 1372, 1194; EIMS (*m/z*, %) 248 (M⁺, 44), 141 (59), 107 (50), 77 (100). Anal. Calcd for C₁₃H₁₂O₃S: C, 62.89; H, 4.87. Found: C, 63.04; H, 4.70.

5-(*N,N*-Diethylamino)-2-formylphenyl benzenesulfonate (7f). Benzenesulfonyl chloride (99%, 8.4 mL, 65.4 mmol) was added to a stirred suspension of 4-(*N,N*-diethylamino)salicylaldehyde (9.86 g, 51.0 mmol) and ground K₂CO₃ (96%, 8.44 g, 59.0 mmol) in Me₂CO (90 mL) at ambient temperature. The resultant suspension was left under stirring for 2 h, filtered and the solvent was removed under reduced pressure. The orange crude material was flash chromatographed on silica gel eluting with the gradient 75→80% EtOAc/hexanes to afford the sulfonate **7f** (8.8 g, 52%) as an off-red powder: mp 105-106°C (MeOH); *Rf* 0.24 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.15 (6H, t, *J* = 7.1 Hz), 3.36 (4H, q, *J* = 7.1 Hz), 6.31 (1H, d, *J* = 2.4 Hz), 6.52 (1H, dd, *J* = 9.2, 2.4 Hz), 7.50-7.57 (2H, m), 7.65-7.71 (2H, m), 7.87 (2H, dd, *J* = 8.4, 1.2 Hz), 9.60 (1H, s); ¹³C NMR (CDCl₃) δ 12.0, 44.6, 103.8, 109.5, 116.4, 128.5, 129.2, 130.0, 134.5, 152.7, 153.3, 184.9; FTIR (neat film, cm⁻¹): 1669, 1374, 1194; EIMS (*m/z*, %) 333 (M⁺, 38), 318 (100), 149 (57), 120 (37), 77 (31). An analytical sample of **7f** was obtained by recrystallization from MeOH as a white solid. Anal. Calcd for C₁₇H₁₉NO₄S: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.41; H, 5.68; N, 4.32.

Synthesis of Aminonitriles (8).

2-(Cyano-*N,N*-dimethylamino)methylphenyl tosylate (8a). **Typical procedure.** To a stirred solution of NaCN (98%, 1.72 g, 34.4 mmol) (**CAUTION! Extremely toxic**) and Me₂NH.HCl (99%, 4.78 g, 58.0 mmol) in H₂O (34 mL), aldehyde **7a** (5.80 g, 21.0 mmol) dissolved in hot CH₃CN (85 mL) was slowly added dropwise. Stirring was continued for 10 h at ambient temperature until reaction went to completion as determined by inspection of ¹H NMR of worked-up aliquots. The solvent was evaporated *in vacuo* and the residue was taken up in H₂O (150 mL) and extracted with Et₂O (4 x 30 mL). The organic layer was successively washed with saturated aqueous NaHSO₃ (3 x 15 mL), H₂O (1 x 50 mL) and brine (1 x 50 mL), dried (anh. Na₂SO₄), filtered off and the solvent was evaporated under reduced pressure. The crude material was crystallized from Et₂O to afford α-aminonitrile **8a** (6.10 g, 88%) as a pale yellow powder: mp 77-79°C (Et₂O); *Rf* 0.35 (20% DCM/hexanes); ¹H NMR (CDCl₃) δ 2.20 (6H, s), 2.47 (3H, s), 4.89 (1H, s), 7.18 (1H, dd, *J* = 7.9, 1.8 Hz), 7.30-7.41 (4H, m), 7.55 (1H, dd, *J* = 7.4, 2.4 Hz), 7.77 (2H, d, *J* = 2.9 Hz); ¹³C NMR (CDCl₃) δ 21.4, 41.3, 57.3, 114.2, 122.5, 126.5, 126.7, 128.1, 129.9, 130.4, 131.2, 145.8, 147.6; FTIR (neat film, cm⁻¹): 1376, 1180; EIMS (*m/z*, %) 305 (6), 150 (49), 134 (12), 107 (22), 77 (21), 57 (100). Anal. Calcd for C₁₇H₁₈N₂O₃S: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.89; H, 5.64; N, 8.31.

Pure α-aminonitriles should be kept under atmosphere of Ar at low temperature, since they may undergo slow decomposition. By using the same procedure and starting from the appropriate intermediate compound of preceding step, the following products were obtained:

1-(Cyano-*N,N*-dimethylamino)methylnaphthalen-2-yl benzenesulfonate (8e): 56%, as a pale yellow oil; *Rf* 0.39 (70% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.32 (6H, s), 4.79 (1H, s), 7.29 (1H, d, *J* = 8.2 Hz), 7.51-7.69 (5H, m), 7.71 (1H, dd, *J* = 7.5, 7.5 Hz), 7.83 (1H, d, *J* = 8.4 Hz), 7.92 (2H, dd, *J* = 7.5, 1.2 Hz), 8.67 (1H, d, *J* = 7.5 Hz); ¹³C NMR (CDCl₃) δ 43.3, 54.5, 117.2, 120.0, 121.4, 125.5, 126.7, 127.5, 128.2, 128.5, 129.7, 131.3, 131.8, 132.3, 134.9, 135.2, 145.9; FTIR (neat film, cm⁻¹): 2224, 1380, 1183; EIMS (*m/z*, %) 341 (12), 200 (53), 198 (10), 184 (12), 170 (21), 157 (21), 141 (24), 129 (20), 115 (29), 77 (100). An analytical sample of **8e** was obtained by silica gel flash column rechromatography. Anal. Calcd for C₂₀H₁₈N₂O₃S: C, 65.56; H, 4.95; N, 7.64. Found: C, 65.89; H, 5.04; N, 7.71.

2-(Cyano-*N,N*-dimethylamino)methyl-5-*N,N*-diethylaminophenyl benzenesulfonate (8f): 84%, as a red oil; *Rf* 0.35 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 1.12 (6H, d, *J* = 7.1 Hz), 2.18 (6H, s), 3.24 (4H, q, *J* = 7.1 Hz), 4.72 (1H, s), 6.32 (1H, d, *J* = 2.8 Hz), 6.49 (1H, dd, *J* = 8.8, 2.7 Hz), 7.28 (1H, d, *J* = 8.7 Hz), 7.55 (2H, dd, *J* = 7.9, 7.9 Hz), 7.69 (1H, dd, *J* = 7.9, 7.9 Hz), 7.92 (2H, dd, *J* = 7.9, 1.2 Hz); ¹³C NMR (CDCl₃) δ 12.3, 41.3, 44.2, 57.2, 105.0, 109.0, 111.8, 115.0, 128.2, 129.2, 130.5, 134.3, 135.9, 148.9, 149.1; FTIR (neat film, cm⁻¹): 2224, 1376, 1196; EIMS (*m/z*, %) 387 (M⁺, 10), 343 (100), 202 (19), 159 (11), 77 (11). An analytical sample of **8f** was obtained by silica gel flash rechromatography. Anal. Calcd for C₂₀H₂₅N₃O₃S: C, 61.99; H, 6.50; N, 10.84. Found: C, 62.24; H, 6.57; N, 10.70.

Preparation of arylmethyl alcohols (9) and arylmethyl bromides/acetates (10).

4-Chloro-2-hydroxymethylphenyl benzenesulfonate (9b). Typical procedure. A solution of aldehyde **7c** (15.72 g, 53.1 mmol) in anhydrous THF (30 mL) was added dropwise to a stirred suspension of LAH (98%, 4.10 g, 0.106 mol) in the same solvent (100 mL) cooled at -19°C under atmosphere of Ar. After total addition, the green-colored solution was stirred for 3 h. at this temperature, followed by the careful addition of 1.4 M HCl (400 mL) over 20 min, allowing the temperature to rise to ambient temperature. Stirring was continued for 30 min until complete redissolution of the gelatinous reaction mixture, and then was partitioned between DCM (200 mL) and water (600 mL). The aqueous layer was backwashed with DCM (4 x 100 mL), and the combined organic extracts were successively washed with H₂O (3 x 50 mL) and brine (1 x 50 mL), dried (anh. Na₂SO₄), filtered off and the solvent was evaporated *in vacuo*. The yellowish residue was crystallized from hot Et₂O affording the alcohol **9b** (15.35 g, 97%) as a snowy white solid: mp 139-140°C (Et₂O); *Rf* 0.46 (40% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.86 (1H, bs), 4.54 (2H, s), 6.78 (1H, d, *J* = 8.8 Hz), 7.16 (1H, dd, *J* = 8.7, 2.4 Hz), 7.50 (1H, d, *J* = 2.6 Hz), 7.59 (2H, dd, *J* = 7.3, 7.3 Hz), 7.72 (1H, dddd, *J* = 7.3, 7.3, 1.2, 1.2 Hz), 7.87 (2H, dd, *J* = 7.3, 1.2 Hz); ¹³C NMR (CDCl₃) δ 58.9, 123.5, 128.3, 128.5, 129.6, 133.1, 134.8, 136.3, 144.8; FTIR (neat film, cm⁻¹): 3382, 1376, 1191; EIMS (*m/z*, %) 298 (M⁺, 3), 281 (2), 157 (26), 140 (85), 77 (100). Anal. Calcd for C₁₃H₁₁ClO₄S: C, 52.27; H, 3.71. Found: C, 51.99; H, 3.84.

By using the same procedure and starting from the appropriate intermediate compound of preceding steps, the following products were obtained:

2,4-Dichloro-6-hydroxymethylphenyl benzenesulfonate (9a): 99%, as a light red solid; mp 160-161°C (Et₂O); *Rf* 0.36 (DCM); ¹H NMR (CDCl₃) δ 2.59 (1H, t, *J* = 6.7 Hz), 4.74 (2H, d, *J* = 6.7, Hz), 7.30 (1H, d, *J* = 2.4 Hz), 7.52 (1H, d, *J* = 2.4, Hz), 7.60 (2H, dd, *J* = 8.4, 7.5 Hz), 7.75 (1H, dddd, *J* = 7.5, 7.5, 2.0, 2.0 Hz), 7.99 (2H, dd, *J* = 8.4, 2.0 Hz); ¹³C NMR (CDCl₃) δ 59.5, 128.2, 128.5, 128.7, 129.2, 133.2, 134.8, 135.6, 139.2, 141.4; FTIR (neat film, cm⁻¹): 3373, 1376, 1191; EIMS (*m/z*, %) 334 (M+2, 2), 332 (M⁺, 2), 176 (47), 174 (76), 141 (17), 128 (14), 77 (100). Anal. Calcd for C₁₃H₁₀Cl₂O₄S: C, 46.86; H, 3.02. Found: C, 47.11; H, 2.89.

1-Hydroxymethylnaphthalen-2-yl benzenesulfonate (9c): 85%, as prismatic crystals; mp 93-95°C (CHCl₃); *Rf* 0.20 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.89 (1H, t, *J* = 4.2 Hz), 5.05 (2H, d, *J* = 4.2 Hz), 6.79 (1H, d, *J* = 8.9 Hz), 7.46-7.59 (6H, m), 7.76 (1H, dd, *J* = 8.7, 1.4 Hz), 7.87 (2H, dd, *J* = 8.1, 1.5 Hz), 8.28 (1H, d, *J* = 8.5 Hz); ¹³C NMR (CDCl₃) δ 55.1, 120.1, 124.7, 125.9, 126.9, 128.0, 128.9, 129.1, 129.6, 131.9, 132.3, 134.2, 134.4, 144.1; FTIR (neat film, cm⁻¹): 3563, 1371, 1168; EIMS (*m/z*, %) 314 (M⁺, 23), 173 (64), 156 (71), 145 (72), 127 (100), 77 (70). Anal. Calcd for C₁₇H₁₄O₄S: C, 64.95; H, 4.49. Found: C, 65.11; H, 4.58.

2-Bromomethyl-4,6-dichlorophenyl benzenesulfonate (10a). Typical procedure. A solution of alcohol **9a** (17.82 g, 53.5 mmol) and CBr₄ (99%, 26.9 g, 80.25 mmol) in anhydrous DCM (175 mL) under atmosphere of Ar was stirred for 10 min at ambient temperature. The mixture was cooled 0°C, and PPh₃ (99%, 21.26 g, 80.25 mmol) was added portionwise over a period of 40 min. After an additional 1.5 h, the reaction mixture was allowed to warm up to ambient temperature and the solvent was evaporated *in vacuo*.

The yellowish slurry was flash chromatographed on silica gel using 10% EtOAc/hexanes as eluant to afford the bromide **10a** (14.41 g, 68%) as colorless needles: mp 117-118°C (50% EtOAc/hexanes); *R_f* 0.36 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 4.55 (2H, s), 7.34 (1H, d, *J* = 2.5 Hz), 7.44 (1H, d, *J* = 2.5 Hz), 7.61 (2H, dd, *J* = 8.7, 7.5 Hz), 7.75 (1H, ddd, *J* = 7.5, 7.5, 1.4 Hz), 8.05 (2H, dd, *J* = 8.7, 1.4 Hz); ¹³C NMR (CDCl₃) δ 26.6, 128.3, 129.3, 129.6, 130.2, 130.4, 132.9, 134.8, 136.4, 142.2; FTIR (neat film, cm⁻¹): 1381, 1195; EIMS (*m/z*, %) 398 (M+2, 1), 396 (M⁺, 3), 394 (M-2, 2), 174 (73), 217 (10), 141 (17), 77 (100). Anal. Calcd for C₁₃H₉BrCl₂O₃S: C, 39.42; H, 2.29. Found: C, 39.67; H, 2.44.

The same procedure applied to alcohol **9b** provided **2-bromomethyl-4-chlorophenyl benzenesulfonate (10b)**: 72%, as a white powder; mp 98-99°C (50% EtOAc/hexanes); *R_f* 0.42 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 4.27 (2H, s), 7.03 (1H, d, *J* = 8.8 Hz), 7.22 (1H, dd, *J* = 8.8, 2.5 Hz), 7.42 (1H, d, *J* = 2.5 Hz), 7.58 (2H, ddd, *J* = 8.2, 8.2, 2.3 Hz), 7.71 (1H, ddd, *J* = 8.2, 8.2, 2.3 Hz), 7.92 (2H, dd, *J* = 8.2, 2.3 Hz); ¹³C NMR (CDCl₃) δ 26.9, 123.6, 128.1, 129.2, 130.2, 132.3, 132.4, 134.7, 145.3; FTIR (neat film, cm⁻¹): 1380, 1163; EIMS (*m/z*, %) 362 (M+1, 12), 360 (M-1, 12), 281 (17), 217 (10), 140 (59), 77 (100). Anal. Calcd for C₁₃H₁₀BrClO₃S: C, 43.18; H, 2.79. Found: C, 43.29; H, 2.58.

The same procedure applied to alcohol **9c** eluting with the gradient 5% EtOAc/hexanes→DCM provided **1-bromomethylnaphthalen-2-yl benzenesulfonate (10c)**: 62%, as a white powder; mp 141-142°C (Et₂O); *R_f* 0.34 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 4.82 (2H, s), 7.27 (1H, d, *J* = 8.4 Hz), 7.49-7.71 (4H, m), 7.76-7.89 (3H, m), 7.92 (1H, d, *J* = 8.1 Hz), 8.04 (2H, dd, *J* = 8.4 Hz); ¹³C NMR (CDCl₃) δ 23.1, 120.6, 124.0, 125.2, 126.5, 127.5, 128.3, 128.7, 129.4, 130.7, 131.5, 132.1, 134.6, 135.5, 145.0; FTIR (neat film, cm⁻¹): 1376, 1188; EIMS (*m/z*, %) 378 (M+1, 5), 376 (M-1, 5), 297 (59), 233 (38), 205 (10), 156 (33), 128 (100). Anal. Calcd for C₁₇H₁₃BrO₃S: C, 54.12; H, 3.47. Found: C, 54.26; H, 3.49.

2-Bromomethylphenyl benzenesulfonate (10d). A stirred suspension of *o*-tolyl benzenesulfonate (5.21 g, 21.0 mmol), NBS (6.35 g, 35.7 mmol) and AIBN (0.29 g, 1.8 mmol) in anhydrous CCl₄ (75 mL) under atmosphere of Ar, was heated to reflux for 6 h. After cooling, the suspension was filtered and the filtrate evaporated under reduced pressure. The resultant brown oil was crystallized from a mixture of Et₂O/hexanes affording the bromide **10d** (5.7 g, 83%) as a white powder; mp 65-66°C (Et₂O/hexanes), *R_f* 0.50 (30% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 4.36 (2H, s), 7.09 (1H, d, *J* = 8.7 Hz), 7.24-7.28 (3H, m), 7.67 (2H, dd, *J* = 7.5, 7.1 Hz), 7.68 (1H, dd, *J* = 7.2, 7.2 Hz), 7.93 (2H, d, *J* = 7.5 Hz); ¹³C NMR (CDCl₃) δ 26.7, 121.8, 122.5, 127.5, 128.3, 129.3, 129.6, 129.8, 131.7, 134.5, 147.1; FTIR (neat film, cm⁻¹): 1376, 1194; EIMS (*m/z*, %) 328 (M+1, 1), 326 (M-1, 1), 247 (59), 183 (17), 141 (19), 77 (100). Anal. Calcd for C₁₃H₁₁BrO₃S: C, 47.72; H, 3.39. Found: C, 47.72; H, 3.31.

2-(Benzenesulfonyloxy)-5-chlorobenzyl acetate (10e). HBr (33% solution in HOAc, 28 mL) was added dropwise to a stirred suspension of alcohol **10b** (3.54 g, 12.0 mmol) in glacial HOAc (3 mL) precooled at -19°C. The reaction mixture was further stirred for 45 min, diluted with H₂O (160 mL) at that temperature, and extracted with DCM (5 x 30 mL). The organic layer was washed successively with saturated aqueous NaHCO₃ (3 x 30 mL) and brine (1 x 50 mL), dried (anh. Na₂SO₄), filtered off and the solvent was evaporated *in vacuo*. The resultant orange crude oil was flash chromatographed on silica gel using 15%

EtOAc/hexanes as eluant to afford acetate **10e** (1.68 g, 41%) as an off-yellow oil; *R_f* 0.30 (40% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.06 (3H, s), 4.88 (2H, s), 7.02 (1H, d, *J* = 8.8 Hz), 7.20 (1H, dd, *J* = 8.5, 2.5 Hz), 7.34 (1H, d, *J* = 2.5 Hz), 7.54 (2H, ddd, *J* = 7.3, 7.3, 1.5 Hz), 7.70 (1H, ddd, *J* = 7.8, 7.8, 2.4 Hz), 7.87 (2H, dd, *J* = 7.3, 1.5 Hz); ¹³C NMR (CDCl₃) δ 20.2, 59.5, 100.0, 123.4, 127.8, 128.8, 129.1, 131.2, 132.3, 134.4, 134.6, 145.1, 169.8; FTIR (neat film, cm⁻¹): 1744, 1379, 1193; EIMS (*m/z*, %) 340 (M⁺, 2), 298 (17), 140 (70), 77 (100). An analytical sample of **10b** was obtained by rechromatography of the title compound through a shorth path of neutral alumina using 30% EtOAc/hexanes as eluant. Anal. Calcd for C₁₅H₁₃ClO₅S: C, 52.87; H, 3.84. Found: C, 53.25; H, 3.59.

Synthesis of Deoxybenzoins (**4**) via α-aminonitriles.

Method A. 2-[2-(2-iodophenyl)acetyl]phenyl tosylate (4a). A solution of 2-iodobenzyl chloride (98%, 5.46 g, 21.2 mmol) in anhydrous degassed DMF (18 mL) was quickly added to a stirred suspension of NaH (95% in oil dispersion, 0.84 g, 33.3 mmol) in the same solvent (17 mL) precooled at -19°C under atmosphere of Ar. A solution of α-aminonitrile **8a** (4.98 g, 15.1 mmol) in anhydrous degassed DMF (18 mL) was immediately added dropwise to this mixture. After total addition, the deep orange-colored solution was stirred for 3.5 h at this temperature, followed by careful addition of MeOH until hydrogen bubbling ceased. The solvent was distilled off under vacuum (1.5 mmHg, 90°C). The resultant brown crude oil was taken up in a mixture of MeOH (20 mL) and 12 M HCl (50 mL) and heated at 90°C for 5 h. After cooling, the reaction mixture was partially concentrated (~2/3 v.) under reduced pressure and extracted with DCM (3 x 15 mL). The organic layer was successively washed with saturated aqueous NaHCO₃ (3 x 15 mL), dried (anh. Na₂SO₄), filtered off and the solvent was evaporated *in vacuo*. The crude mixture was flash chromatographed on silica gel eluting with the gradient 50→70% EtOAc/hexanes to afford the deoxybenzoin **4a** (4.98 g, 67%) as a white powder; mp 122-123°C (80% EtOAc/hexanes); *R_f* 0.69 (80% DCM/hexanes); ¹H NMR (CDCl₃) δ 2.46 (3H, s), 4.35 (2H, s), 6.95 (1H, ddd, *J* = 7.9, 7.9, 1.9 Hz), 7.11 (1H, dd, *J* = 7.9, 1.2 Hz), 7.23 (1H, dd, *J* = 7.9, 1.2 Hz), 7.30-7.47 (5H, m), 7.71 (1H, dd, *J* = 7.5, 2.0 Hz), 7.73 (2H, d, *J* = 8.3 Hz), 7.81 (1H, dd, *J* = 7.9, 1.2 Hz); ¹³C NMR (CDCl₃) δ 21.6, 54.0, 101.3, 122.9, 127.2, 128.3, 128.6, 130.1, 131.2, 131.6, 132.6, 133.8, 138.1, 139.0, 139.5, 145.9, 146.4, 196.5; FTIR (neat film, cm⁻¹): 1698, 1376, 1196; EIMS (*m/z*, %) 365 (6), 275 (100), 217 (10), 181 (7), 155 (48). Anal. Calcd for C₂₁H₁₇IO₄S: C, 51.23; H, 3.48. Found: C, 51.58; H, 3.69.

Applying the same procedure but increasing the temperature of acidic hydrolysis up to 110°C, desulfonylation of the deoxybenzoin (**4a**) was promoted, affording after flash chromatography on silica gel using 60% DCM/hexanes as eluant **1-(2-hydroxyphenyl)-2-(2-iodophenyl)ethanone (4j)**: 58%, as white needles; mp 178-179°C (Et₂O); *R_f* 0.48 (15% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 4.51 (2H, s), 6.93-7.05 (3H, m), 7.23 (1H, dd, *J* = 8.0, 1.8 Hz), 7.36 (1H, ddd, *J* = 7.3, 7.3, 1.2 Hz), 7.52 (1H, ddd, *J* = 7.3, 7.3, 1.3 Hz), 7.88 (1H, dd, *J* = 7.9, 1.3 Hz), 7.91 (1H, dd, *J* = 8.0, 1.9 Hz), 12.07 (1H, s, OH, exc. D₂O); ¹³C NMR (CDCl₃) δ 50.0, 101.4, 118.7, 119.1, 128.5, 129.0, 129.9, 130.9, 136.6, 137.8, 139.5, 162.5, 202.5; FTIR

(neat film, cm^{-1}): 3307, 1643; EIMS (m/z , %) 338 (M^+ , 2), 217 (3), 211 (25), 121 (100). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{IO}_2$: C, 49.73; H, 3.28. Found: C, 50.01; H, 3.31.

Method B. 4-Chloro-2-[2-(2-iodophenyl)-2-oxo-ethyl]phenyl benzenesulfonate (4b). Typical procedure. A solution of α -aminonitrile **8g** (2.70 g, 9.44 mmol) in anhydrous degassed DMF (8 mL) was added dropwise to a stirred suspension of NaH (95% in oil dispersion, 0.52 g, 20.8 mmol) in the same solvent (5 mL) precooled at -19°C under atmosphere of Ar. After total addition, the deep red-colored solution was stirred at this temperature for 1 h and a solution of arylmethyl bromide **10b** (5.70 g, 15.8 mmol) in anhydrous degassed DMF (12 mL) was added dropwise over a period of 20 min. The resultant mixture was kept stirring at this temperature for 3 h, allowed to warm gradually to ambient temperature and further stirred for additional 2 h. The reaction was quenched by careful addition of MeOH until hydrogen bubbling ceased. The solvent was distilled off under vacuum (1.5 mmHg, 90°C). The resultant brown crude oil was taken up in a mixture of MeOH (12.5 mL) and 12 M HCl (31 mL) and heated at 90°C for 5 h. After cooling, the reaction mixture was partially concentrated ($\sim 2/3$ v.) under reduced pressure and extracted with DCM (3 x 10 mL). The organic layer was successively washed with saturated aqueous NaHCO_3 (3 x 10 mL), dried (anh. Na_2SO_4), filtered off and the solvent was evaporated *in vacuo*. The crude mixture was flash chromatographed on silica gel using 70% EtOAc/hexanes as eluant to afford deoxybenzoin **4b** (3.14 g, 65%) as a clear oil, which solidified upon prolonged storage at 4°C . *Rf* 0.53 (40% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 4.11 (2H, s), 6.89 (1H, d, $J = 7.9$ Hz), 7.11-7.18 (2H, m), 7.33 (1H, d, $J = 2.6$ Hz), 7.42-7.47 (2H, m), 7.56 (2H, ddd, $J = 8.2, 7.9, 1.6$ Hz), 7.68 (1H, ddd, $J = 7.9, 7.9, 1.6$ Hz), 7.83 (2H, dd, $J = 8.2, 1.6$ Hz), 7.92 (1H, d, $J = 7.9$ Hz); ^{13}C NMR (CDCl_3) δ 42.7, 91.1, 123.5, 128.1, 128.3, 129.0, 129.3, 131.2, 132.1, 132.6, 134.6, 135.0, 140.6, 143.2, 146.4, 199.3; FTIR (neat film, cm^{-1}): 1702, 1376, 1193; EIMS (m/z , %) 512 (M^+ , 2), 217 (3), 211 (25), 121 (100). Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{ClIO}_4\text{S}$: C, 46.85; H, 2.75. Found: C, 47.19; H, 2.67.

The same procedure on α -aminonitrile **8g** and bromide **10a** provided **2,4-Dichloro-6-[2-(2-iodophenyl)-2-oxo-ethyl]phenyl benzenesulfonate (4c)**: 83%, as an amber powder; mp $119\text{-}120^\circ\text{C}$ (MeOH); *Rf* 0.50 (30% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 4.42 (2H, s), 7.16 (1H, ddd, $J = 7.9, 7.9, 1.6$ Hz), 7.30 (1H, d, $J = 2.6$ Hz), 7.32 (1H, d, $J = 2.6$ Hz), 7.45 (1H, ddd, $J = 7.9, 7.9, 1.2$ Hz), 7.52-7.61 (3H, m), 7.70 (1H, ddd, $J = 7.5, 7.5, 1.2$ Hz), 7.94 (2H, dd, $J = 7.9, 1.2$ Hz), 7.97 (2H, d, $J = 7.5, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 43.9, 91.3, 128.2, 128.6, 129.0, 129.2, 129.4, 129.6, 130.9, 132.0, 132.8, 134.7, 135.8, 140.7, 143.1, 143.4, 198.9; FTIR (neat film, cm^{-1}): 1702, 1376, 1195; EIMS (m/z , %) 231 (100), 203 (17), 141 (7), 77 (29). Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{Cl}_2\text{IO}_4\text{S}$: C, 43.90; H, 2.39. Found: C, 44.18; H, 2.64.

The same procedure on α -aminonitrile **8h** and bromide **10d** provided **2-[2-(4,5-dimethoxy-2-iodophenyl)-2-oxo-ethyl]phenyl benzenesulfonate (4d)**: 72%, as an off-white powder; mp $125\text{-}126^\circ\text{C}$ (MeOH); *Rf* 0.26 (30% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 3.88 (6H, s), 4.13 (2H, s), 6.90 (1H, dd, $J = 7.7, 1.8$ Hz), 7.16 (1H, s), 7.20-7.29 (3H, m), 7.30 (1H, s), 7.52 (2H, dd, $J = 7.5, 7.5$ Hz), 7.65 (1H, dd, $J = 7.1, 7.1$ Hz), 7.82 (2H, dd, $J = 7.1, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 42.3, 56.0, 56.2, 81.5, 112.1, 122.2, 123.1,

127.3, 128.3, 128.5, 129.3, 132.1, 134.4, 135.4, 147.7, 148.7, 151.1, 198.2; FTIR (neat film, cm^{-1}): 1692, 1370, 1194; EIMS (m/z , %) 430 (42), 291 (100), 136 (10), 77 (41). Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{IO}_6\text{S}$: C, 49.08; H, 3.56. Found: C, 49.17; H, 3.38.

The same procedure on α -aminonitrile **8f** and 2-iodobenzyl bromide provided **5-*N,N*-diethylamino-2-[2-(2-iodophenyl)acetyl]phenyl benzenesulfonate (4e)**: 54%, as an off-orange powder; mp 124-126°C (MeOH); R_f 0.36 (40% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 1.11 (6H, d, $J = 7.1$ Hz), 3.28 (4H, t, $J = 7.1$ Hz), 4.25 (2H, s), 6.26 (1H, d, $J = 2.5$ Hz), 6.50 (1H, dd, $J = 9.0, 2.5$ Hz), 6.93 (1H, ddd, $J = 7.5, 7.5, 1.6$ Hz), 7.14 (1H, dd, $J = 7.5, 1.5$ Hz), 7.28 (1H, ddd, $J = 7.5, 7.5, 1.5$ Hz), 7.56 (1H, dd, $J = 8.0, 7.3$ Hz), 7.66 (2H, dd, $J = 7.5, 1.6$ Hz), 7.72 (1H, d, $J = 9.0$ Hz), 7.77 (1H, dd, $J = 8.0, 8.0$ Hz), 7.95 (2H, dd, $J = 7.3, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 12.4, 44.6, 53.4, 101.4, 104.4, 109.1, 118.5, 128.1, 128.3, 128.5, 129.2, 131.0, 132.9, 134.3, 135.8, 139.1, 139.5, 150.1, 151.5, 193.2; FTIR (neat film, cm^{-1}): 1669, 1376, 1195; EIMS (m/z , %) 549 (M^+ , 4), 281 (9), 332 (100), 254 (10), 207 (16), 192 (27), 176 (15), 148 (15). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{INO}_4\text{S}$: C, 52.47; H, 4.40, N, 2.55, Found: C, 52.09; H, 4.56; N, 2.69.

The same procedure on α -aminonitrile **8g** and bromide **10c** provided **1-[2-(2-iodophenyl)-2-oxoethyl]naphthalen-2-yl benzenesulfonate (4f)**: 51%, as an amber oil; R_f 0.39 (15% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 4.61 (2H, s), 7.07 (1H, d, $J = 8.7$ Hz), 7.14 (1H, dd, $J = 7.6, 2.0$ Hz), 7.29 (1H, ddd, $J = 7.5, 7.5, 1.2$ Hz), 7.43-7.59 (5H, m), 7.65-7.73 (2H, m), 7.82-7.93 (5H, m), 7.95 (2H, dd, $J = 7.3, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 39.7, 91.2, 120.5, 123.0, 124.8, 126.2, 127.3, 128.0, 128.1, 128.4, 129.3, 129.4, 131.7, 132.1, 133.0, 134.5, 135.5, 140.5, 143.7, 145.9, 200.0; FTIR (neat film, cm^{-1}): 1706, 1373, 1206; EIMS (m/z , %) 528 (M^+ , 10), 281 (14), 231 (100), 203 (18), 141 (10), 128 (13). Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{IO}_4\text{S}$: C, 54.56; H, 3.24. Found: C, 54.38; H, 3.60.

Synthesis of Deoxybenzoins (4) via Friedel-Crafts acylation and ester derivatives.

2-Bromo-4,5-dimethoxyphenylacetic acid (12a). Bromine (97%, 16.4 mL, 0.31 mol) dissolved in glacial HOAc (10 mL) was added dropwise to a stirred solution of homoveratric acid (50.0 g, 0.254 mol) in the same solvent (200 mL), keeping stirring at ambient temperature for 3 h. Addition of H_2O (400 mL) led to a white solid that was collected by filtration and thoroughly washed with H_2O . The filter cake was recrystallized from 20% MeOH/ H_2O and dried under vacuum (1 mmHg) over P_2O_5 affording 6-bromohomoveratric acid (**12a**) (63.56 g, 91%) as a white powder; mp 113-114°C (MeOH/ H_2O) (Lit.² 110-120°C (H_2O)); R_f 0.50 (80% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 3.77 (2H, s), 3.86 (6H, s), 6.78 (1H, s), 7.03 (1H, s); ^{13}C NMR (CDCl_3) δ 40.1, 56.0, 113.8, 115.0, 115.4, 125.2, 148.3, 148.9, 176.6; FTIR (KBr, cm^{-1}): 3550, 1688; EIMS (m/z , %) 276 ($\text{M}+1$, 51), 274 ($\text{M}-1$, 51), 231 (100), 229 (99), 195 (34).

4,5-Dimethoxy-2-iodophenylacetic acid (12b). Iodine monochloride (29.08 g, 0.179 mol) dissolved in glacial HOAc (240 mL) was added to a stirred solution of homoveratric acid (26.0 g, 0.132 mol) in the same solvent (650 mL), keeping stirring at ambient temperature for 1.5 h. The reaction was poured into H_2O (500 mL) and $\text{Na}_2\text{S}_2\text{O}_5$ (sodium metabisulfite) was added in portions until the purple colour was discharged to yellow. Vigorous stirring and slow addition of H_2O (500 mL) over 20 min led to the precipitation of a white solid, that was collected by filtration and thoroughly washed with H_2O . The filter cake was recrystallized

from 40% MeOH/H₂O and dried under vacuum (1 mmHg) over P₂O₅ affording 6-iodohomoveratric acid (**12b**) (39.10 g, 92%) as a white crystalline solid; mp 162-163°C (MeOH/H₂O) (Lit.³: 165-166.5°C); *R_f* 0.25 (5% MeOH/DCM); ¹H NMR (CDCl₃) δ 3.77 (2H, s), 3.84 (6H, s), 6.79 (1H, s), 7.26 (1H, s); ¹³C NMR (CDCl₃) δ 45.4, 56.1, 56.4, 88.9, 113.5, 121.5, 129.2, 148.7, 149.3, 177.0; FTIR (KBr, cm⁻¹): 3347, 1727; EIMS (*m/z*, %) 322 (M⁺, 56), 277 (78), 195 (100), 167 (27), 150 (37).

2-(4,5-Dimethoxy-2-iodophenyl)-1-(3,4-dimethoxy-2-hydroxyphenyl)ethanone (13b). **Typical procedure.** Freshly distilled SOCl₂ (11.2 mL, 0.153 mol) was added dropwise to a stirred solution of 4,5-dimethoxy-2-iodophenylacetic acid **12b** (15.0 g, 46.5 mmol) in anhydrous PhMe (150 mL) under atmosphere of Ar. The reaction mixture was heated at 135°C for 3.5 h, and after cooling, the solvent was removed under reduced pressure. The resultant brown oil was dissolved in anhydrous DCM (75 mL), cooled at 0°C, and a solution of 1,2,3-trimethoxybenzene (98%, 9.97 g, 58.1 mmol) in the same solvent (16 mL) was added dropwise under atmosphere of Ar. Anhydrous AlCl₃ (98.5%, 9.44 g, 69.7 mmol) was added in small portions at this temperature, and stirring was continued for 15 min. The reaction mixture was heated to reflux for 4 h, and after cooling to ambient temperature, was poured into a mixture of crushed ice (~50 g) and 12M HCl (20 mL). The phases were separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (1 x 20 mL), dried (anh. Na₂SO₄), filtered off, and the solvent was evaporated under reduced pressure. The brown crude oil was crystallized from MeOH affording deoxybenzoin **13b** (15.97 g, 75%) as a white powder; mp 164-165°C (MeOH); *R_f* 0.37 (20% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.84 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.95 (3H, s), 4.37 (2H, s), 6.55 (1H, d, *J* = 9.2 Hz), 6.76 (1H, s), 7.27 (1H, s), 7.67 (1H, d, *J* = 9.2 Hz), 12.4 (1H, s, OH, exc. D₂O); ¹³C NMR (CDCl₃) δ 49.1, 55.8, 56.0, 60.5, 89.0, 103.0, 113.2, 114.5, 121.3, 126.3, 130.0, 136.3, 148.4, 149.1, 157.0, 158.4, 201.4; FTIR (neat film, cm⁻¹): 1634; EIMS (*m/z*, %) 331 (14), 181 (100). Anal. Calcd for C₁₈H₁₉IO₆: C, 47.18; H, 4.18. Found: C, 47.39; H, 4.59.

By using the same procedure and starting from the appropriate intermediate compound of preceding steps, **2-(2-Bromo-4,5-dimethoxyphenyl)-1-(3,4-dimethoxy-2-hydroxyphenyl)ethanone (13a)** was obtained: 45%, as white flakes; mp 178-179°C (MeOH) (Lit.⁴: 162-163°C (MeOH)); *R_f* 0.41 (DCM); ¹H NMR (CDCl₃) δ 3.84 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 3.95 (3H, s), 4.35 (2H, s), 6.53 (1H, d, *J* = 9.1 Hz), 6.76 (1H, s), 7.06 (1H, s), 7.68 (1H, d, *J* = 9.1 Hz), 12.40 (1H, s, exc. D₂O); ¹³C NMR (CDCl₃) δ 44.8, 55.9, 60.4, 102.7, 113.5, 114.5, 115.2, 125.6, 135.8, 147.6, 148.0, 156.4, 157.8, 200.7; FTIR (neat film, cm⁻¹): 1641; EIMS (*m/z*, %) 331 (14), 181 (100), 148 (10).

When the same procedure applied to acid **12b** was performed substituting 1,2,3-trimethoxybenzene for 2,4,6-trimethoxybenzene as counterpart, **2-(4,5-dimethoxy-2-iodophenyl)-1-(2,4,6-trimethoxyphenyl)ethanone (13d)** was obtained: 79%, as a white powder; mp: 147-148°C (EtOAc/hexanes), *R_f* 0.35 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 3.76 (6H, s), 3.80 (3H, s), 3.82 (6H, s), 4.17 (2H, s), 6.06 (1H, s), 6.78 (2H, s), 7.18 (1H, s); ¹³C NMR (CDCl₃) δ 55.3, 55.7, 55.9, 89.0, 90.2, 112.5, 113.1, 121.0, 130.8, 147.9, 148.7, 158.1, 162.3, 200.1; FTIR (neat film, cm⁻¹): 1711; EIMS (*m/z*, %) 345 (1), 195 (100). Anal. Calcd for C₁₉H₂₁IO₆: C, 48.32; H, 4.48. Found: C, 48.39; H, 4.31.

2-(4,5-Dimethoxy-2-iodophenyl)-1-(4,6-dimethoxy-2-hydroxyphenyl)ethanone (13c). Freshly distilled SOCl₂ (9.3 mL, 0.128 mol) was added dropwise to a stirred solution of 4,5-dimethoxy-2-iodophenylacetic acid **12b** (12.27 g, 38.1 mol) in anhydrous PhMe (125 mL) under atmosphere of Ar. The resultant mixture was heated at 135°C for 3.5 h. After cooling, a solution of 1,3,5-trimethoxybenzene (99%, 8.08 g, 47.6 mmol) and freshly distilled BF₃·OEt₂ (5.3 mL, 41.9 mmol) in anhydrous PhMe (95 mL) was added dropwise. The reaction mixture was heated to reflux for additional 7 h, and after cooling to ambient temperature, was poured into a mixture of crushed ice (~50 g) and 12M HCl (12 mL). The phases were separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (1 x 20 mL), dried (anh. Na₂SO₄), filtered off, and the solvent was evaporated under reduced pressure. The brown crude oil was crystallized from acetone/MeOH affording deoxybenzoin **13c** (11.34 g, 65%) as white powder: mp 177-178°C (acetone/EtOH); *R*_f 0.59 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 3.83 (6H, s), 3.86 (3H, s), 3.91 (3H, s), 4.42 (2H, s), 5.98 (1H, d, *J* = 2.4 Hz), 6.09 (1H, d, *J* = 2.4 Hz), 6.71 (1H, s), 7.28 (1H, s), 13.73 (1H, s, exc. D₂O); ¹³C NMR (CDCl₃) δ 55.0, 55.5, 55.7, 55.8, 56.0, 89.5, 90.8, 93.6, 113.2, 121.2, 131.6, 148.1, 149.0, 162.7, 166.1, 167.4, 201.4; FTIR (neat film, cm⁻¹): 1622; EIMS (*m/z*, %) 331 (19), 181 (100). Anal. Calcd for C₁₈H₁₉IO₆: C, 47.18; H, 4.18. Found: C, 47.24; H, 4.36.

6-[2-(4,5-dimethoxy-2-iodophenyl)acetyl]-2,3-dimethoxyphenyl acetate (4k). **Typical procedure.** To a stirred solution of deoxybenzoin **13a** (0.63 g, 1.53 mmol) in anhydrous 1,4-dioxane (20 mL) under atmosphere of Ar, ground NaOH (99%, 0.18 g, 4.59 mmol) was added in one portion at ambient temperature. After 5 min, as the solution turned off-brown, a mixture of TEBA (98%, 17.8 mg, 76.5 μmol) and freshly distilled AcCl (0.43 mL, 6.12 mmol) was added dropwise. Stirring was continued for 6 h, the reaction was filtered and the solvent was removed under reduced pressure (*T* ≈ 70°C). The residual black oil was crystallized from MeOH affording acetate **4k** (0.75 g, 98%) as a white powder: mp 124-125°C (MeOH); *R*_f 0.45 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 2.37 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.94 (3H, s), 4.25 (2H, s), 6.69 (1H, s), 6.85 (1H, d, *J* = 8.6 Hz), 7.24 (1H, s), 7.70 (1H, d, *J* = 8.6 Hz); ¹³C NMR (CDCl₃) δ 21.0, 52.3, 55.8, 56.1, 60.9, 89.1, 108.1, 113.2, 121.4, 123.8, 126.0, 141.2, 144.3, 148.4, 149.2, 157.2, 169.1, 194.7; FTIR (neat film, cm⁻¹): 1769, 1684; EIMS (*m/z*, %) 373 (7), 223 (34), 181 (100). Anal. Calcd for C₂₀H₂₁IO₇: C, 48.02; H, 4.23. Found: C, 47.89; H, 4.02.

When the same procedure applied to deoxybenzoin **13b** was performed substituting acetyl chloride for benzoyl chloride as reagent, **6-[2-(4,5-dimethoxy-2-iodophenyl)acetyl]-2,3-dimethoxyphenyl benzoate (4h)** was obtained after purification by silica gel flash column chromatography eluting with the gradient 2→10% EtOAc/DCM: 91%, as a white glassy solid, mp 112-114°C (EtOAc/hexanes); *R*_f 0.60 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.77 (3H, s), 3.80 (6H, s), 3.96 (3H, s), 4.25 (2H, s), 6.64 (1H, s), 6.91 (1H, d, *J* = 8.7 Hz), 7.15 (1H, s), 7.48 (2H, dd, *J* = 7.1, 7.1 Hz), 7.61 (1H, dddd, *J* = 7.1, 7.1, 1.6, 1.6 Hz), 7.72 (1H, d, *J* = 8.7 Hz), 8.22 (2H, dd, *J* = 7.1, 1.6 Hz); ¹³C NMR (CDCl₃) δ 52.7, 55.7, 56.0, 56.1, 60.9, 89.1, 109.1, 113.1, 121.2, 124.5, 125.8, 128.9, 130.3, 130.7, 133.6, 141.4, 144.4, 148.2, 149.0, 157.1, 164.6,

194.9; FTIR (neat film, cm^{-1}): 1743, 1685; EIMS (m/z , %) 435 (9), 285 (74), 105 (100), 77 (29). Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{IO}_7$: C, 53.40; H, 4.12. Found: C, 53.37; H, 4.31.

2-[2-(4,5-dimethoxy-2-iodophenyl)acetyl]-3,5-dimethoxyphenyl benzoate (4i). Typical procedure. To a stirred solution of deoxybenzoin **13c** (1.40 g, 3.06 mmol) in anhydrous THF (160 mL) under atmosphere of Ar, ground NaOH (99%, 0.37 g, 9.19 mmol) was added in one portion at ambient temperature. After stirring for 55 min, as the dissolution turned slowly off-orange, TEBA (99%, 35 mg, 153 μmol) was added, and 15 min later, freshly distilled BzCl (0.71 mL, 12.2 mmol) was added dropwise. Stirring was continued for 4 h, the reaction was filtered and the solvent was removed under reduced pressure ($T \approx 70^\circ\text{C}$). The dark crude oil was purified by flash chromatographed on silica gel eluting with the gradient 80% DCM/hexanes \rightarrow 10% EtOAc/DCM to afford the benzoate **4i** (1.63 g, 95%) as an off-yellow powder: mp 125-126 $^\circ\text{C}$ (EtOH), R_f 0.33 (40% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 3.59 (3H, s), 3.80 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 4.30 (2H, s), 6.38 (1H, d, $J = 2.0$ Hz), 6.41 (1H, d, $J = 2.0$ Hz), 6.63 (1H, s), 7.15 (1H, s), 7.44 (2H, dd, $J = 7.6, 7.2$ Hz), 7.58 (1H, dd, $J = 7.2, 7.2$ Hz), 8.04 (2H, dd, $J = 7.6, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 54.8, 55.5, 55.9, 56.1, 89.2, 96.4, 100.1, 113.1, 116.7, 121.1, 128.4, 128.9, 130.0, 130.6, 133.5, 148.1, 149.6, 158.8, 162.1, 164.8, 198.0; FTIR (neat film, cm^{-1}): 1731, 1692; EIMS (m/z , %) 331 (2), 317 (10), 181 (100). Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{IO}_7$: C, 53.40; H, 4.12. Found: C, 53.63; H, 4.14.

The same procedure on deoxybenzoin **13b** provided, after purification by silica gel flash column chromatography eluting with the gradient 0 \rightarrow 10% EtOAc/DCM, **6-[2-(2-bromo-4,5-dimethoxyphenyl)acetyl]-2,3-dimethoxyphenyl benzoate (4g)**: 88%; as prismatic crystals; mp 106-108 $^\circ\text{C}$ (acetone/EtOH), R_f 0.38 (2% EtOAc/DCM); ^1H NMR (CDCl_3) δ 3.77 (3H, s), 3.85 (6H, s), 3.96 (3H, s), 4.24 (2H, s), 6.64 (1H, s), 6.91 (1H, d, $J = 8.7$ Hz), 6.95 (1H, s), 7.51 (2H, dd, $J = 7.9, 7.2$ Hz), 7.64 (1H, dd, $J = 7.9, 7.9$ Hz), 7.72 (1H, d, $J = 8.7$ Hz), 8.21 (2H, dd, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3) δ 47.9, 55.9, 56.0, 60.9, 109.1, 113.7, 114.7, 115.1, 124.3, 125.8, 126.7, 128.9, 130.3, 133.6, 141.4, 144.1, 148.1, 148.3, 157.0, 164.6, 194.8; FTIR (neat film, cm^{-1}): 1742, 1683; EIMS (m/z , %) 285 (33), 105 (100), 77 (17). Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{BrO}_7$: C, 58.26; H, 4.50. Found: C, 58.49; H, 4.39.

Synthesis of Enaminoketones (3).

2-[3-(*N,N*-Dimethylamino)-2-(2-iodophenyl)acryloyl]phenyl tosylate (3a). Typical procedure. DMFDMA (94%, 2.73 mL, 19.3 mmol) was added dropwise to a stirred suspension of deoxybenzoin **4a** (7.28 g, 14.8 mol) in anhydrous PhMe (120 mL) under atmosphere of Ar at ambient temperature. The resultant mixture was heated at 90 $^\circ\text{C}$ for 32 h, adding dropwise a supplementary amount of DMFDMA (94%, 7 x (0.5 mL, 3.54 mmol)) until complete consumption of starting material was confirmed by tlc (50% EtOAc/hexanes). After cooling, the solvent was removed under reduced pressure and the crude mixture was crystallized from Et_2O . Mother liquors were flash chromatographed on silica gel eluting with the gradient 50 \rightarrow 100% EtOAc/hexanes affording an additional amount of enaminoketone **4a** (comb. yield 3.72 g, 46%) as a yellow glassy solid, mp 68-69 $^\circ\text{C}$ (Et_2O), R_f 0.19 (40% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 2.44 (3H, s), 2.41-3.17 (6H, bs), 6.94-6.96 (2H, m), 7.23-7.45 (9H, m), 7.82 (2H, d, $J = 8.2$ Hz); ^{13}C NMR (CDCl_3) δ 40.8, 46.2, 105.4, 116.1, 121.3, 126.2, 127.3, 128.0, 128.3, 129.3, 132.8, 135.6, 137.8, 141.3, 145.0, 145.6,

155.1, 188.8; FTIR (neat film, cm^{-1}): 1635, 1587, 1315, 1196; EIMS (m/z , %) 547 (M^+ , 2), 420 (30), 221 (100), 145 (15). Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{INO}_4\text{S}$: C, 52.66; H, 4.05; N, 2.56. Found: C, 52.96; H, 3.86; N, 2.39.

By using the same procedure and starting from the appropriate intermediate compound of preceding steps, the following products were obtained:

4-Chloro-2-[2-(*N,N*-dimethylamino)-1-(2-iodobenzoyl)vinyl]phenyl benzenesulfonate (3b): 58%, as a viscous orange oil; R_f 0.37 (60% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 2.36-3.05 (6H, bs), 6.84 (1H, s), 7.01-7.41 (6H, m), 7.55 (2H, dd, $J = 7.7, 7.7$ Hz), 7.64 (1H, dd, $J = 7.7, 7.7$ Hz), 7.78 (1H, d, $J = 7.7$ Hz), 7.91 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (CDCl_3) δ 39.7, 47.2, 93.5, 104.5, 120.4, 125.9, 128.9, 129.3, 131.1, 132.0, 133.3, 134.0, 135.6, 138.5, 146.0, 147.0, 155.7, 192.6; FTIR (neat film, cm^{-1}): 1636, 1576, 1315, 1189; EIMS (m/z , %) 569 ($M+2$, 2), 567 (M^+ , 4), 426 (14), 410 (24), 231 (100), 203 (19), 77 (38). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{ClINO}_4\text{S}$: C, 48.65; H, 3.37; N, 2.47 Found: C, 48.56; H, 3.49; N, 2.56.

2,4-Dichloro-6-[2-(*N,N*-dimethylamino)-1-(2-iodobenzoyl)vinyl]phenyl benzenesulfonate (3c): 41%, as a glassy orange solid; mp 111-112°C (EtOAc/hexanes), R_f 0.32 (50% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 2.56-3.15 (6H, bs), 6.89 (1H, s), 7.05 (1H, m), 7.30-7.58 (6H, m), 7.68 (1H, dd, $J = 7.5, 7.5$ Hz), 7.81 (1H, d, $J = 7.5$ Hz), 7.99 (2H, d, $J = 7.6$ Hz); ^{13}C NMR (CDCl_3) δ 40.2, 47.1, 94.0, 105.5, 127.8, 128.1, 128.4, 128.9, 129.6, 131.8, 132.1, 134.2, 134.9, 137.0, 138.9, 144.5, 146.2, 156.6, 192.8; FTIR (neat film, cm^{-1}): 1638, 1588, 1313, 1190; EIMS (m/z , %) 604 ($M+2$, 1), 602 (M^+ , 1), 460 (10), 444 (14), 231 (100), 203 (21), 77 (34). Anal. Calcd for $\text{C}_{23}\text{H}_{18}\text{Cl}_2\text{INO}_4\text{S}$: C, 45.87; H, 3.01; N, 2.32. Found: C, 46.09; H, 3.17; N, 2.09.

2-[2-(*N,N*-Dimethylamino)-1-(4,5-dimethoxy-2-iodobenzoyl)vinyl]phenyl benzenesulfonate (3d): 47%, as a glassy white solid; mp 152-153°C (Et_2O); R_f 0.29 (80% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 2.27-3.07 (6H, bs), 3.86 (6H, s), 6.61-7.39 (6H, m), 7.56 (2H, dd, $J = 7.5, 7.5$ Hz), 7.66 (1H, dd, $J = 7.5, 7.5$ Hz), 7.78 (1H, d, $J = 7.7$ Hz), 7.94 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (CDCl_3) δ 40.2, 46.4, 81.6, 105.5, 111.3, 120.6, 125.9, 127.6, 128.8, 130.4, 134.3, 136.2, 139.1, 148.5, 155.7, 192.8; FTIR (neat film, cm^{-1}): 1637, 1578, 1356, 1194; EIMS (m/z , %) 593 (M^+ , 2), 466 (16), 436 (12), 325 (12), 291 (100), 283 (26), 77 (37). Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{INO}_6\text{S}$: C, 50.60; H, 4.08; N, 2.36. Found: C, 50.72; H, 4.09; N, 2.39.

5-*N,N*-diethylamino-2-[3-(*N,N*-Dimethylamino)-2-(2-iodophenyl)acryloyl]phenyl benzenesulfonate (3e): 58%, as a glassy yellow solid; mp 81-83°C (EtOAc/hexanes); R_f 0.38 (70% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 1.03 (6H, t, $J = 7.1$ Hz), 2.65 (6H, s), 3.24 (4H, q, $J = 7.1$ Hz), 6.33 (1H, d, $J = 2.3$ Hz), 6.42 (1H, dd, $J = 8.6, 2.3$ Hz), 6.85 (1H, ddd, $J = 8.0, 7.7, 1.7$ Hz), 7.04 (1H, s), 7.18-7.29 (3H, m), 7.45 (1H, dd, $J = 7.7, 7.7$ Hz), 7.56 (1H, ddd, $J = 7.7, 7.7, 1.7$ Hz), 7.76 (1H, d, $J = 7.8$ Hz), 7.91 (2H, dd, $J = 7.7, 1.7$ Hz); ^{13}C NMR (CDCl_3) δ 12.0, 42.5, 44.0, 104.0, 105.2, 108.4, 115.7, 121.3, 127.0, 127.8, 128.6, 131.1, 132.8, 133.6, 135.8, 137.6, 142.0, 147.4, 148.5, 153.9, 189.1; FTIR (neat film, cm^{-1}): 1611, 1571, 1373, 1195; EIMS (m/z , %) 305 (27), 290 (100), 149 (66), 136 (21), 77 (31). Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{IN}_2\text{O}_4\text{S}$: C, 53.65; H, 4.84; N, 4.63. Found: C, 53.89; H, 4.76; N, 4.48.

1-[2-(*N,N*-Dimethylamino)-1-(2-iodobenzoyl)vinyl]naphthalen-2-yl benzenesulfonate (3f): 45%, as a colorless oil, mp 148-150°C (Et₂O); *R_f* 0.30 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.32 (3H, bs), 2.98 (3H, bs), 7.06-7.13 (2H, m), 7.36-7.63 (6H, m), 7.71 (2H, m), 7.83 (2H, dd, *J* = 7.9, 7.1 Hz), 8.02 (2H, d, *J* = 7.5 Hz), 8.23 (1H, d, *J* = 7.5 Hz); ¹³C NMR (CDCl₃) δ 38.3, 46.7, 93.6, 103.3, 119.8, 126.0, 126.9, 127.8, 128.1, 128.3, 129.2, 129.4, 131.8, 133.9, 135.1, 137.1, 139.0, 146.6, 147.3, 157.2, 193.3; FTIR (neat film, cm⁻¹): 1636, 1589, 1369, 1168; EIMS (*m/z*, %) 583 (M⁺, 1), 442 (16), 426 (46), 299 (14), 271 (14), 231 (100), 211 (41), 77 (38). Anal. Calcd for C₂₇H₂₂INO₄S: C, 55.58; H, 3.80; N, 2.40. Found: C, 55.89; H, 3.49; N, 2.56.

6-[3-(*N,N*-Dimethylamino)-2-(2-bromo-4,5-dimethoxyphenyl)acryloyl]-2,3-dimethoxyphenyl benzoate (3g): 81%, as a glassy white solid; mp 199-201°C (Et₂O); *R_f* 0.17 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 2.25-2.95 (6H, bs), 3.80 (9H, s), 3.91 (3H, s), 6.53 (1H, s), 6.83 (1H, d, *J* = 8.4 Hz), 6.95 (1H, s), 7.10-7.14 (2H, m), 7.47 (2H, dd, *J* = 7.5, 7.1 Hz), 7.57 (1H, dd, *J* = 7.1, 7.1 Hz), 8.19 (2H, d, *J* = 7.5 Hz); ¹³C NMR (CDCl₃) δ 39.9, 45.5, 55.5, 55.8, 56.0, 60.5, 109.5, 111.9, 114.2, 115.8, 116.8, 123.1, 128.7, 129.3, 130.2, 140.8, 141.4, 147.2, 148.2, 153.5, 155.5, 164.2, 189.8; FTIR (neat film, cm⁻¹): 1737, 1637, 1575; EIMS (*m/z*, %) 490 (15), 341 (100), 325 (20), 310 (10), 181 (16), 77 (18). Anal. Calcd for C₂₈H₂₈BrNO₇: C, 58.96; H, 4.95; N, 2.46. Found: C, 59.19; H, 4.67; N, 2.39. Flash chromatography on silica gel of mother liquors eluting with the gradient 30→60% EtOAc/hexanes led to the isolation of **3-(2-bromo-4,5-dimethoxyphenyl)-7,8-dimethoxychromen-4-one (14b):** 16%, as a white powder; mp 203-204°C (50% EtOAc/hexanes); *R_f* 0.32 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.86 (3H, s), 3.92 (3H, s), 4.02 (6H, s), 6.85 (1H, s), 7.07 (1H, d, *J* = 9.1 Hz), 7.13 (1H, s), 7.96 (1H, s), 8.03 (1H, d, *J* = 9.1 Hz); ¹³C NMR (CDCl₃) δ 55.6, 55.9, 61.5, 110.0, 114.5, 114.7, 118.9, 121.6, 124.4, 124.7, 136.4, 148.0, 149.5, 150.5, 154.4, 156.4, 175.2; FTIR (neat film, cm⁻¹): 1649, 1599; EIMS (*m/z*, %) 341 (100), 325 (18), 297 (8). Anal. Calcd for C₁₉H₁₇BrO₆: C, 54.18; H, 4.07. Found: C, 54.46; H, 4.18.

6-[3-(*N,N*-Dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)acryloyl]-2,3-dimethoxyphenyl benzoate (3h): 58%, as a white powder; mp 208-209°C (Et₂O); *R_f* 0.17 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.45-2.95 (6H, bs), 3.82 (6H, s), 3.91 (6H, s), 6.49 (1H, s), 6.85 (1H, d, *J* = 8.3 Hz), 7.15 (2H, dd, *J* = 7.5, 2.3 Hz), 7.16 (2H, s), 7.46 (2H, dd, *J* = 7.5, 7.5 Hz), 7.59 (1H, dd, *J* = 7.5, 7.5 Hz), 8.20 (2H, dd, *J* = 7.5, 1.6 Hz); ¹³C NMR (CDCl₃) δ 38.7, 46.2, 55.5, 55.8, 56.0, 60.7, 93.1, 109.6, 114.9, 115.9, 120.2, 123.3, 128.0, 130.2, 133.4, 134.1, 140.9, 141.6, 148.0, 148.5, 153.6, 155.3, 164.4, 189.8; FTIR (neat film, cm⁻¹): 1740, 1636, 1577; EIMS (*m/z*, %) 618 (M+1, 2), 490 (58), 341 (26), 105 (100), 77 (39). Anal. Calcd for C₂₈H₂₈INO₇: C, 54.47; H, 4.57; N, 2.27. Found: C, 54.59; H, 4.46; N, 2.38.

2-[3-(*N,N*-Dimethylamino)-2-(4,5-dimethoxy-2-iodophenyl)acryloyl]-3,5-dimethoxyphenyl benzoate (3i): 58%, as a white powder; mp 212-213°C (Et₂O); *R_f* 0.29 (80% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 2.48-3.00 (6H, bs), 3.80 (6H, s), 3.84 (6H, s), 6.09 (1H, s), 6.37 (1H, d, *J* = 2.0 Hz), 6.39 (1H, d, *J* = 2.0 Hz), 7.10 (1H, s), 7.19 (1H, s), 7.46 (2H, dd, *J* = 7.5, 7.5 Hz), 7.58 (1H, dd, *J* = 7.5, 7.5 Hz), 8.18 (2H, d, *J* = 7.5 Hz); ¹³C NMR (CDCl₃) δ 39.1, 45.5, 55.0, 55.5, 55.9, 56.2, 92.1, 97.2, 99.5, 114.7, 115.6, 115.6, 117.8, 120.4, 128.3, 128.6, 129.4, 130.1, 130.6, 133.5, 134.2, 148.1, 148.4, 148.9, 155.4, 158.5, 160.5, 164.9, 187.9;

FTIR (neat film, cm^{-1}): 1736, 1648, 1610; EIMS (m/z , %) 618 ($M^+ + 1$, 3), 490 (90), 341 (19), 105 (100), 77 (49). Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{INO}_7$: C, 54.47; H, 4.57; N, 2.27. Found: C, 54.41; H, 4.69; N, 2.18.

3-(4,5-dimethoxy-2-iodophenyl)-7,8-dimethoxychromen-4-one (14a). DMFDMA (94%, 1.8 mL, 12.6 mmol) was added dropwise to a stirred suspension of deoxybenzoin **4k** (5.58 g, 11.0 mmol) in anhydrous PhMe (85 mL) under atmosphere of Ar at ambient temperature. The reaction mixture was stirred for 1 h and the solvent was removed under reduced pressure. The residual yellow oil was absorbed on silica gel (33 g) and flash chromatographed eluting with the gradient 30→40% EtOAc/hexanes affording the isoflavone **14a** (3.14 g, 61%) as white powder: mp 184-187°C (EtOAc/hexanes), R_f 0.42 (2% EtOAc/DCM); ^1H NMR (CDCl_3) δ 3.85 (3H, s), 3.89 (3H, s), 4.00 (6H, s), 6.83 (1H, s), 7.06 (1H, d, $J = 9.1$ Hz), 7.38 (1H, s), 7.91 (1H, s), 8.01 (1H, d, $J = 9.1$ Hz); ^{13}C NMR (CDCl_3) δ 55.9, 56.1, 56.4, 61.6, 89.0, 110.0, 113.9, 119.1, 121.5, 121.8, 127.9, 136.5, 149.1, 149.4, 150.7, 154.5, 156.4, 175.2; FTIR (neat film, cm^{-1}): 1647, 1602; EIMS (m/z , %) 341 (100), 326 (12), 325 (24), 297 (11), 171 (16). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{IO}_6$: C, 48.74; H, 3.66. Found: C, 48.99; H, 3.39.

Synthesis of 4,5-Diarylpyrazoles (15-16).

2-[4-(2-Iodophenyl)-2-phenyl-2H-pyrazol-3-yl]phenyl tosylate (15a). **Typical procedure.** Phenylhydrazine hydrochloride (99%, 2.26 g, 15.5 mmol) was added in portions to a stirred suspension of enaminoketone **3a** (7.38 g, 13.5 mmol) and ground Na_2CO_3 (99%, 1.09 g, 10.2 mmol) in MeOH (145 mL) and H_2O (290 mL) under atmosphere of Ar at ambient temperature. The resultant mixture was acidified to pH 4 with glacial acetic acid (5.5 mL) and heated at 145°C for 5 h. After cooling, the mixture was partially concentrated (~1/2 v.) in vacuo, and extracted with DCM (5 x 50 mL). The organic extract was successively washed with brine (1 x 25 mL) and H_2O (1 x 25 mL), dried (anh. Na_2SO_4), filtered off and the solvent was removed in vacuo. The crude mixture was flash chromatographed on silica gel with 15% EtOAc/hexanes as eluant, and the adequate combined fractions were crystallized from 50% EtOAc/hexanes to afford pyrazole **15a** (7.19 g, 90%) as a yellow glassy solid; mp 167-168°C (EtOAc/hexanes); R_f 0.50 (80% DCM/hexanes); ^1H NMR (CDCl_3) δ 2.38 (3H, s), 6.85-6.92 (4H, m), 7.09-7.17 (6H, m), 7.24-7.28 (4H, m), 7.47 (2H, dd, $J = 8.3, 1.9$ Hz), 7.82 (1H, dd, $J = 7.9, 1.7$ Hz), 7.91 (1H, s); ^{13}C NMR (CDCl_3) δ 21.6, 100.5, 122.8, 123.6, 123.8, 126.5, 127.0, 127.9, 128.5, 128.8, 129.7, 130.4, 131.5, 132.5, 132.9, 134.8, 137.3, 139.2, 139.9, 140.9, 145.6, 146.6; FTIR (neat film, cm^{-1}): 1596, 1380, 1195; EIMS (m/z , %) 592 (M^+ , 34), 437 (9), 310 (100), 282 (17), 254 (16). Anal. Calcd for $\text{C}_{28}\text{H}_{21}\text{IN}_2\text{O}_3\text{S}$: C, 56.76; H, 3.57; N, 4.73. Found: C, 56.89; H, 3.61; N, 4.62.

By using the same procedure and starting from the appropriate intermediate compound of preceding step, the following products were obtained:

4-Chloro-2-[5-(2-iodophenyl)-1-phenyl-1H-pyrazol-4-yl]phenyl benzenesulfonate (15b) after purification by flash chromatography on silica gel eluting with the gradient 30→50% EtOAc/hexanes and subsequent crystallization from Et_2O : 63%, as an off-red powder; mp 134-135°C (Et_2O); R_f 0.44 (60% EtOAc/hexanes); ^1H NMR (CDCl_3) δ 6.88 (1H, d, $J = 2.4$ Hz), 6.93 (1H, dd, $J = 7.5, 1.6$ Hz), 7.03 (1H, ddd,

$J = 7.6, 7.6, 1.9$ Hz), 7.16-7.33 (8H, m), 7.46 (2H, dd, $J = 7.6, 7.5$ Hz), 7.61 (1H, dddd, $J = 7.6, 7.6, 1.2, 1.2$ Hz), 7.63 (1H, s), 7.71 (2H, dd, $J = 8.5, 1.4$ Hz), 7.76 (1H, dd, $J = 7.9, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 100.3, 116.3, 124.3, 127.4, 127.9, 128.2, 128.9, 129.3, 130.7, 132.0, 132.3, 134.2, 134.7, 135.3, 139.2, 140.1, 142.0, 145.1; FTIR (neat film, cm^{-1}): 1597, 1379, 1196; EIMS (m/z , %) 614 ($\text{M}+2$, 6), 612 (M^+ , 13), 473 (15), 471 (43), 346 (239), 344 (67), 308 (16), 281 (22), 254 (10), 77 (100). Anal. Calcd for $\text{C}_{27}\text{H}_{18}\text{ClIN}_2\text{O}_3\text{S}$: C, 52.91; H, 2.96; N, 4.57. Found: C, 56.12; H, 2.94; N, 4.61.

2,4-Dichloro-6-[5-(2-iodophenyl)-1-phenyl-1H-pyrazol-4-yl]phenyl benzenesulfonate (15c) after purification by flash chromatography on silica gel eluting with the gradient 80→100% DCM/hexanes and subsequent crystallization from 50% Et_2O /hexanes: 12%, as a yellow powder; mp 154-156°C (Et_2O /hexanes); R_f 0.36 (90% DCM/hexanes); ^1H NMR (CDCl_3) δ 6.86 (1H, d, $J = 2.3$ Hz), 7.07 (1H, ddd, $J = 7.9, 7.2, 2.0$ Hz), 7.11-7.28 (8H, m), 7.36 (1H, dd, $J = 7.2, 1.2$ Hz), 7.42-7.49 (2H, m), 7.57 (1H, ddd, $J = 7.5, 7.2, 1.2$ Hz), 7.72 (1H, s), 7.80 (1H, dd, $J = 7.5, 1.2$ Hz), 7.85 (1H, dd, $J = 7.5, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ 100.3, 116.7, 124.1, 127.3, 127.8, 128.5, 128.6, 128.9, 129.7, 129.9, 130.6, 130.8, 132.0, 132.4, 134.5, 136.7, 139.3, 139.4, 140.1, 141.8, 142.7; FTIR (neat film, cm^{-1}): 1597, 1383, 1193; EIMS (m/z , %) 649 ($\text{M}+2$, 1), 647 (M^+ , 1), 507 (16), 505 (24), 380 (27), 379 (18), 378 (41), 343 (8), 279 (16), 77 (100). Anal. Calcd for $\text{C}_{27}\text{H}_{17}\text{Cl}_2\text{IN}_2\text{O}_3\text{S}$: C, 50.10; H, 2.65; N, 4.33. Found: C, 49.95; H, 2.68; N, 4.41.

2-[5-(4,5-Dimethoxy-2-iodophenyl)-1-phenyl-1H-pyrazol-4-yl]phenyl benzenesulfonate (15d) after purification by flash chromatography with 30% EtOAc /hexanes as eluant and subsequent crystallization from Et_2O : 94%, as a white powder; mp 133-134°C (Et_2O); R_f 0.43 (50% EtOAc /hexanes); ^1H NMR (CDCl_3) δ 3.72 (3H, s), 3.84 (3H, s), 6.78 (1H, s), 7.01 (1H, dd, $J = 7.6, 1.6$ Hz), 7.11 (1H, s), 7.13-7.35 (9H, m), 7.45 (2H, dd, $J = 7.9, 7.5$ Hz), 7.54 (1H, s), 7.63 (1H, dd, $J = 7.9, 7.9$ Hz), 7.70 (1H, dd, $J = 7.7, 1.1$ Hz); ^{13}C NMR (CDCl_3) δ 55.9, 56.0, 89.1, 114.8, 117.8, 120.8, 122.8, 124.1, 126.8, 127.1, 127.4, 128.1, 128.6, 128.9, 131.6, 134.0, 135.7, 139.8, 140.2, 141.8, 146.7, 149.0, 149.6; FTIR (neat film, cm^{-1}): 1597, 1376, 1194; EIMS (m/z , %) 638 (M^+ , 8), 511 (20), 370 (100), 295 (13), 77 (78). Anal. Calcd for $\text{C}_{29}\text{H}_{23}\text{IN}_2\text{O}_5\text{S}$: C, 54.56; H, 3.63; N, 4.39. Found: C, 54.63; H, 3.59; N, 4.44.

5-(*N,N*-Diethylamino)-2-[4-(2-iodophenyl)-2-phenyl-2H-pyrazol-3-yl]phenyl benzenesulfonate (15e) after purification by flash chromatography on silica gel eluting with the gradient 30→50% EtOAc /hexanes and subsequent crystallization from 30% Et_2O /hexanes: 91%, as a yellow powder; mp 136-137°C (Et_2O /hexanes), R_f 0.51 (50% EtOAc /hexanes); ^1H NMR (CDCl_3) δ 1.11 (6H, t, $J = 7.1$ Hz), 3.26 (4H, q, $J = 7.1$ Hz), 6.73 (1H, d, $J = 2.5$ Hz), 6.39 (1H, dd, $J = 8.6, 2.5$ Hz), 6.81 (1H, d, $J = 8.6$ Hz), 6.89-6.99 (5H, m), 7.13-7.19 (4H, m), 7.47 (2H, dd, $J = 8.5, 7.8$ Hz), 7.58 (2H, d, $J = 8.5$ Hz), 7.88 (1H, s), 7.90 (1H, dd, $J = 7.9, 1.8$ Hz); ^{13}C NMR (CDCl_3) δ 12.1, 44.1, 100.5, 104.7, 108.7, 109.7, 123.3, 125.3, 126.4, 127.8, 128.2, 128.9, 131.5, 132.5, 133.9, 135.7, 136.0, 137.7, 138.9, 140.5, 140.6, 147.5, 148.9; FTIR (neat film, cm^{-1}): 1598, 1378, 1195; EIMS (m/z , %) 649 (M^+ , 40), 634 (31), 381 (10), 368 (38), 353 (28), 337 (19), 310 (10), 281 (33), 269 (10), 254 (14), 77 (100). Anal. Calcd for $\text{C}_{31}\text{H}_{28}\text{IN}_3\text{O}_3\text{S}$: C, 57.32; H, 4.34; N, 6.47. Found: C, 57.41; H, 4.37; N, 6.40.

6-[4-(2-Bromo-4,5-dimethoxyphenyl)-2-phenyl-2H-pyrazol-3-yl]-2,3-dimethoxyphenyl benzoate (15g) after crystallization of the crude extract from MeOH/H₂O: 91%, as a white powder; mp 158-160°C (MeOH/H₂O), *R_f* 0.77 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.56 (3H, s), 3.63 (3H, s), 3.88 (6H, s), 6.63 (1H, s), 6.75 (1H, d, *J* = 8.7 Hz), 6.84 (1H, d, *J* = 8.7 Hz), 7.06 (1H, s), 7.33-7.41 (7H, m), 7.57 (1H, dd, *J* = 7.1, 7.1 Hz), 7.67 (2H, d, *J* = 7.5 Hz), 7.92 (1H, s); ¹³C NMR (CDCl₃) δ 55.5, 55.9, 60.7, 110.0, 113.3, 115.0, 115.1, 117.2, 122.5, 123.6, 125.3, 126.3, 126.8, 128.5, 130.2, 133.5, 135.4, 140.2, 141.3, 141.7, 142.9, 147.8, 148.1, 154.2, 163.8; FTIR (neat film, cm⁻¹): 1739, 1599; EIMS (*m/z*, %) 512 (5), 510 (5), 341 (24), 105 (100), 77 (21). Anal. Calcd for C₃₂H₂₇BrN₂O₆: C, 62.45; H, 4.42; N, 4.55. Found: C, 62.40; H, 4.35; N, 4.49.

2,3-Dimethoxy-6-[4-(4,5-dimethoxy-2-iodophenyl)-2-phenyl-2H-pyrazol-3-yl]phenyl benzoate (15h) after crystallization of the crude extract from MeOH/H₂O: 92%, as a white powder; mp 186-187°C (MeOH/H₂O), *R_f* 0.76 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.60 (3H, s), 3.62 (3H, s), 3.88 (6H, s), 6.63 (1H, s), 6.75 (1H, d, *J* = 8.8 Hz), 6.84 (1H, d, *J* = 8.8 Hz), 7.28-7.42 (8H, m), 7.58 (1H, dd, *J* = 7.8, 7.8 Hz), 7.66 (2H, d, *J* = 7.2 Hz), 7.89 (1H, s); ¹³C NMR (CDCl₃) δ 55.5, 55.9, 56.0, 60.7, 87.5, 110.0, 114.6, 117.1, 121.1, 123.4, 125.7, 126.3, 126.8, 128.5, 130.0, 133.6, 135.4, 140.6, 141.1, 148.2, 148.8, 154.6, 163.7; FTIR (neat film, cm⁻¹): 1740, 1599; EIMS (*m/z*, %) 662 (M⁺, 6), 558 (2), 431 (4), 105 (100), 77 (26). Anal. Calcd for C₃₂H₂₇IN₂O₆: C, 58.02; H, 4.11; N, 4.23. Found: C, 57.92; H, 4.08; N, 4.39.

3,5-Dimethoxy-2-[4-(4,5-dimethoxy-2-iodophenyl)-2-phenyl-2H-pyrazol-3-yl]phenyl benzoate (15i) after purification by flash chromatography on silica gel eluting with the gradient 40→60% EtOAc/hexanes and subsequent crystallization from Et₂O: 58%, as a white powder; mp 175-177°C (Et₂O); *R_f* 0.48 (50% EtOAc/hexanes); ¹H NMR (CDCl₃) δ 3.46 (3H, s), 3.53 (3H, s), 3.77 (3H, s), 3.86 (3H, s), 6.27 (1H, d, *J* = 2.0 Hz), 6.32 (1H, d, *J* = 2.0 Hz), 6.66 (1H, s), 7.26-7.43 (8H, m), 7.58 (1H, dd, *J* = 7.5, 7.5 Hz), 7.73 (2H, d, *J* = 8.3 Hz), 7.95 (1H, s); ¹³C NMR (CDCl₃) δ 55.3, 55.4, 55.8, 86.8, 96.5, 99.7, 105.7, 113.3, 121.3, 123.1, 125.6, 126.6, 128.1, 130.1, 130.3, 131.8, 133.4, 140.3, 140.7, 147.7, 148.4, 150.5, 158.8, 161.6, 163.7; FTIR (neat film, cm⁻¹): 1737, 1613; EIMS (*m/z*, %) 662 (M⁺, 8), 430 (4), 105 (100), 77 (34). Anal. Calcd for C₃₂H₂₇IN₂O₆: C, 58.02; H, 4.11; N, 4.23. Found: C, 58.16; H, 4.01; N, 4.15.

1-[5-(2-Iodophenyl)-1H-pyrazol-4-yl]naphthalen-2-yl benzenesulfonate (16). Hydrazine dihydrochloride (98%, 2.07 mL, 27.4 mmol) was added dropwise to a stirred suspension of enaminoketone **3f** (1.60 g, 2.74 mmol) and ground Na₂CO₃ (99%, 0.19 g, 1.81 mmol) in MeOH (15 mL) and H₂O (30 mL) under atmosphere of Ar at ambient temperature. The resultant mixture was acidified to pH 4 with glacial acetic acid (1.1 mL) and heated at 100°C for 3 h. After cooling, the mixture was partially concentrated (~1/2 v.) in vacuo, and extracted with DCM (5 x 10 mL). The organic extract was successively washed with brine (1 x 10 mL) and H₂O (1 x 10 mL), dried (anh. Na₂SO₄), filtered off and the solvent was removed in vacuo. The crude mixture was flash chromatographed on silica gel with 88% DCM/EtOAc as eluant affording pyrazole **16** (0.98 g, 65%) as a viscous yellow oil; *R_f* 0.42 (20% EtOAc/DCM); ¹H NMR (CDCl₃) δ 4.85 (1H, bs), 6.89 (1H, dd, *J* = 8.8, 2.4 Hz), 7.05-7.14 (3H, m), 7.36-7.61 (8H, m), 7.73-8.89 (4H, m); ¹³C NMR (CDCl₃) δ 98.1, 121.1, 122.8, 126.0, 126.6, 126.8, 127.7, 128.0, 129.4, 129.8, 131.3, 132.0, 133.1, 133.9,

135.7, 136.6, 139.3, 144.9; FTIR (neat film, cm^{-1}): 3350, 1580, 1370, 1170; EIMS (m/z , %) 552 (M^+ , 10), 412 (47), 284 (7), 255 (62), 77 (100). Anal. Calcd for $\text{C}_{25}\text{H}_{18}\text{IN}_2\text{O}_3\text{S}$: C, 54.36; H, 3.10; N, 5.07. Found: C, 54.04; H, 2.73; N, 5.33

Synthesis of *o,o'*-Halohydroxy-4,5-diarylpyrazoles (**2**).

5-(2-Hydroxyphenyl)-4-(2-iodophenyl)-1-phenylpyrazole (2a). To a suspension of pyrazole **3a** (2.0 g, 3.38 mmol) and TEBA (98%, 6.3 mg, 27 μmol) in MeOH (140 mL) in a screw-capped tube, 3.25 M NaOH (140 mL) was added and after homogenization and closure of the tube, the resultant mixture was heated in an autoclave at 140°C for 9 h. After cooling to ambient temperature, the formed gel was decanted and the phases were separated. The aqueous layer was acidified with 12M HCl at pH 4, as a gelatinous white solid deposited, and extracted with DCM (3 x 25 mL). The combined organic extracts were washed with saturated aqueous NaHCO_3 (1 x 50 mL), dried (anh. Na_2SO_4), filtered off and the solvent was removed in vacuo. The residue was absorbed on silica gel (6 g) and flash chromatographed using DCM as eluant. The resultant pure oil was crystallized from 10% DCM/hexanes affording halophenolic pyrazole **2a** (1.30 g, 88%) as a white powder: mp 123-124°C (DCM/hexanes); *Rf* 0.5 (2% EtOAc/DCM); ^1H NMR (CDCl_3) δ 5.40 (1H, bs, exc. D_2O), 6.74-6.81 (2H, m), 6.92-7.00 (2H, m), 7.15-7.34 (8H, m), 7.89 (1H, d, $J = 8.5$ Hz), 7.90 (1H, s); ^{13}C NMR (CDCl_3) δ 100.6, 116.1, 120.3, 124.0, 126.1, 127.3, 127.9, 128.5, 128.9, 130.7, 131.2, 131.6, 136.3, 137.3, 139.2, 139.6, 140.9, 154.0; FTIR (neat film, cm^{-1}): 3150, 1596; EIMS (m/z , %) 438 (M^+ , 100), 311 (74), 293 (16), 284 (17), 181 (17), 152 (14), 77 (29). Anal. Calcd for $\text{C}_{21}\text{H}_{15}\text{IN}_2\text{O}$: C, 57.55; H, 3.45; N, 6.39. Found: C, 57.25; H, 3.59; N, 6.28.

4-(5-Chloro-2-hydroxyphenyl)-5-(2-iodophenyl)-1-phenylpyrazole (2b). Typical procedure. To a stirred suspension of K^tBuO (95%, 0.54 g, 4.57 mmol) in anhydrous DMF (5 mL) cooled at 0°C under atmosphere of Ar, a solution of pyrazole **3b** (0.56 g, 0.91 mmol) in the same solvent (1.5 mL) was added dropwise. After stirring for 25 min, the reaction mixture was poured into 1.37 M HCl (65 mL) and further stirred for additional 30 min. The mixture was extracted with DCM (3 x 15 mL). The organic layer was washed with saturated aqueous NaHCO_3 (1 x 10 mL), dried (anh. Na_2SO_4), filtered off and the solvent was removed in vacuo. The crude oil was flash chromatographed on silica gel eluting with the gradient 2→5% EtOAc/DCM. The pure eluate was crystallized from 10% DCM/hexanes affording halophenolic pyrazole **2b** (0.30 g, 69%) as a snowy white solid: mp 226-227°C (DCM/hexanes); *Rf* 0.38 (4% EtOAc/DCM); ^1H NMR (CDCl_3) δ 5.30 (1H, bs, OH, exc D_2O), 6.81 (1H, d, $J = 8.6$ Hz), 6.93 (1H, d, $J = 2.5$ Hz), 7.03 (1H, dd, $J = 8.6, 2.5$ Hz), 7.22-7.31 (7H, m), 7.36 (1H, dd, $J = 8.0, 1.6$ Hz), 7.78 (1H, dd, $J = 8.0, 1.6$ Hz), 7.91 (1H, s); ^{13}C NMR (CDCl_3) δ 100.3, 116.9, 120.0, 124.4, 124.9, 127.7, 128.4, 128.8, 130.3, 130.8, 132.1, 134.7, 139.7, 139.6, 140.2, 152.1; FTIR (neat film, cm^{-1}): 3100, 1594; EIMS (m/z , %) 474 ($\text{M}+2$, 34), 472 (M^+ , 100), 346 (46), 345 (84), 77 (89). Anal. Calcd for $\text{C}_{21}\text{H}_{14}\text{ClIN}_2\text{O}$: C, 53.36; H, 2.98; N, 5.93. Found: C, 53.11; H, 3.19; N, 5.69.

By using the same procedure and starting from the appropriate intermediate compound of preceding step, the following products were obtained:

4-(3,5-Dichloro-2-hydroxyphenyl)-5-(2-iodophenyl)-1-phenylpyrazole (2c): 82%, as a white powder; mp 195-196°C (DCM/hexanes); *R_f* 0.45 (4% EtOAc/DCM); ¹H NMR (CDCl₃) δ 5.76 (1H, bs, OH, exc. D₂O), 6.75 (1H, d, *J* = 2.4 Hz), 7.06 (1H, ddd, *J* = 8.0, 7.4, 1.8 Hz), 7.20 (1H, d, *J* = 2.4 Hz), 7.22-7.37 (7H, m), 7.81 (1H, d, *J* = 8.0, 1.6 Hz), 8.06 (1H, s); ¹³C NMR (CDCl₃) δ 100.5, 116.8, 120.9, 121.7, 124.6, 124.8, 127.3, 127.5, 128.4, 128.7, 130.7, 132.2, 135.2, 139.6, 140.6, 142.2, 147.8; FTIR (neat film, cm⁻¹): 3190, 1593; EIMS (*m/z*, %) 510 (M+4, 9), 508 (M+2, 48), 506 (M⁺, 70), 381 (61), 379 (93), 218 (35), 77 (100). Anal. Calcd for C₂₁H₁₃Cl₂IN₂O: C, 49.73; H, 2.58; N, 5.52. Found: C, 49.59; H, 2.67; N, 5.59.

5-(4,5-Dimethoxy-2-iodophenyl)-4-(2-iodophenyl)-1-phenylpyrazole (2d): 79%, as a white powder; mp 225-226°C (EtOAc); *R_f* 0.33 (10% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.66 (3H, s), 3.83 (3H, s), 5.52 (1H, bs, OH, exc. D₂O), 6.68 (1H, s), 6.78 (1H, ddd, *J* = 8.5, 7.6, 1.2 Hz), 6.88 (1H, dd, *J* = 8.3, 1.2 Hz), 6.97 (1H, dd, *J* = 7.7, 1.9 Hz), 7.13 (1H, s), 7.17 (1H, ddd, *J* = 8.5, 8.3, 1.9 Hz), 7.28-7.32 (5H, m), 7.93 (1H, s); ¹³C NMR (CDCl₃) δ 56.0, 89.0, 114.3, 115.5, 117.6, 118.6, 120.3, 121.2, 124.2, 125.3, 127.2, 128.2, 128.9, 130.7, 139.8, 140.3, 142.4, 149.1, 149.7, 153.4; FTIR (neat film, cm⁻¹): 3261, 1596; EIMS (*m/z*, %) 498 (M⁺, 39), 371 (100), 370 (20), 355 (25), 77 (35). Anal. Calcd for C₂₃H₁₉IN₂O₃: C, 55.44; H, 3.84; N, 5.62. Found: C, 55.39; H, 3.80; N, 5.69.

4-(5-*N,N*-Diethylamino-2-hydroxyphenyl)-4-(2-iodophenyl)-1-phenylpyrazole (2e), after purification by flash chromatography on silica gel eluting with the gradient 5→10% EtOAc/DCM: 64%, as an off-red oil; *R_f* 0.46 (4% EtOAc/DCM); ¹H NMR (CDCl₃) δ 1.10 (6H, t, *J* = 7.2 Hz), 3.25 (4H, q, *J* = 7.2 Hz), 4.92 (1H, bs, OH, exc. D₂O), 6.02 (1H, d, *J* = 1.8 Hz), 6.06 (1H, dd, *J* = 8.2, 1.9 Hz), 6.71 (1H, dd, *J* = 8.3, 1.4 Hz), 6.94 (1H, ddd, *J* = 8.0, 7.6, 2.0 Hz), 7.09 (1H, dd, *J* = 8.0, 1.6 Hz), 7.20 (1H, dd, *J* = 7.6, 1.2 Hz), 7.24-7.40 (5H, m), 7.89 (1H, s), 7.90 (1H, dd, *J* = 8.0, 1.2 Hz); ¹³C NMR (CDCl₃) δ 12.3, 44.1, 98.1, 100.7, 100.2, 104.7, 124.0, 125.9, 126.9, 128.1, 128.8, 128.9, 131.3, 132.0, 136.2, 137.6, 139.3, 140.0, 141.2, 150.0, 154.5; FTIR (neat film, cm⁻¹): 3218, 1621; EIMS (*m/z*, %) 509 (M+1, 82), 494 (100), 366 (23), 338 (20), 191 (22), 77 (47). Anal. Calcd for C₂₅H₂₄IN₃O: C, 58.95; H, 4.75; N, 8.25. Found: C, 59.02; H, 4.77; N, 8.39.

4-(2-Hydroxy-naphthalen-1-yl)-5-(2-iodophenyl)-1-phenylpyrazole (17): 61%, as a white powder; mp 123-124°C (DCM/hexanes); *R_f* 0.44 (20% Et₂O/DCM); ¹H NMR (CDCl₃) δ 6.85-6.93 (1H, m), 7.08 (2H, d, *J* = 4.3 Hz), 7.14 (1H, d, *J* = 9.1 Hz), 7.28-7.39 (2H, m), 7.59 (1H, d, *J* = 7.9 Hz), 7.69-7.78 (4H, m), 9.0 (1H, bs); ¹³C NMR (CDCl₃) δ 98.2, 110.6, 117.1, 123.2, 124.7, 126.5, 128.0, 128.6, 129.9, 130.3, 130.9, 134.1, 135.5, 139.5, 151.8; FTIR (neat film, cm⁻¹): 3500, 3170, 1590; EIMS (*m/z*, %) 413 (M+1, 19), 412 (M⁺, 100), 285 (31), 257 (29), 255 (22), 240 (21). Anal. Calcd for C₁₉H₁₃IN₂O: C, 55.36; H, 3.18; N, 6.80. Found: C, 55.61.02; H, 3.54; N, 6.46.

4-(2-Bromo-4,5-dimethoxyphenyl)-5-(3,4-dimethoxy-2-hydroxyphenyl)-1-phenyl pyrazole (2f). Typical procedure. A stirred suspension of pyrazole **3g** (4.01 g, 6.52 mmol) and ground KOH (99%, 1.75 g, 30.9 mmol) in a mixture of MeOH (97 mL) and H₂O (50 mL) was heated at 70°C for 2 h. After cooling, the solvent was partially concentrated (~2/3 v.) under reduced pressure. The reaction mixture was acidified with 12M HCl at pH~4 and extracted with DCM (3 x 25 mL). The organic layer was washed with saturated aqueous NaHCO₃ (1 x 10 mL), dried (anh. Na₂SO₄), filtered off and the solvent was removed in

vacuo. The residual crude oil was purified by flash chromatography on silica gel eluting with the gradient 10→20% EtOAc/DCM, and the pure eluate was crystallized from MeOH affording halophenolic pyrazole **3f** (2.70 g, 81%) as a white powder: mp 166-167°C (MeOH); *R_f* 0.39 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.57 (3H, s), 3.73 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 5.73 (1H, bs, OH, exc. D₂O), 6.34 (1H, d, *J* = 8.7 Hz), 6.60 (1H, s), 6.67 (1H, d, *J* = 8.7 Hz), 7.03 (1H, s), 7.20-7.36 (5H, m), 7.93 (1H, s); ¹³C NMR (CDCl₃) δ 55.6, 56.0, 60.3, 60.8, 103.9, 110.0, 113.8, 114.3, 115.2, 122.4, 123.6, 125.9, 126.4, 126.7, 128.4, 135.4, 136.6, 140.6, 147.6, 147.8, 148.2, 152.9; FTIR (neat film, cm⁻¹): 3418, 1601; EIMS (*m/z*, %) 512 (M+1, 100), 510 (M-1, 87), 437 (56), 399 (48), 368 (22). Anal. Calcd for C₂₅H₂₃BrN₂O₅: C, 58.72; H, 4.53; N, 5.48. Found: C, 58.61; H, 4.71; N, 5.59.

By using the same procedure and starting from the appropriate intermediate compound of preceding step, the following products were obtained:

4-(4,5-Dimethoxy-2-iodophenyl)-5-(3,4-dimethoxy-2-hydroxyphenyl)-1-phenylpyrazole (2g): 98%, as a white powder; mp 173-174°C (MeOH); *R_f* 0.39 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.61 (3H, s), 3.72 (3H, s), 3.80 (3H, s), 3.84 (3H, s), 5.76 (1H, bs, OH, exc. D₂O), 6.35 (1H, d, *J* = 8.7 Hz), 6.64 (1H, s), 6.69 (1H, d, *J* = 8.7 Hz), 7.21-7.30 (4H, m), 7.36 (2H, dd, *J* = 8.3, 1.5 Hz), 7.89 (1H, s); ¹³C NMR (CDCl₃) δ 55.5, 55.6, 56.0, 60.8, 88.4, 103.8, 110.0, 114.0, 121.1, 123.5, 125.7, 126.4, 126.7, 128.4, 130.6, 135.4, 136.5, 140.6, 147.8, 148.2, 148.5, 152.8; FTIR (neat film, cm⁻¹): 3424, 1598; EIMS (*m/z*, %) 558 (M⁺, 66), 446 (12), 431 (100), 415 (18), 400 (29), 399 (51), 383 (15), 368 (25), 77 (19). Anal. Calcd for C₂₅H₂₃IN₂O₅: C, 53.78; H, 4.15; N, 5.02. Found: C, 54.10; H, 4.26; N, 4.96.

4-(4,5-dimethoxy-2-iodophenyl)-5-(2,4-Dimethoxy-6-hydroxyphenyl)-1-phenylpyrazole (2h): 95%, as a white powder; mp 132-133°C (MeOH); *R_f* 0.33 (4% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.41 (3H, s), 3.52 (3H, s), 3.71 (3H, s), 3.84 (3H, s), 5.37 (1H, bs, OH, exc. D₂O), 5.92 (1H, d, *J* = 2.2 Hz), 6.00 (1H, d, *J* = 2.2 Hz), 6.57 (1H, s), 7.23-7.36 (6H, m), 7.99 (1H, s); ¹³C NMR (CDCl₃) δ 55.3, 55.4, 55.5, 56.0, 87.6, 91.6, 92.9, 98.1, 113.4, 121.2, 123.4, 126.7, 127.1, 128.6, 129.6, 130.1, 133.6, 139.1, 140.1, 141.2, 148.6, 148.8, 155.5, 159.0, 162.7; FTIR (neat film, cm⁻¹): 3389, 1619; EIMS (*m/z*, %) 558 (M⁺, 100), 432 (34), 431 (68), 430 (36), 416 (11), 415 (15), 414 (17), 400 (96), 385 (25), 372 (10), 357 (14), 215 (14), 77 (65). Anal. Calcd for C₂₅H₂₃IN₂O₅: C, 53.78; H, 4.15; N, 5.02. Found: C, 53.91; H, 4.21; N, 5.08.

Attempts at synthesis of arylboronic acids

1,4-Diphenyl-5-[(*p*-toluensulfonyloxy)phenyl]pyrazole (18c). Typical procedure. A stirred solution of pyrazole **15a** (0.91 g, 1.54 mmol) in anhydrous THF (50 mL) precooled at -78°C under atmosphere of Ar, was treated with *n*-BuLi (2.2 mL, 1.48 M solution in hexanes, 3.3 mmol). After total addition, the dark-colored solution was stirred for 35 min at this temperature, followed by the dropwise addition of a solution of freshly tridistilled trimethylborate (0.5 mL, 4.6 mmol) in anhydrous THF (5 mL). The resultant pale yellow reaction mixture was kept under stirring at -78°C for additional 2 h, and at this point was quenched with 0.6 M HCl (100 mL). The mixture was allowed to warm up gradually to ambient temperature, further stirred for 15 min and poured into brine (10 mL). The phases were separated and the aqueous layer was extracted with Et₂O (5 x 25 mL). The combined organic extracts were successively washed with H₂O (1 x 15 mL) and brine

(1 x 15 mL), dried (anh. Na₂SO₄), filtered off, and the solvent was removed in vacuo. The sticky orange residue was cleaned up by flash column chromatography on silica gel eluting with the gradient 15→40% EtOAc/hexanes and purified by preparative HPLC (15% EtOAc/hexanes, 6 ml/min) affording pyrazole **18c** (0.39 g, 54%) as a colorless oil; *R_f* 0.62 (DCM); ¹H NMR (CDCl₃) δ 2.30 (3H, s), 6.96-6.99 (2H, m), 7.13-7.24 (10H, m), 7.36 (2H, d, *J* = 8.7 Hz), 7.85 (1H, s); ¹³C NMR (CDCl₃) δ 21.6, 123.7, 124.1, 124.3, 126.5, 127.2, 127.4, 128.2, 128.5, 129.6, 130.7, 132.1, 132.4, 132.8, 139.4, 139.9, 145.3, 146.8; FTIR (neat film, cm⁻¹): 1597, 1378, 1166; EIMS (*m/z*, %) 466 (M⁺, 100), 311 (63), 284 (20), 254 (15), 181 (12). Anal. Calcd for C₂₈H₂₂N₂O₃S: C, 72.08; H, 4.75; N, 6.00. Found: C, 72.00; H, 4.70; N, 6.09.

The same procedure on halophenolic pyrazole **2a** provided, after crystallization from 20% EtOAc/hexanes, **1,4-diphenylpyrazole-5-(2-hydroxyphenyl)pyrazole (18a)** as prismatic crystals: 71%; mp 182-183°C (EtOAc/hexanes); *R_f* 0.27 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 5.13 (1H, bs), 7.01 (1H, dd, *J* = 7.5, 1.6 Hz), 7.21-7.32 (13H, m); 8.02 (1H, s); ¹³C NMR (CDCl₃) δ 116.3, 116.9, 120.9, 124.4, 126.8, 127.4, 128.7, 128.8, 131.0, 131.7, 139.6, 140.2, 153.9; FTIR (neat film, cm⁻¹): 3265, 1596; EIMS (*m/z*, %) 312 (M⁺, 100), 295 (13), 149 (28), 77 (31). Anal. Calcd for C₂₁H₁₆N₂O: C, 80.75; H, 5.16; N, 8.97. Found: C, 81.03; H, 5.22; N, 8.86.

The same procedure on halophenolic pyrazole **2g** provided, after crystallization from Et₂O, **5-(3,4-dimethoxy-2-hydroxyphenyl)-(3,4-dimethoxyphenyl)pyrazole (18b)**: 44%, as an off-yellow powder; mp 183-185°C (Et₂O); *R_f* 0.38 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.65 (3H, s), 3.80 (3H, s), 3.85 (6H, s), 5.89 (1H, s, exc. D₂O), 6.42 (1H, d, *J* = 8.7 Hz), 6.75 (1H, d, *J* = 2.0 Hz), 6.78 (1H, d, *J* = 8.3 Hz), 6.90 (1H, dd, *J* = 8.3, 2.0 Hz), 7.21-7.35 (5H, m), 7.94 (1H, s); ¹³C NMR (CDCl₃) δ 55.3, 55.7, 60.9, 104.0, 110.3, 110.5, 111.0, 119.3, 122.7, 124.1, 125.7, 126.7, 128.5, 134.6, 135.6, 138.9, 140.3, 147.4, 148.1, 148.5, 153.0; FTIR (neat film, cm⁻¹): 3403, 1603; EIMS (*m/z*, %) 432 (M⁺, 100), 417 (37), 77 (34). Anal. Calcd for C₂₅H₂₄N₂O₅: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.35; H, 5.71; N, 6.68.

The same procedure on *O*-protected pyrazole **15g** provided **4-(2-benzoyl-4,5-dimethoxyphenyl)-5-(3,4-dimethoxy-2-hydroxyphenyl)-1-phenylpyrazole (19)**: 56%, as a colorless oil; *R_f* 0.26 (2% EtOAc/DCM); ¹H NMR (CDCl₃) δ 3.71 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 6.27 (1H, d, *J* = 8.4 Hz), 6.41 (1H, s, exc. D₂O), 6.54 (1H, d, *J* = 8.4 Hz), 6.77 (1H, s), 6.91 (1H, s), 7.18-7.24 (5H, m), 7.35 (2H, dd, *J* = 7.9, 7.9 Hz), 7.47 (1H, d, *J* = 7.2 Hz), 7.54 (1H, s), 7.67 (2H, dd, *J* = 7.1, 1.2 Hz); ¹³C NMR (CDCl₃) δ 55.6, 56.0, 60.7, 103.8, 109.8, 112.3, 113.7, 121.8, 124.1, 126.2, 126.4, 128.0, 128.5, 130.2, 130.9, 132.7, 135.6, 135.9, 140.1, 140.2, 147.1, 148.3, 150.3, 153.2, 197.4; FTIR (neat film, cm⁻¹): 3400, 1657, 1599; EIMS (*m/z*, %) 536 (M⁺, 11), 296 (17), 260 (11), 163 (27), 105 (100), 77 (37). Anal. Calcd for C₃₂H₂₈N₂O₆: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.69; H, 5.42; N, 5.37.

Table S1. Radiolabeled binding assay screen for selected dibenzoxepino[4,5-*d*]pyrazoles 1 on central and peripheral nervous system receptors.

Receptor	Subtype ^c	Radioligand	Species ^d /Tissue	Inhibition (%) ^{a,b}					
				1a	1b	1c	1d	1g	1h
Serotonin	5-HT _{1A}	[³ H]-8-OH-DPAT	R/ Hippocampus	-3.91	0.86	-5.44	-4.44	-4.18	-4.49
	5-HT _{2A}	[³ H]-Ketanserine	R/ total Cortex	9.02	9.02	7.64	1.34	0.35	3.2
	5-HT ₃	[³ H]-LY278584	R/ entorrinal. Cortex	12.2	6.33	7.14	-5.28	4.48	1.13
Muscarinic	5-HT uptake	[³ H]-Paroxetine	R/ total Cortex	10.22	1.4	23.08	16.88	13.39	11.15
	Inespecific	[³ H]-QNB	R/ total Cortex	13.64	13.37	13.47	11.97	7.86	16.98
Dopamine	D ₁	[³ H]-SCH-23390	R/ striatum.	7.09	4.75	6.73	5.89	2.86	6.21
	D ₂	[³ H]-Raclopride	R/ striatum.	23.76	19.19	32.26	27.91	19.6	40.62
	DOPA uptake	[³ H]-WIN-35,428	R/ striatum.	1.43	-2.02	-9.65	11.9	7.79	-5.55
Noradrenaline	α ₁	[³ H]-Prazosin	R/ total Cortex	7.03	7.55	5.01	10.63	12.21	12.57
	α ₂	[³ H]-RX-821002	R/ total Cortex	15.85	13.2	17.3	10.84	13.43	15.95
Histamine	NA uptake	[³ H]-Nisoxetine	R/ total Cortex	1.41	6.23	-8.66	4.86	-3.15	-3.24
	H ₁	[³ H]-Pirylamine	G/ Cerebellum	12.64	19.61	18.48	10.94	6.61	18.35

^a Percentage of inhibition of specific binding at 1μM concentration. ^b The tested compounds were dissolved in DMSO and then dilute with the appropriate buffer for each receptor binding assay. ^c HT: Hydroxytryptamine, DOPA: Dopamine, NA: Noradrenaline. ^d G: Guinea-pig R: Rat.

5-HT_{1A} receptor⁵

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Hippocampus used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 0.32 mol/l sucrose buffer, centrifuged at 900 x g for 10 min (4°C) and the supernatant was recentrifuged at 48000 x g for 25 min (4°C). The resultant pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4), incubated at 37°C for 15 min and then centrifuged once more at 48000 x g for 25 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer containing 2 mmol/l CaCl₂, 1 mmol/l MgCl₂, 1 mmol/l MnCl₂ and 0.1 % ascorbate, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer with 10 µmol/l pargyline (final dilution 1:100, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-8-OH-DPAT (Amersham, 221 Ci/mmol) in buffer (final concentration 0.3-0.5 nmol/l). Non-specific binding was determined using 10 µmol/l cold 5-HT. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (450-600 µg of protein). After incubation for 60 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.4) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

5-HT_{2A} receptor⁶

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Prefrontal cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 0.25 mol/l sucrose buffer, centrifuged at 1080 x g for 10 min (4°C) and the supernatant was recentrifuged at 35000 x g for 10 min (4°C). The resultant pellet was resuspended in 40 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.7), and then centrifuged once more at 35000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer (final dilution 1:60, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration in Tris-HCl buffer with 10% ethanol (0.1 ml of Tris-ethanol buffer if no competing drug was added) and 0.1 ml of [³H]Ketanserin (NEN, 60-90 Ci/mmol) in Tris-ethanol buffer (final concentration 0.8 nmol/l). Non-specific binding was determined using 1 µmol/l cold methysergide. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (400-500 µg of protein). After incubation for 15 min at 37°C the reaction was stopped for vacuum filtration through Whatman GF/B glass pretreated filters (1 % polyethylenimine in 50 mmol/l Tris-HCl buffer), using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.7) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

5-HT₃ receptor⁷

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Entorhinal cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 0.32 mol/l sucrose buffer, centrifuged at 1000 x g for 10 min (4°C) and the supernatant was recentrifuged at 17000 x g for 20 min (4°C). The resultant pellet was resuspended in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4), incubated at 37°C for 10 min and then centrifuged three time more at 48000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer containing 5 mmol/l CaCl₂ and 0.1% ascorbate, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer with 10 µmol/l pargyline (final dilution 1:40, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-**LY278584** (Amersham, 60-85 Ci/mmol) in buffer (final concentration 2 nmol/l). Non-specific binding was determined using 10 µmol/l cold 5-HT. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (500-600 µg of protein). After incubation for 30 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass pretreated filters (1 % polyethylenimine in 50 mmol/l Tris-HCl buffer), using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.4) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

5-HT transporter⁸

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 20 volumes of ice-cold 50 mmol/l Tris-HCl (pH 7.4) buffer and centrifuged at 48000 x g for 10 min (4°C). The resultant pellet was resuspended in 20 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4), incubated at 37°C for 10 min and then centrifuged once more at 48000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer containing 120 mmol/l NaCl and 5 mmol/l KCl, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold Tris-saline buffer (final dilution 1:100, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-Paroxetine (NEN, 15 Ci/mmol) in buffer (final concentration 0.2 nmol/l). Non-specific binding was determined using 10 µmol/l cold Fluoxetine. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (550-600 µg of protein). After incubation for 60 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.4) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

Muscarinic receptors⁹

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 20 volumes of ice-cold 50 mmol/l Phosphate buffer (pH 7.4) centrifuged at 20000 x g for 15 min (4°C). The supernatant was eliminated and the resultant pellet was resuspended in 20 volumes of ice-cold 50 mmol/l Phosphate buffer (pH 7.4), and then centrifuged once more at 20000 x g for 15 min (4°C). The final pellet was resuspended in 100 volumes of ice-cold 50 mmol/l Phosphate buffer and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer (final dilution 1:700, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-QNB (NEN, 49 Ci/mmol) in buffer (final concentration 0.2 nmol/l). Non-specific binding was determined using 10 µmol/l cold Atropine. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (150 µg of protein). After incubation for 60 min at 37°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Phosphate buffer (pH 7.4). Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

D₁ receptor¹⁰

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Striatum used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.7), centrifuged at 48000 x g for 10 min (4°C). The resultant pellet was resuspended in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.7), incubated at 37°C for 10 min and then centrifuged once more at 48000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4) containing: 120 mmol/l NaCl, 5 mmol/l KCl, 2 mmol/l CaCl₂, 10 µmol/l pargylyne and 0.01% ascorbate, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer (final dilution 1:200, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-SCH-23390 (NEN, 70.3 Ci/mmol) in buffer (final concentration 0.35 nmol/l). Non-specific binding was determined using 3 µmol/l cold R(+)-SCH-23390. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (450-500 µg of protein). After incubation for 60 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.7) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

D₂ receptor¹¹

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Striatum used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.7), centrifuged at 48000 x g for 10 min (4°C). The resultant pellet was resuspended in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.7), incubated at 37°C for 10 min and then centrifuged once more at 48000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4) containing: 120 mmol/l NaCl, 5 mmol/l KCl, 2 mmol/l CaCl₂ and 0.01% ascorbate, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer with 10 mol/l pargyline (final dilution 1:150, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-Raclopride (NEN, 60-87 Ci/mmol) in buffer (final concentration 1 nmol/l). Non-specific binding was determined using 1 µmol/l cold (+)-butaclamol. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (300-400 µg of protein). After incubation for 60 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.7) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

Dopamine transporter¹²

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Striatum used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 10 volumes of ice-cold 10 mmol/l phosphate buffer (pH 7.4) + 0.32 mol/l sucrose and centrifuged at 47800 x g for 10 min (4°C). The resultant pellet was resuspended in 10 volumes of ice-cold 10 mmol/l Phosphate buffer (pH 7.4), and then centrifuged twice more at 478000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 10 mmol/l phosphate buffer (pH 7.4) and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer (final dilution 1:140, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-WIN-35428 (NEN, 83.5 Ci/mmol) in buffer (final concentration 0.5 nmol/l). Non-specific binding was determined using 10 µmol/l cold Mazindol. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (400 µg of protein/ml). After incubation for 120 min at 4°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 10 mmol/l Phospahte buffer (pH 7.4). Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

α_1 receptor¹³

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer pH 7.4 with 100 mmol/l NaCl and 2 mmol/l EDTA. The homogenate was filtered through four layers of antiseptic gauze and centrifuged at 47800 x g for 20 min (4°C). The resultant pellet was resuspended in 50 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.4), with 1 mmol/l EDTA, incubated at 37°C for 10 min and then centrifuged three times more at 47800 x g for 20 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer with 1 mmol/l EDTA, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer with (final dilution 1:200, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-Prazosin (NEN, 77.2 Ci/mmol) in buffer (final concentration 0.1-0.2 nmol/l). Non-specific binding was determined using 10 µmol/l cold phentolamine. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (150-200 µg of protein). After incubation for 45 min at 30°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, presoaked in 0.3% polyethylenimine for 5 min, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl (pH 7.4) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

α_2 receptor¹⁴

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 50 volumes of ice-cold 20 mmol/l sodium bicarbonate. The homogenate was filtered through four layers of antiseptic gauze and centrifuged at 1000 x g for 20 min (4°C) and the supernatant was recentrifuged at 47800 x g for 20 min (4°C). The resultant pellet was resuspended in 10 volumes of ice-cold 50 mmol/l Tris-HCl buffer (pH 7.5), with 0.5 mmol/l EDTA and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer with EDTA (final dilution 1:30, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-RX821002 (Amersham, 56 Ci/mmol) in buffer (final concentration 0.5-1 nmol/l). Non-specific binding was determined using 10 µmol/l cold phentolamine. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (600 - 750 µg of protein). After incubation for 60 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l Tris-HCl + EDTA (pH 7.5) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

Noradrenaline transporter¹⁵

Adult male Wistar rats weighing 220-280 g, were used. Animals were killed by decapitation and the whole brain with the exception of the brainstem and cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebral cortex used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 30 volumes of ice-cold 50 mmol/l Tris-HCl buffer containing 120 mmol/l NaCl and 5 mmol/l KCl (pH 7.4) and centrifuged at 40000 x g for 10 min (4°C). The resultant pellet was resuspended in 30 volumes of ice-cold 50 mmol/l Tris-HCl saline buffer (pH 7.4), incubated at 37°C for 10 min and then centrifuged once more at 40000 x g for 10 min (4°C). The resuspension and centrifugation of the resultant pellet was repeated twice more in the same conditions. The final pellet was resuspended in 5 volumes of ice-cold 10 mmol/l phosphate buffer containing 120 mmol/l NaCl and 5 mmol/l KCl, and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold phosphate-saline buffer (final dilution 1:70, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-**Nisoxetine** (NEN, 85 Ci/mmol) in buffer (final concentration 0.5-1 nmol/l). Non-specific binding was determined using 10 µmol/l cold Mazindol. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (550-600µg of protein). After incubation for 30 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 10 mmol/l phosphate-saline (pH 7.4) buffer. Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

H₁ receptor¹⁶

Adult male guinea-pigs weighing 400-600 g, were used. Animals were killed by decapitation and the whole brain with the cerebellum was quickly removed and the various areas dissected, weighed and immediately frozen at -70°C. Cerebellum used for the binding experiments was homogenized with an Ultra-Turrax (setting 5 for 20 s) in 30 volumes of ice-cold 50 mmol/l phosphate buffer (pH 7.5), centrifuged at 30000 x g for 10 min (4°C). The resultant pellet was resuspended in 30 volumes of ice-cold 50 mmol/l phosphate buffer (pH 7.5), and then centrifuged three times more at 30000 x g for 10 min (4°C). The final pellet was resuspended in 10 volumes of ice-cold 50 mmol/l phosphate buffer (pH 7.5) and was stored at -70°C until use. At time of experiment, the membranes were diluted in the same ice-cold buffer (final dilution 1:80, wt./vol.). Competition assays were performed in triplicate, in a final volume of 1 ml. To each assay tube were added the following: 0.1 ml of the displacer drug concentration (0.1 ml of vehicle if no competing drug was added) and 0.1 ml of [³H]-Pyrilamine (NEN, 23 Ci/mmol) in buffer (final concentration 1 nmol/l). Non-specific binding was determined using 10 µmol/l cold Astemizole. Binding experiment was initiated by addition of 0.8 ml of membrane suspension (600 µg of protein/ml). After incubation for 30 min at 25°C the reaction was stopped for vacuum filtration through Whatman GF/B glass filters, using a Brandel Cell Harvester, followed by two washes with 5 ml of ice-cold 50 mmol/l phosphate buffer (pH 7.5). Filters were placed in scintillating polyethylene vials (with 5 ml scintillation cocktail), equilibrated, and filter-retained radioactivity measured in a liquid scintillation counter (Kontron Beta V).

References

- (1) Olivera, R.; SanMartin, R.; Domínguez, E. *J. Org. Chem.*, **2000**, *65*, 6398-6411.
- (2) Rousell-Uclaf **Fr. M.** 4771 (CA: 69: 59475).
- (3) Weispraber, K.H.; Weiss, U. *J. Chem. Soc., Perkin Trans 1*, **1972**, 83-88.
- (4) Domínguez, E.; Lete, E.; Villa, M.J.; Iriando, C. *Heterocycles*, **1984**, *22*, 1217-1224.
- (5) Hoyer, D.; Engel, G.; Kalkman, H.O. "Molecular pharmacology of 5-HT_{1A} and 5-HT₂ recognition sites in rat and pig brain membranes: radioligand binding studies with [³H]-5-HT, [³H]-8-OH-DPAT, (-) [¹²⁵I]-iodocyanopindolol, [³H]-mesulergine and [³H]-ketanserin". *Eur. J. Pharmacol.*, **1985**, *118*, 13-23.
- (6) Leysen, J.E.; Niemegeers, C.J.E.; Van Nueten, J.M.; Laduron, P.M. "[³H]-Ketanserin (R 41 468), a selective ³H-ligand for serotonin₂ receptor binding sites". *Mol. Pharmacol.*, **1982**, *21*, 301-304.
- (7) Wong, D.T.; Robertson, D.W.; Reid, L.R. "Specific [³H]-LY278584 binding to 5-HT₃ recognition sites in rat cerebral cortex". *Eur. J. Pharmacol.*, **1989**, *166*, 107-110.
- (8) Mathis, C.A.; Taylor, S.E.; Enas, J.D.; Akgün, E. "Binding potency of 6-nitroquipazine analogues for the 5-hydroxytryptamine reuptake complex". *J. Pharm. Pharmacol.*, **1994**, *46*, 751-754.

- (9) Watson, M.; Roeske, W.R.; Yamamura, H.I. “[³H]-Pirenzepine and [³H]-Quinuclidinyl Benzilate binding to rat cerebral cortical and cardiac muscarinic cholinergic sites: Characterization and regulation of antagonist binding to putative muscarinic subtypes”. *J. Pharmacol. Exp. Ther.*, **1986**, *237*, 419-427.
- (10) Hess, E.J.; Battaglia, G.; Norman, A.B.; Iorio, L.C.; Creese, I. “Guanine nucleotide agonist interactions at [³H]-SCH23390-labeled D₁ receptor in rat striatum”. *Eur. J. Pharmacol.*, **1986**, *121*, 28-31.
- (11) Kohler, C.; Hall, H.; Ogren, S.O.; Gawell, L. “Specific *in vitro* and *in vivo* binding of [³H]-Raclopride. A potent substituted benzamide drug with high affinity for dopamine D₂ receptors in the rat brain”. *Biochem. Pharmacol.*, **1985**, *34*, 2251-2259
- (12) Madras, B.K.; Spealmen, R.D.; Fahey, M.A.; Neumeyer, J.L.; Saha, J.K.; Milius, R.A. “Cocaine receptors labeled with [³H]-2β-carbomethoxy-3β-(4-fluorophenyl)tropane”. *Mol. Pharmacol.*, **1989**, *36*, 518-524
- (13) Oshita, M.; Kigoshi, S.; Muramatsu, I. “Three distinct binding sites for [³H]-Prazosin in the rat cerebral cortex”. *Br. J. Pharmacol.*, **1991**, *104*, 961-965
- (14) Erdbrügger, W.; Raulf, M.; Otto, T.; Michel, M.C. ”Does [³H]-2-methoxy-Idazoxan (RX821002) detect more alpha₂-adrenoceptor agonist high affinity sites than [³H]-Rauwolscine?. A comparison of nine tissues and cell lines”. *J. Pharmacol. Exp. Ther.*, **1995**, *273*, 1287-1294
- (15) Tejani-Butt, S.M. “[³H]Nisoxetine: a radioligand for quantitation of norepinephrine uptake sites by autoradiography or by homogenate binding”. *J. Pharmacol. Exp. Ther.*, **1992**, *260*, 427-436
- (16) Benavides, J.; Schoemaker, C.; Dana, Y.; Claustre, M.; Delahaye, M.; Prouteau, P.; Manoury, P.; Allen, J.; Scatton, B.; Langer, S.Z.; Arbilla, S. “*In vivo* and *in vitro* interaction of the novel selective histamine H₁ receptor antagonist Mizolastine with H₁ receptors in the rodent”. *Arzneim. Forsch/Drug Res.*, **1995**, *45*, 551-558.