4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Derivatives. II.[1] Their Renal Vasodilation Activity and Structure–Activity Relationship

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A series of 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline derivatives showed potent DA_1 agonistic activities. We investigated the structure–activity relationship of the racemic compounds of this series. 4-(3,4-Dihydroxyphenyl)-7-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline (43) was identified as a potent renal vasodilator with activity almost equal to that of YM435 (1).

Key words 4-phenyltetrahydroisoquinoline; structure–activity relationship; renal vasodilation; methanesulfonamide; DA_1

There are at least two distinct subtypes of peripheral dopamine receptors[2] and stimulation of the DA_1 receptor leads to direct smooth muscle relaxation.[1] Previously, we reported that YM435, (*S*)-(−)-4-(3,4-dihydroxyphenyl)-7,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**1**), is a potent DA_1 agonist and cause renal vasodilation, while its *R*-isomer has no agonistic activity on the DA_1 receptor.[1,3] In the case of the benzazepin derivatives, fenoldopam and SKF-87516 (**2**), however, only the *R*-isomer showed agonistic activity on the DA_1 receptor.[4] As shown in the figure, both **1** and (*R*)-**2** involve a dopamine skeleton, namely N(2)–C(3)–C(4)–Ar[C(1′)–C(6′)] for **1**, and N(3)–C(4)–C(5)–Ar[C(5a)–C(9a)] for (*R*)-**2**. After comparing these compounds, it was found that the relative configurations around the asymmetric carbons of the dopamine skeletons, C(4) for **1** and C(1) for (*R*)-**2**, were the same. We postulated that the dopamine skeleton is essential for DA_1 agonistic activity. Thus, we studied the effects of substituents on the 5, 6, 7, and 8 positions in a series of 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline derivatives to identify a more potent agonist. In this paper, we describe the synthesis and structure–activity relationships (SAR) of the 4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline derivatives.

Chemistry

We previously reported the synthesis of **37** and **39**.[1] Many compounds described in this report could be synthesized using the same method. They are shown in Chart 1. A secondary aminoalcohol **4** was prepared from the corresponding benzaldehyde or benzoic acid. When benzaldehyde was used, 1-(3,4-dimethoxyphenyl)-2-aminoethanol was condensed with benzaldehyde to give the imine, which was reduced *in situ* with sodium borohydride to **4**. In contrast, benzoic acid was isolated as the hydroxyamide derivative, followed by reduction to **4** with borane. Compound **4** was then cyclized to **5** under acidic conditions. Finally, deprotection with boron tribromide or aqueous hydrobromic acid gave the desired compounds.

As shown in Chart 2, during the synthesis of **32** and of **38**, each bearing methoxy groups, the above method could not be used, because of the difficulty in selectively deprotecting the methyl groups on the 3′- and 4′-position. We therefore used Bobbitt's method,[5] in which reductive condensation of *o*-anisaldehyde or 2,3-dimethoxybenzaldehyde and 1-amino-3,3-diethoxypropane gave the diethylacetal intermediate **7**. Treatment of **7** with catechol in 6 N aqueous hydrochloric acid gave the 4-(3,4-dihydroxyphenyl)tetrahydroisoquinolines **32** and **38**.

The 8-chloro-7-hydroxy compound **41** was prepared from the corresponding intermediate **8** (Chart 3). A nitro group on the 7 position of **9**, whose N(2) was protected with the benzyl group, was hydrogenated using Raney nickel as a catalyst. The obtained amino group of **10** was converted to a chloro group *via* the diazonium salt by means of the Sandmeyer reaction.[6] The protecting groups of **11** were then removed in sequence, by hydrogenation for the benzyl group and heating in aqueous hydrobromic acid for the O-methyl groups, to give **41**.

The above intermediate **9** was also converted to **42** (Chart 4). Removal of the O-methyl groups by boron tribromide treatment gave **13** and subsequent hydrogenation achieved simultaneous reduction of the nitro group and deprotection of N(2).

The synthesis of **43** is shown in Chart 5. The N(2) of **14** was protected with an acetyl group. Compound **15** thus obtained was treated with boron tribromide to give **16**,

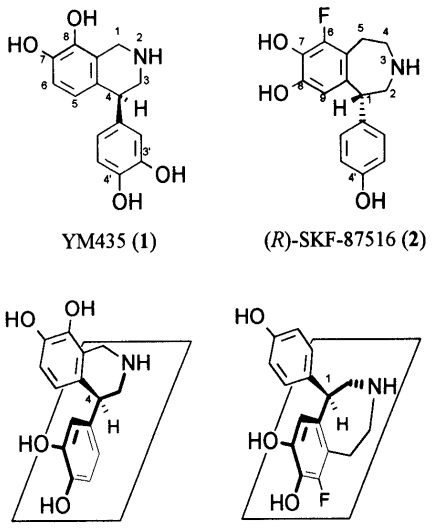

Fig. 1

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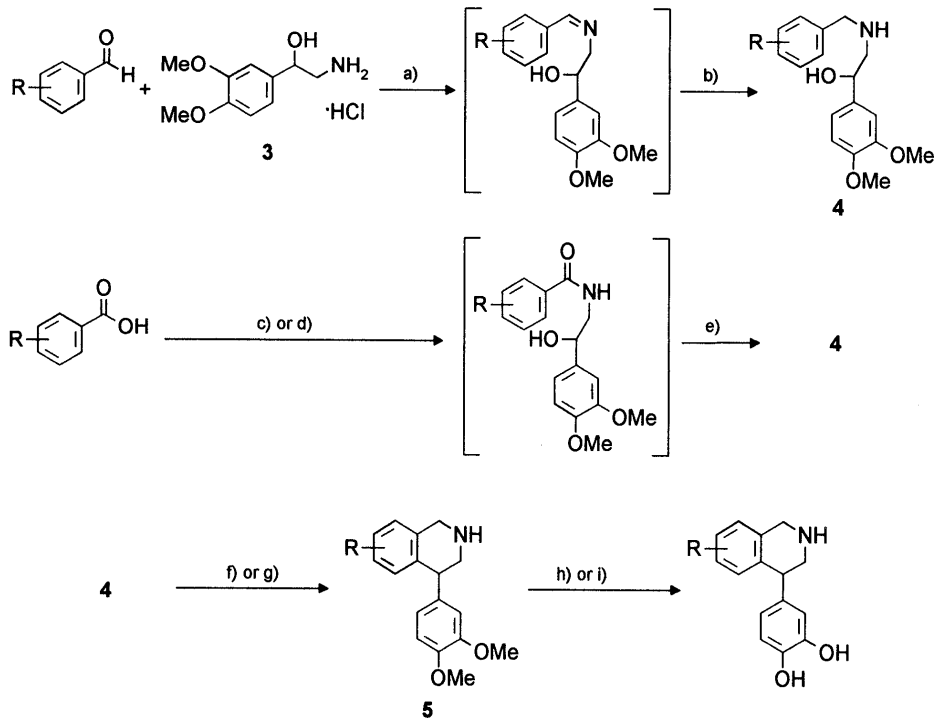
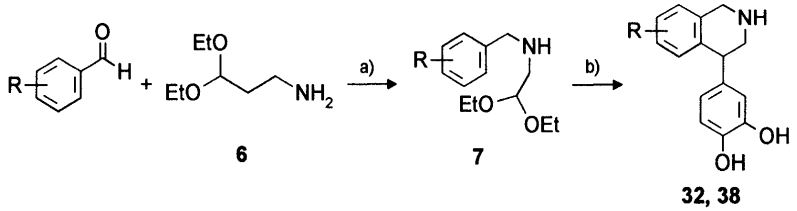


a) Et_3N, MeOH; b) $NaBH_4$, MeOH; c) $EtNCN(CH_2)_3NMe_2 \cdot HCl$, N-methylmorpholine, CH_2Cl_2 then **3**; d) $SOCl_2$ then **3**, Et_3N, CH_2Cl_2; e) BH_3, THF; f) H_2SO_4, CF_3CO_2H; g) aqueous HCl; h) BBr_3, CH_2Cl_2; i) 48% aqueous HBr

Chart 1



a) $NaBH_4$, MeOH; b) catechol, aqueous 6N HCl

Chart 2

the acetyl group of which was hydrolyzed with refluxed aqueous hydrochloric acid–ethanol to afford **43**. Compounds **44** and **46** were prepared by the same method.

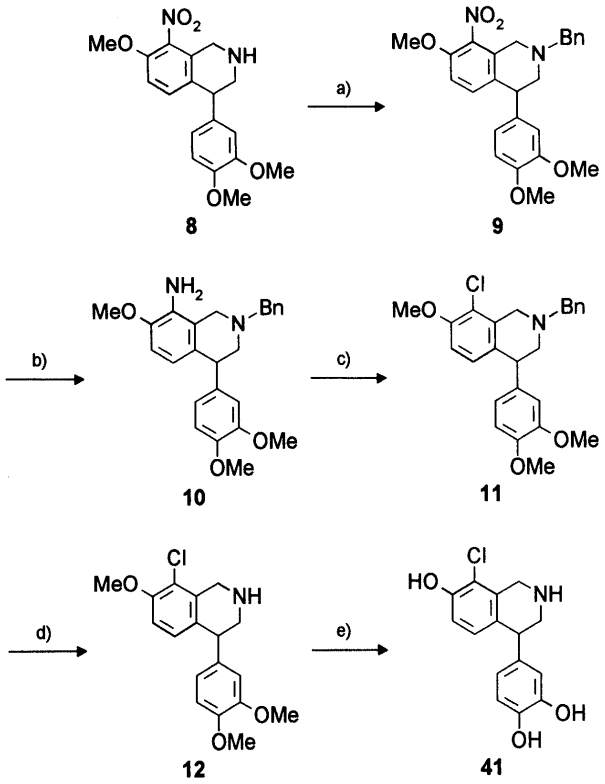
Furthermore, **45** was derived from another intermediate, **10** (Chart 6). The primary amino group at the 8 position of **10** was converted to the methanesulfonamide. The obtained **17** was then deprotected in sequence, by hydrogenation for the benzyl group on N(2) and by boron tribromide treatment for the O-methyl groups to give **45**.

Results and Discussion

DA_1 agonist activity was evaluated as renal vasodilation resulting from increased renal blood flow in pentobarbital-anesthetized dogs.[7] Flow was measured with an electromagnetic flowmeter. The test compounds were injected into the renal artery. The doses (ED_{20}) of the test compounds that caused a 20% increase in renal blood flow were calculated and compared. Furthermore, it was confirmed that the renal vasodilatory effects of the test compounds were antagonized by a selective DA_1 antagonist, SCH23390.[8]

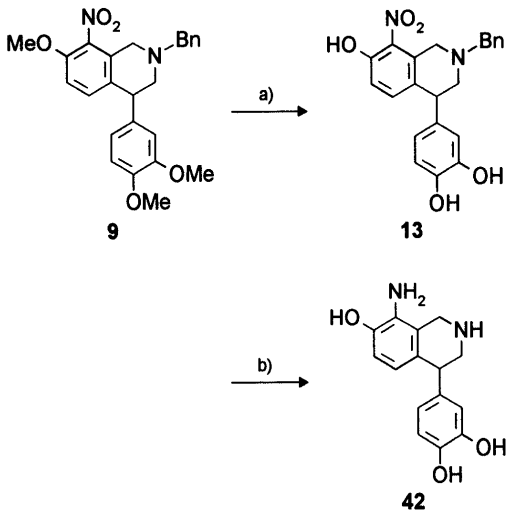
Considering the previous report on **37** and **39**, the effects of hydroxy and methyl groups were first investigated. Hydroxy groups enhanced the activity of **19** by about 4 to 6 times except at the 5 position (**20**—**23**), but the activities were weaker than that of **37** or **39**. A methyl group decreased the activity (**24**—**27**). The chloro (**28**—**31**) and methoxy groups (**32**) also decreased the activity, and the 7-amino group (**33**) was only slightly effective.

When two hydroxy groups were introduced at various positions, only **37** (racemate of **1**) showed strong activity. Various other positions were not effective (**34**—**36**). Compound **38**, which has methoxy groups on the 7 and 8 positions instead of the hydroxy groups of **37**, was not active at all. Moreover, exchanging the position of the hydroxy and methyl groups of **39**, which was as active as **37**, decreased the activity (**40**). These results indicate a requirement for an acidic hydrogen at the 7 position for DA_1 agonistic activity.



a) BnBr, K_2CO_3, acetone; b) H_2, Raney-Ni, EtOH; c) $NaNO_2$, CuCl, aqueous HCl; d) H_2, Pd/C, HCl (cat.), EtOH; e) 48% aqueous HBr

Chart 3

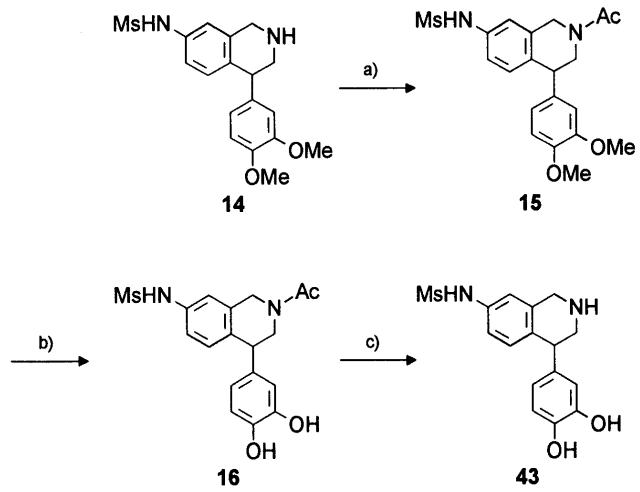


a) BBr_3, CH_2Cl_2; b) H_2, Pd/C, EtOH

Chart 4

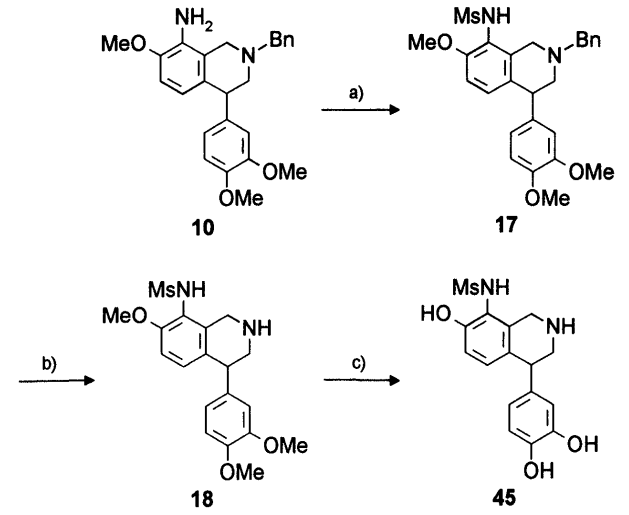
Thus, we investigated the activities of the compounds bearing hydroxy groups on the 7 position (**41**, **42**). Both compounds, bearing a chloro (**41**) or amino group (**42**) on the 8 position, were active.

Considering these results, we postulated that electron-donating groups or moderately acidic groups such as hydroxy groups are necessary on the 7 position. Also, the substituents on the 6 or 8 position could affect the activities. We therefore examined sulfonamido groups instead of the hydroxy group.



a) Ac_2O, CH_2Cl_2; b) BBr_3, CH_2Cl_2; c) aqueous 2N HCl, EtOH

Chart 5



a) MsCl, pyridine; b) H_2, Pd/C, HCl (cat.), EtOH; c) BBr_3, CH_2Cl_2

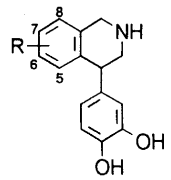
Chart 6

Based on the previous results, sulfonamido groups were introduced at the 7 position (**43**, **44**). They enhanced the vasodilation activities of the compounds. In particular, **43**, which has a methanesulfonamido group, showed almost the same activity as **1**. Also, the ethanesulfonamido group was more effective than the hydroxy group.

The effect of the combination of the methanesulfonamido and hydroxy or methyl groups was then investigated. The activity was decreased with an 8-methanesulfonamido group. In the case of a methanesulfonamido group on the 7 position, not only 6- and 8-hydroxy (**46**, **47**), but also 8-methyl groups (**48**) decreased the activity.

The results may be summarized as follows. 1) On the 7 position, a weakly acidic group, such as a phenolic hydroxy or a sulfonamido group, is necessary for DA_1 agonistic activity. 2) Moderate bulkiness is required around the acidic proton. Thus, substituents on the 8 position enhance

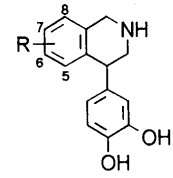
Table 1. Monosubstituted 4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines



Compd.	R	Synthetic method[a]	Formula[b]	ED_{20}[c] (μg) (i.a.)
19	H	[d]		72.7
20	5-OH	A	$C_{15}H_{16}BrNO_3$	>1000
21	6-OH	A	$C_{15}H_{16}BrNO_3$	12.3
22	7-OH	A	$C_{15}H_{16}BrNO_3 \cdot 1/5H_2O$	19.1
23	8-OH	[e]		14.3
24	5-Me	A	$C_{16}H_{18}BrNO_2 \cdot 1/3H_2O$	—
25	6-Me	A	$C_{16}H_{18}BrNO_2$	>1000
26	7-Me	A	$C_{16}H_{18}BrNO_2$	84.7
27	8-Me	A	$C_{16}H_{18}BrNO_2$	270.0
28	5-Cl	A	$C_{15}H_{15}ClNO_2$[f]	—
29	6-Cl	A	$C_{15}H_{15}BrClNO_2$	—
30	7-Cl	A	$C_{15}H_{15}ClNO_2$[f]	>1000
31	8-Cl	[e]		88.0
32	7-OMe	B	$C_{16}H_{18}ClNO_3 \cdot 1/4H_2O$	555.3
33	7-NH_2	A	$C_{15}H_{18}Br_2N_2O_2$	60.1

a) Refer to Charts 1 and 2 for A and B, respectively, and see the experimental section. *b*) Analyses within ±0.4% of theoretical for C, H, and N were obtained for all indicated formulas, unless otherwise stated. *c*) Dose giving a 20% increase in renal blood flow. *d*) See reference 9. *e*) See reference 10. *f*) Indicated by precise mass.

Table 2. Disubstituted 4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines



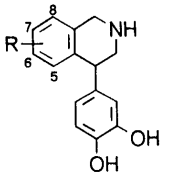
Compd.	R	Synthetic method[a]	Formula[b]	ED_{20}[c] (μg) (i.a.)
1 (YM435)	7-OH, 8-OH[d]	[e]		2.0
34	5-OH, 8-OH	A	$C_{15}H_{16}BrNO_4$	—
35	6-OH, 7-OH	A	$C_{15}H_{16}BrNO_4 \cdot H_2O \cdot 1/2CH_2Cl_2$	286.8
36	6-OH, 8-OH	A	$C_{15}H_{16}BrNO_4 \cdot 1/4H_2O$	—
37	7-OH, 8-OH	[e]		3.0
38	7-OMe, 8-OMe	B	$C_{17}H_{20}ClNO_4$	>1000
39	7-OH, 8-Me	[e]		5.0
40	7-Me, 8-OH	A	$C_{16}H_{18}BrNO_3$	167.0
41	7-OH, 8-Cl	C	$C_{15}H_{15}BrClNO_3$	16.8
42	7-OH, 8-NH_2	D	$C_{15}H_{17}BrN_2O_3$	13.8

a) Refer to Charts 1—4 for A to D, respectively, and see the experimental section. *b*) Analyses within ±0.4% of theoretical for C, H, and N were obtained for all indicated formulas. *c*) Dose giving a 20% increase in renal blood flow. *d*) The *S* isomer of **37**. *e*) See reference 1.

activity in the 7-hydroxy series. However, the 7-methanesulfonamido group is quite large, and in this case 8-substituents gave decreased activities.

During this study we identified **43**, which showed renal vasodilation activity as potent as that of **1**.

Table 3. Sulfonamide-Bearing Compounds



Compd.	R	Synthetic method[a]	Formula[b]	ED_{20}[c] (μg) (i.a.)
43	7-$NHSO_2Me$	E	$C_{16}H_{19}ClN_2O_4S \cdot 1/3H_2O$	4.3
44	7-$NHSO_2Et$	E	$C_{17}H_{21}ClN_2O_4S \cdot C_3H_8O$	11.1
45	7-OH, 8-$NHSO_2Me$	F	$C_{16}H_{19}N_2O_5S$[d]	>1000
46	6-OH, 7-$NHSO_2Me$	E	$C_{16}H_{19}ClN_2O_5S$	37.3
47	7-$NHSO_2Me$, 8-OH	A	$C_{16}H_{19}BrN_2O_5S \cdot 1/3H_2O$	88.4
48	7-$NHSO_2Me$, 8-Me	A	$C_{17}H_{21}BrN_2O_4S \cdot 1/3H_2O$	24.2

a) Refer to Charts 1, 5, and 6 for A, E and F, respectively, and see the experimental section. *b*) Analyses within ±0.4% of theoretical for C, H, and N were obtained for all indicated formulas, unless otherwise stated. *c*) Dose giving a 20% increase in renal blood flow. *d*) Indicated by precise mass.

Experimental

Melting points were determined with a Yanaco MP-3 apparatus and were not corrected. NMR spectra were recorded on a JEOL FX90Q or FX100 spectrometer using DMSO-d_6 as the solvent and Me_4Si as the internal standard. The following abbreviations are used; s, singlet, d, doublet, t, triplet, m, multiplet, br, broadened. Mass spectra were determined with a JEOL JMS-DX300 or VG Analytical ZAB-VSE. Elemental analyses are reported with the symbols of the elements and the results were within ±0.4% of the calculated values. For TLC, silica gel F_{254} (Merck) was used. For column chromatography, Kieselgel 60 (Merck) was used. Concentration of solutions by evaporation was carried out *in vacuo*.

Representative reactions are described in detail. Syntheses of **1**, **37**, and **39** appeared in a previous report, and **19**, **23**, and **31** were prepared by known procedures.

Example of Method A: 4-(3,4-Dihydroxyphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (27·HBr) A mixture of 1.0 g of 1-(3,4-dimethoxyphenyl)-2-aminoethanol hydrochloride (**3**), 0.5 ml of *o*-tolualdehyde, 0.63 ml of triethylamine and 5 ml of methanol was heated under reflux for 10 min. The reaction mixture was then cooled to 4 °C, followed by portionwise addition of 0.24 g of sodium borohydride. After the reaction was completed, the mixture was concentrated. The residue was dissolved in chloroform and water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The residual crystalline solid was recrystallized from chloroform–hexane to give 0.97 g of **4** (R=2-Me). mp 103—104 °C.

A solution of 0.9 g of **4** (R=2-Me) in 7 ml of trifluoroacetic acid was treated with 0.21 ml of sulfuric acid at 4 °C, and the mixture was stirred at the same temperature for 1 h. After concentration of the mixture, the residue was taken up in chloroform and the solution was made basic with 28% ammonia water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The residual crystalline solid was recrystallized from ethyl acetate–hexane to give 0.44 g of **5** (R=8-Me). mp 86—88 °C.

A mixture of 0.42 g of **5** (R=8-Me) and 8.4 ml of 48% hydrobromic acid was refluxed under an argon atmosphere for 3 h. After cooling, 0.42 g of crystals (**27**·HBr) was collected by filtration. mp 250 °C (dec.). ^{1}H-NMR δ: 2.28 (s, 3H), 3.36 (d, 1H, J=11.4 Hz), 3.60 (dd, 1H, J=5.7, 11.4 Hz), 4.12—4.42 (m, 3H), 6.42—6.82 (m, 4H), 7.12 (d, 2H, J=4.8 Hz). FAB-MS *m/z*: 256 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}BrNO_2$: C, 57.16; H, 5.40; Br, 23.76; N, 4.17. Found: C, 57.04; H, 5.43; Br, 23.73; N, 4.17.

Method B. 4-(3,4-Dihydroxyphenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (32·HCl) A solution of 13.6 g of *o*-anisaldehyde and 17.3 ml of 1-amino-3,3-diethoxypropane in 68 ml of methanol was heated under reflux for 30 min, followed by the portionwise addition

of 5.67 g of sodium borohydride in an ice-cooled bath. After the reaction was completed, excess sodium borohydride was quenched by the addition of acetone. The mixture was concentrated and the residue dissolved in chloroform and water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to give crude **7** as an oil. This was used in the next reaction without further purification.

A portion of **7** (3.0 g) and 1.44 g of catechol were stirred overnight at room temperature in 24 ml of 6 N hydrochloric acid. The precipitated crystals of **32**·HCl (1.74 g) were then collected by filtration. mp >230 °C. ^{1}H-NMR δ: 3.08—3.70 (m, 2H), 3.75 (s, 3H), 4.10—4.45 (m, 3H), 6.42—6.60 (m, 2H), 6.62—6.90 (m, 4H). FAB-MS *m/z*: 272 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}ClNO_3 \cdot 1/4H_2O$: C, 61.54; H, 5.97; Cl, 11.35; N, 4.49. Found: C, 61.80; H, 5.92; Cl, 11.55; N, 4.53.

Method C. 8-Chloro-4-(3,4-dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (41·HBr) A mixture of 7.0 g of **8** (R = 7-OMe, 8-NO_2) derived from 3-methoxy-2-nitrobenzaldehyde in the same manner as above, 4.2 g of potassium carbonate, 2.3 ml of benzyl bromide and 70 ml of acetone was heated under reflux for 1 h. After cooling to 4 °C, the mixture was filtered and the filtrate was concentrated. The residual solid was recrystallized from ethanol to give 7.76 g of **9**. mp 118—119 °C.

A mixture of 4.8 g of **9**, Raney nickel and 78 ml of ethanol was vigorously stirred at 40 °C under an H_2 atmosphere. After the theoretical volume of H_2 had been absorbed, the mixture was filtered and the filtrate was concentrated. The residual crystalline solid was recrystallized from chloroform–ethanol to give 3.45 g of **10**. mp 142—143 °C.

A solution of 0.38 g of sodium nitrite in 1.9 ml of water was added to a solution of 2.02 g of **10** in 10 ml of 20% hydrochloric acid at 4 °C. The solution was added dropwise to 0.55 g of copper(I) chloride in 11 ml of 20% hydrochloric acid and the whole was stirred at the same temperature. After the reaction was completed, 4.84 g of sodium hydroxide was added and the mixture was repeatedly extracted with chloroform. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The residual crystalline solid was recrystallized from ethanol to give 1.23 g of **11**. mp 88—91 °C.

A mixture of 1.13 g of **11**, 0.22 ml of 12 N hydrochloric acid, 0.1 g of 10% palladium on carbon and 28 ml of ethanol was vigorously stirred at 50 °C under an H_2 atmosphere. After the theoretical volume of H_2 had been absorbed, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in chloroform and the solution was washed with saturated sodium hydrogencarbonate aqueous solution and water, dried over Na_2SO_4 and concentrated. The residual crystalline solid was recrystallized from ethyl acetate–hexane to give 0.58 g of **12**. mp 130—132 °C.

A mixture of 0.54 g of **12** and 11 ml of 48% hydrobromic acid was refluxed under an argon atmosphere for 3 h. After cooling, 0.52 g of crystals (**41**·HBr) was collected by filtration. mp 260 °C (dec.). ^{1}H-NMR δ: 3.35 (d, 1H, J = 11.4 Hz), 3.60 (dd, 1H, J = 5.7, 11.4 Hz), 4.05—4.50 (m, 3H), 6.48 (d, 1H, J = 8.0 Hz), 6.56 (s, 1H), 6.62 (d, 1H, J = 10.8 Hz), 6.75 (d, 1H, J = 8.0 Hz), 6.92 (d, 1H, J = 10.8 Hz). FAB-MS *m/z*: 292 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{15}BrClNO_3$: C, 48.35; H, 4.06; N, 3.76. Found: C, 48.32; H, 4.05; N, 3.75.

Method D. 8-Amino-4-(3,4-dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (42·HBr) A mixture of 700 mg of **13**·HBr, derived from 3-methoxy-2-nitrobenzaldehyde in the same manner as above, 70 mg of 10% palladium on carbon and 14 ml of ethanol was vigorously stirred at 40 °C under an H_2 atmosphere. After the reaction was completed, the mixture was filtered and the filtrate was concentrated. The residue was treated with chloroform and the precipitate was collected by filtration to give 590 mg of **42**·HBr. Amorphous. ^{1}H-NMR δ: 3.10—3.65 (m, 2H), 3.95—4.30 (m, 3H), 5.96 (d, 1H, J = 8.5 Hz), 6.40—6.70 (m, 3H), 6.76 (d, 1H, J = 8.0 Hz). FAB-MS *m/z*: 273 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{17}BrN_2O_3$: C, 51.01; H, 4.85; Br, 22.62; N, 7.93. Found: C, 50.72; H, 4.53; Br, 22.43; N, 7.91.

Method E. 4-(3,4-Dihydroxyphenyl)-7-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline Hydrochloride (43·HCl) Synthesis of 3-methanesulfonamidobenzoic acid: A solution of 10 g of ethyl 3-aminobenzoate and 14.7 ml of pyridine in 50 ml of dichloromethane was treated with 5.62 ml of methanesulfonyl chloride in an ice-cooled bath and the mixture was stirred at room temperature for 1 h. The solution was made acidic with 2 N HCl and extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was taken up in 134 ml of 1 N NaOH, followed by heating under reflux for 1 h. The solution was cooled to 4 °C, then 12 ml of 12 N HCl was added. The precipitated crystals were collected and washed with ether to give 12.8 g of 3-methanesulfonamidobenzoic acid. This was then converted to 4-(3,4-dimethoxyphenyl)-7-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline (**14**) in the same manner as before.

A solution of 4.0 g of **14** in 40 ml of dichloromethane was treated with 2.08 ml of acetic anhydride at room temperature. The mixture was stirred at room temperature for 30 min. Then water was added, followed by 28% ammonia water, and the whole was extracted with dichloromethane. The combined organic layers were washed with 1 N HCl and brine, dried over $MgSO_4$ and concentrated to give 4.73 g of **15**.

A 1 M solution of boron tribromide in dichloromethane (128 ml) was added dropwise to a solution of 8.62 g of **15** in 130 ml of dichloromethane below −30 °C, followed by stirring at room temperature for 1 h. The mixture was then cooled to below −40 °C, 50 ml of methanol was added, and the whole was allowed to return to room temperature again. After concentration, the residue was dissolved in 30 ml of methanol and 50 ml of toluene and concentrated again. The residue was dissolved in ethyl acetate, and the solution was washed with water and brine, dried over $MgSO_4$ and concentrated. The residual solid was recrystallized from methanol to give 7.51 g of **16**.

A mixture of 8.25 g of **16**, 80 ml of ethanol and 80 ml of 2 N HCl was heated under reflux overnight. After cooling and concentration, the residue was dissolved in water. The aqueous solution was washed three times with ethyl acetate and concentrated. The residue was treated with acetonitrile and the precipitate was collected by filtration to give 7.51 g of **43**·HCl. Amorphous. ^{1}H-NMR δ: 3.02 (s, 3H), 3.1—3.7 (s, 2H), 3.35 (br s, 2H), 4.24 (m, 1H), 6.4—7.2 (m, 6H). FAB-MS *m/z*: 335 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{19}ClN_2O_4S \cdot 1/3H_2O$: C, 50.99; H, 5.26; Cl, 9.40; N, 7.43; S, 8.50. Found: C, 51.20; H, 5.31; Cl, 9.63; N, 7.29; S, 8.73.

Method F. 4-(3,4-Dihydroxyphenyl)-7-hydroxy-8-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline Hydrobromide (45·HBr) A solution of 2.89 g of **10** in 29 ml of pyridine was treated with 0.83 ml of methanesulfonyl chloride at 4 °C, followed by stirring overnight at room temperature. After concentration, the residue was treated with phosphate buffer (pH 7) followed by extraction with chloroform. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated. The crude **17** was used for the next step without further purification.

A mixture of the crude **17**, 0.6 ml of 12 N hydrochloric acid, 0.36 g of 10% palladium on carbon and 72 ml of ethanol was vigorously stirred at 50 °C under an H_2 atmosphere. After the theoretical volume of H_2 had been absorbed, the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography (chloroform–methanol–28% aqueous ammonia) to give 1.46 g of **18**.

A solution of 1.0 g of **18** in 10 ml of dichloromethane was treated dropwise with 20.1 ml of 1 M boron tribromide in dichloromethane at −20 °C, followed by stirring of the mixture for 3 h at ambient temperature. The mixture was cooled to below −40 °C, then 5.1 ml of methanol was added and the whole was warmed to room temperature then concentrated. The residue was treated with chloroform and the precipitate was collected by filtration to give **45**·HBr. Amorphous. ^{1}H-NMR δ: 3.02 (s, 3H), 3.10—3.70 (m, 2H), 4.05—4.55 (m, 3H), 6.40—6.80 (m, 4H), 6.88 (d, 1H, J = 9.4 Hz). FAB-MS *m/z*: 351.1020 (Calcd for $C_{16}H_{19}N_2O_5S$: 351.1015).

4-(3,4-Dihydroxyphenyl)-5-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (20·HBr) Synthesized from *m*-anisaldehyde by method A. mp >250 °C. ^{1}H-NMR δ: 3.15—3.70 (m, 2H), 4.10—4.40 (m, 3H), 6.28—6.46 (m, 2H), 6.58—6.85 (m, 3H), 7.17 (dd, 1H, J = 6.7, 8.6 Hz). FAB-MS *m/z*: 258 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; Br, 23.63; N, 4.14. Found: C, 52.99; H, 4.68; Br, 23.76; N, 4.07.

4-(3,4-Dihydroxyphenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (21·HBr) Synthesized from *p*-anisaldehyde by method A. mp >250 °C. ^{1}H-NMR δ: 3.24 (d, 1H, J = 12.0 Hz), 3.49 (dd, 1H, J = 5.7, 12.0 Hz), 4.04—4.40 (m, 3H), 6.23 (d, 1H, J = 2.3 Hz), 6.48—6.84 (m, 4H), 7.08 (d, 1H, J = 8.5 Hz). FAB-MS *m/z*: 258 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; Br, 23.63; N, 4.14. Found: C, 53.16; H, 4.70; Br, 23.35; N, 4.16.

4-(3,4-Dihydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (22·HBr) Synthesized from *m*-anisaldehyde by method A. mp 220 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 3.22 (d, 1H, J = 11.8 Hz), 3.48 (dd, 1H, J = 5.9, 11.8 Hz), 4.00—4.45 (m, 3H), 6.40—6.70 (m, 6H). FAB-MS *m/z*: 258 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_3 \cdot 1/5H_2O$: C, 52.71; H, 4.84; Br, 23.38; N, 4.10. Found: C, 52.66; H, 4.79; Br, 23.63;

N, 4.07.

4-(3,4-Dihydroxyphenyl)-5-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (24·HBr) Synthesized from *m*-tolualdehyde by method A. mp 247—250 °C. ^{1}H-NMR δ: 1.90 (s, 3H), 3.20—3.80 (m, 2H), 4.20—4.50 (m, 3H), 6.20—6.50 (m, 2H), 6.70 (d, 1H, J=7.7 Hz), 7.00—7.35 (m, 3H). FAB-MS *m/z*: 256 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}BrNO_2 \cdot 1/3H_2O$: C, 56.16; H, 5.50; Br, 23.35; N, 4.09. Found: C, 56.00; H, 5.41; Br, 23.33; N, 4.09.

4-(3,4-Dihydroxyphenyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (25·HBr) Synthesized from *p*-tolualdehyde by method A. mp 250 °C (dec.). ^{1}H-NMR δ: 2.20 (s, 3H), 3.28 (d, 1H, J=11.7 Hz), 3.64 (dd, 1H, J=5.7, 11.7 Hz), 4.10—4.50 (m, 3H), 6.45—6.75 (m, 3H), 6.75 (d, 1H, J=8.0 Hz), 7.04 (dd, 1H, J=1.1, 7.4 Hz), 7.18 (d, 1H, J=7.4 Hz). FAB-MS *m/z*: 256 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}BrNO_2$: C, 57.16; H, 5.40; Br, 23.76; N, 4.17. Found: C, 56.95; H, 5.44; Br, 24.06; N, 4.02.

4-(3,4-Dihydroxyphenyl)-7-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (26·HBr) Synthesized from *m*-tolualdehyde by method A. mp 192—195 °C. ^{1}H-NMR δ: 2.27 (s, 3H), 3.26 (d, 1H, J=12.0 Hz), 3.59 (dd, 1H, J=6.0, 12.0 Hz), 6.42—6.56 (m, 2H), 6.72 (d, 2H, J=7.4 Hz), 7.02 (d, 1H, J=7.4 Hz), 7.08 (s, 1H). FAB-MS *m/z*: 256 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}BrNO_2$: C, 57.16; H, 5.40; Br, 23.76; N, 4.17. Found: C, 57.21; H, 5.29; Br, 23.83; N, 4.03.

5-Chloro-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (28·HBr) Synthesized from 3-chlorobenzaldehyde by method A. mp >250 °C. ^{1}H-NMR δ: 3.25—3.80 (m, 2H), 4.25—4.55 (m, 3H), 6.20—6.40 (m, 2H), 6.68 (d, 1H, J=7.7 Hz), 7.30—7.45 (m, 3H). FAB-MS *m/z*: 276.0799 (Calcd for $C_{15}H_{15}ClNO_2$: 276.0791).

6-Chloro-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (29·HBr) Synthesized from 4-chlorobenzaldehyde by method A. mp 230 °C (dec.). ^{1}H-NMR δ: 3.10—3.80 (m, 2H), 4.15—4.55 (m, 3H), 6.45—6.65 (m, 2H), 6.70—6.87 (m, 2H), 7.30—7.45 (m, 2H). FAB-MS *m/z*: 276 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{15}BrClNO_2$: C, 50.52; H, 4.24; Br, 22.40; Cl, 9.94; N, 3.93. Found: C, 50.21; H, 4.21; Br, 22.57; Cl, 9.98; N, 3.87.

7-Chloro-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide (30·HBr) Synthesized from 3-chlorobenzaldehyde by method A. mp 223 °C. ^{1}H-NMR δ: 3.16—3.75 (m, 2H), 4.10—4.55 (m, 3H), 6.45—6.63 (m, 2H), 6.77 (d, 1H, J=8.3 Hz), 6.86 (d, 1H, J=8.6 Hz), 7.30 (dd, 1H, J=2.0, 8.6 Hz), 7.44 (d, 1H, J=2.0 Hz). FAB-MS *m/z*: 276.0800 (Calcd for $C_{15}H_{15}ClNO_2$: 276.0791).

7-Amino-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Dihydrobromide (33·2HBr) Synthesized from 2-nitrobenzaldehyde by method A. mp 194 °C (dec.). ^{1}H-NMR δ: 6.56 (s, 2H), 6.72 (d, 1H), 6.92 (d, 1H), 7.12 (s, 2H). FAB-MS *m/z*: 257 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{18}Br_2N_2O_2$: C, 43.09; H, 4.34; Br, 38.22; N, 6.70. Found: C, 43.36; H, 4.59; Br, 37.89; N, 6.50.

4-(3,4-Dihydroxyphenyl)-5,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (34·HBr) Synthesized from 2,5-dimethoxybenzaldehyde by method A. mp 240 °C (dec.). ^{1}H-NMR δ: 3.10—3.65 (m, 2H), 3.95—4.35 (m, 3H), 6.25—6.42 (m, 2H), 6.50—6.75 (m, 3H). FAB-MS *m/z*: 274 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_4$: C, 50.87; H, 4.55; Br, 22.56; N, 3.95. Found: C, 50.63; H, 4.44; Br, 22.67; N, 3.98.

4-(3,4-Dihydroxyphenyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (35·HBr) Synthesized from veratraldehyde by method A. Amorphous. ^{1}H-NMR δ: 3.00—3.80 (m, 2H), 3.95—4.50 (m, 3H), 5.90—6.80 (m, 5H). FAB-MS *m/z*: 274 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_4 \cdot H_2O \cdot 1/2CH_2Cl_2$: C, 44.90; H, 4.62; N, 3.38. Found: C, 44.54; H, 4.35; N, 3.60.

4-(3,4-Dihydroxyphenyl)-6,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrobromide (36·HBr) Synthesized from 2,4-dimethoxybenzaldehyde by method A. mp 250 °C (dec.). ^{1}H-NMR δ: 3.10—3.60 (m, 2H), 4.00—4.60 (m, 3H), 6.20 (dd, 1H, J=2.0, 8.3 Hz), 6.22 (s, 1H), 6.39 (d, 1H, J=2.0 Hz), 6.58 (s, 1H), 6.70 (d, 1H, J=8.3 Hz). FAB-MS *m/z*: 274 ($M+H^+$). *Anal.* Calcd for $C_{15}H_{16}BrNO_4 \cdot 1/4H_2O$: C, 50.23; H, 4.64; Br, 22.28; N, 3.90. Found: C, 50.34; H, 4.57; Br, 22.02; N, 3.94.

4-(3,4-Dihydroxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (38·HCl) Synthesized from 2,3-dimethoxybenzaldehyde by method B. mp 220 °C (dec.). ^{1}H-NMR δ: 3.00—3.62 (m, 2H), 3.82 (s, 6H), 4.06—4.36 (m, 3H), 6.42—6.60 (m, 3H), 6.75 (d, 1H, J=7.7 Hz), 6.96 (d, 1H, J=9.1 Hz). FAB-MS *m/z*: 302 ($M+H^+$). *Anal.* Calcd for $C_{17}H_{20}ClNO_4$: C, 60.45; H, 5.97; Cl, 10.50; N, 4.15. Found: C, 60.26; H, 5.94; Cl, 10.38; N, 4.10.

4-(3,4-Dihydroxyphenyl)-8-hydroxy-7-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (40·HBr) Synthesized from 2-methoxy-3-methylbenzoic acid by method A. mp >230 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.16 (s, 3H), 3.10—3.65 (m, 2H), 4.05—4.30 (m, 3H), 6.24 (d, 1H, J=8.0 Hz), 6.42—6.56 (m, 2H), 6.72 (d, 1H, J=7.4 Hz), 6.95 (d, 1H, J=8.0 Hz). FAB-MS *m/z*: 272 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; Br, 22.69; N, 3.98. Found: C, 54.35; H, 5.08; Br, 22.83; N, 3.97.

4-(3,4-Dihydroxyphenyl)-7-ethanesulfonamido-1,2,3,4-tetrahydroisoquinoline Hydrochloride 2-Propanolate (44·HCl·PrOH) Synthesized from ethyl 3-aminobenzoate by method E. mp 161—162 °C. ^{1}H-NMR δ: 1.21 (t, 3H, J=7.4 Hz), 3.10 (q, 2H, J=7.4 Hz), 3.2—3.9 (m, 2H), 4.20 (m, 1H), 4.34 (br s, 2H), 6.4—7.2 (m, 6H). FAB-MS *m/z*: 349 ($M+H^+$). *Anal.* Calcd for $C_{17}H_{21}ClN_2O_4S \cdot C_3H_8O$: C, 53.98; H, 6.57; Cl, 7.97; N, 6.30; S, 7.21. Found: C, 53.74; H, 6.50; Cl, 8.17; N, 6.25; S, 7.29.

4-(3,4-Dihydroxyphenyl)-6-hydroxy-7-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline Hydrochloride (46·HCl) Synthesized from methyl 3-amino-4-methoxybenzoate *via* 3-methanesulfonamido-4-methoxybenzoic acid by method E. mp 235—237 °C. ^{1}H-NMR δ: 2.96 (s, 3H), 3.1—3.7 (m, 2H), 4.1—4.4 (m, 3H), 6.39—6.63 (m, 3H), 6.76 (d, 1H, J=7.1 Hz), 7.08 (s, 1H). FAB-MS *m/z*: 351 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{19}ClN_2O_5S$: C, 49.68; H, 4.95; Cl, 9.16; N, 7.24; S, 8.29. Found: C, 49.73; H, 5.01; Cl, 9.42; N, 7.15; S, 8.17.

4-(3,4-Dihydroxyphenyl)-8-hydroxy-7-methanesulfonamido-1,2,3,4-tetrahydroisoquinoline Hydrobromide (47·HBr) Synthesized from *o*-anisaldehyde *via* 3-methanesulfonamido-2-methoxybenzaldehyde by method A. mp 160—162 °C. ^{1}H-NMR δ: 2.98 (s, 3H), 3.2—3.8 (m, 2H), 4.1—4.4 (m, 3H), 6.3—7.2 (m, 5H). FAB-MS *m/z*: 351 ($M+H^+$). *Anal.* Calcd for $C_{16}H_{19}BrN_2O_5S \cdot 1/3H_2O$: C, 43.95; H, 4.53; Br, 18.27; N, 6.41; S, 7.33. Found: C, 44.00; H, 4.55; Br, 18.31; N, 6.63; S, 7.43.

4-(3,4-Dihydroxyphenyl)-7-methanesulfonamido-8-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (48·HBr) Synthesized from 3-amino-*o*-toluic acid *via* 3-methanesulfonamido-4-methylbenzoic acid by method A. mp 237—239 °C. ^{1}H-NMR δ: 2.22 (s, 3H), 2.98 (s, 3H), 3.1—3.7 (m, 2H), 4.1—4.4 (m, 3H), 6.4—7.2 (m, 5H). FAB-MS *m/z*: 349 ($M+H^+$). *Anal.* Calcd for $C_{17}H_{21}BrN_2O_4S \cdot 1/3H_2O$: C, 46.90; H, 5.02; Br, 18.35; N, 6.43; S, 7.36. Found: C, 47.20; H, 4.84; Br, 18.53; N, 6.54; S, 7.52.

Biological Testing Mongrel dogs of either sex were anesthetized using sodium pentobarbital. The left renal artery was exposed by a flank incision using the retroperitoneal approach. An electromagnetic blood flow probe was attached at the renal artery to measure renal blood flow with an electromagnetic flowmeter. A curved 25-gauge needle connected to a polyethylene tube was inserted into the renal artery proximal to the flow probe for injection of the compounds. The effects of compounds on the renal blood flow were evaluated. The dose of each compound required to increase renal blood flow by 20% (ED_{20}) was calculated from the log dose-response curve to compare the potency of the compounds.

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