New Norepinephrine Potentiators: Synthesis and Structure–Activity Relationships of a Series of 4-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols

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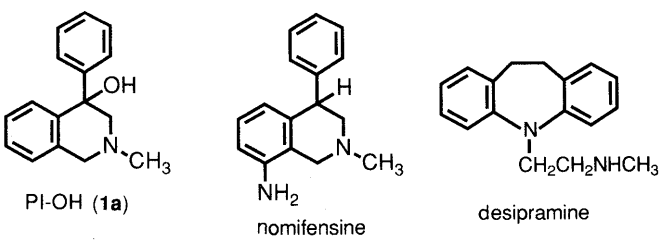
A variety of 1,2,3,4-tetrahydroisoquinolin-4-ols (1—6) were prepared as part of our search for new norepinephrine (NE) potentiators and to clarify the structure–activity relationships. These compounds and some previously prepared compounds were compared with 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (PI-OH) (1a) for ability to potentiate NE. The potency, for 2-substitution, was found to be in the order: Me > Et > iso-Pr > H. The compounds substituted by a halogen atom at the *para* position in the 4-phenyl group of PI-OH showed greater activities than did PI-OH, and the observed order of potency for the substitution was Cl > Br > F > H. The compound (4) methylated at the hydroxy group in PI-OH had greatly diminished activity. Although the desoxy compound (6) of PI-OH potentiated the response to NE at low concentrations, the potentiation was progressively masked by an inhibitory activity as the concentration of 6 was increased. In addition, the 4-cyclohexyl analogue (5) failed to potentiate NE. These results show the importance of the β-phenylethanolamine skeleton of PI-OH for producing NE potentiation without accompanying inhibitory action. The racemic 4-chlorophenyl analogue (2a) was resolved by HPLC to (*R*)-(+)-2a and (*S*)-(−)-2a. The NE-potentiating activity was found to reside exclusively in (*R*)-(+)-2a, which had the highest activity among compounds tested in this study; the activity ratio was 25 at 3×10^{-6} M. The antidepressant activity of racemic 2a was evaluated by a forced swimming test. The activity of racemic 2a on the reduction of total duration of immobility in rats forced to swim was about 10 times that of desipramine. Thus, compound 2a appears to be a candidate for a new antidepressant.

Keywords norepinephrine potentiator; antidepressant; tetrahydroisoquinolin-4-ol; structure–activity relationship; phenylethanolamine; enantioselectivity

The amine theory of depression was based, in part, upon the observation that the tricyclic antidepressants prevented the neuronal uptake either of norepinephrine (NE) or of serotonin (5-HT).[1] During the past decade a number of nontricyclic antidepressants with diminished cardiovascular and anticholinergic liability have been developed.[2] Recently, atypical antidepressants have also been reported. In particular, antipressants in the 3-aminopyridine,[3] pyrroloisoquinoline,[4] 2-phenylethylamine,[5] and dibenzothiadiazepine,[6] series of compounds have been found and developed. Leonard has claimed[7] that one of the desirable properties of "second generation" antidepressants is an efficient selectivity of action on either the serotonergic or adrenergic system. Nomifensine was reported to have potent activity to inhibit both NE[8] and dopamine (DA)[9] uptake and to possess clinical utility as an antidepressant.[10]

In the previous papers, we reported that racemic 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (PI-OH) (**1a**),[11,12] a compound with a structure similar to that of nomifensine (Chart 1), potentiated the contractile response of rat anococcygeus muscle to NE and electrical nerve stimulation.[13] The potentiating activity of **1a** was found to be due to the inhibition of NE uptake, and was greater than those of nomifensine and desipramine with regard to both responses.[13] Resolution of racemic **1a** by high-performance liquid chromatography (HPLC) gave the optically pure enantiomers, (*R*)-(+)-**1a** and (*S*)-(−)-**1a**. The NE potentiation was found to reside exclusively in (*R*)-(+)-**1a**.[14] Nomifensine and desipramine are known to share an action to postsynaptically inhibit NE. However, (*R*)-(+)-**1a** had no such an effect.[14] Therefore, (*R*)-(+)-**1a** should be a more selective potentiator of NE in adrenergically innervated tissues. We further investigated a variety of analogues of PI-OH (**1a**) in order to find new active compounds and to explore the comparative structure–activity relationships. In this report, we describe the synthesis and pharmacological properties of 1-, 2-, 3- and 4-substituted 1,2,3,4-tetrahydroisoquinolin-4-ols (**1**—**3**) and some related compounds (**4**—**6**).

Chemistry New 2-substituted compounds (**1c** and **1d**) were synthesized by an insertion reaction of *N*-(2-iodobenzyl)phenacylamines (**9c** and **9d**) with zerovalent nickel [Ni(0)] in 60 and 62% yields, respectively (Chart 2). The phenacylamines (**9c** and **9d**) were prepared from benzylamines (**7c** and **7d**) and phenacyl bromide (**8a**). 2-Allyl and 2-propargyl analogues (**1g** and **1h**) were obtained by alkylation of a secondary amine (**1f**), which was prepared by catalytic hydrogenation of an *N*-benzyl derivative (**1e**). In the previous papers,[11,12] we reported the synthesis of PI-OH (**1a**) and its derivatives from phenacylamines using Ni(0) in low yields. However, we have developed a new and efficient method for the preparation of the derivatives of PI-OH (**1a**) by means of



PI-OH (**1a**) nomifensine desipramine

Chart 1

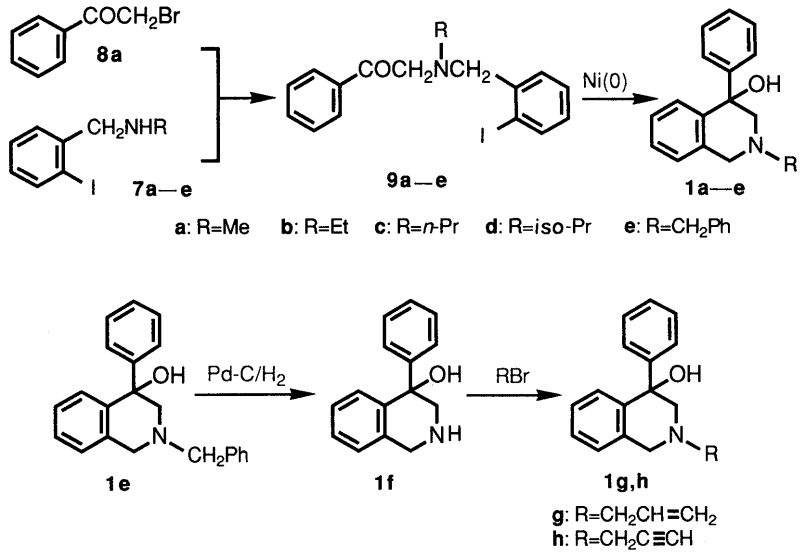
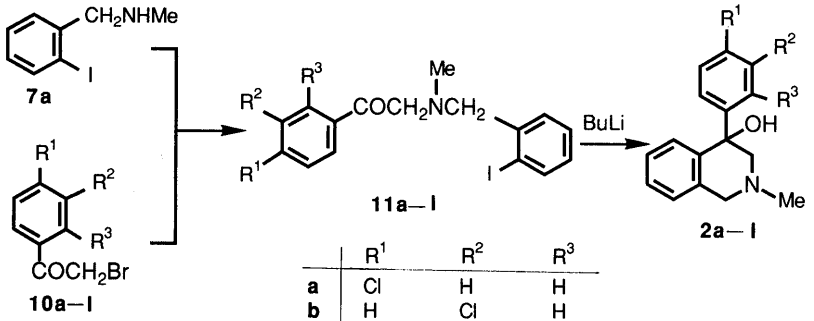


Chart 2



	R^1	R^2	R^3
a	Cl	H	H
b	H	Cl	H
c	Cl	Cl	H
d	Cl	H	Cl
e	Br	H	H
f	F	H	H
g	OMe	H	H
h	H	OMe	H
i	CF_3	H	H
j	H	CF_3	H
k	OCH_2Ph	H	H
l	Me	H	H

Chart 3

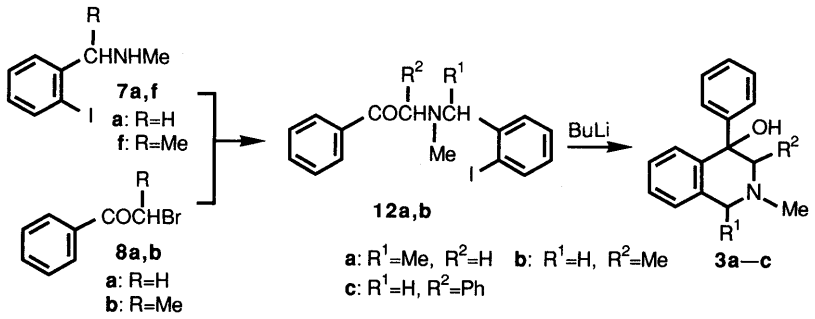


Chart 4

an intramolecular Barbier reaction with *n*-BuLi.[15,16] Therefore, we were able to synthesize new 4-substituted compounds (**2d**, **2i**, **2k** and **2l**) from the corresponding phenacylamines (**11d**, **11i**, **11k** and **11l**) in good yields (Chart 3) by applying the new method. The 1-methyl derivative (**3a**) was also prepared from a phenacylamine (**12a**) with *n*-BuLi (Chart 4). The stereochemical relation between the phenyl groups at C4 and the substituents at C3 in **3b, c** was found to be *trans* in the previous paper.[17] However, the stereochemistry of **3a** could not be

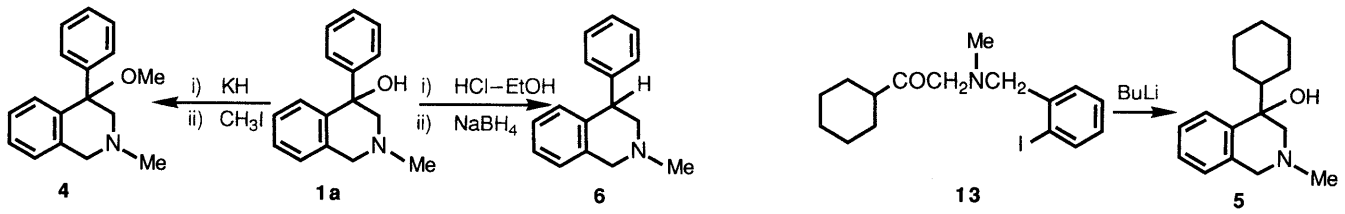


Chart 5

determined in this study. Methylation of **1a** with methyl iodide and potassium hydride gave a 4-methoxy analogue (**4**) in 78% yield (Chart 5). The synthesis of the other 1,2,3,4-tetrahydroisoquinolin-4-ols in Charts 2—5 was reported by us previously.[15-17]

Optical resolution of 4-chlorophenyl analogue (**2a**) was performed by HPLC with a chiral stationary phase (Daicel Chiralcel OJ)[14,17] using hexane–2-propanol as an eluent to give the enantiomers, (+)-**2a**, $[\alpha]_D$ +50.0° and (−)-**2a**, $[\alpha]_D$ −50.1°. The absolute configurations of (+)- and (−)-**2a** were determined by an exciton chirality method.[18] The negative exciton chirality in the circular dichroism (CD) spectrum (see Experimental) of the (+)-enantiomer suggests the stereochemistry at C4 to be *R*. This configuration was supported by a comparison of the CD spectrum of (+)-**2a** with that of (*R*)-(+)-PI-OH.[14] Therefore, the absolute configuration of (−)-**2a** is *S*.

Results and Discussion

The activity of the 4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ols (**1**—**3**) and the related compounds (**4**—**6**) prepared in this study or the previous studies[15-17] to potentiate the contraction of rat anococcygeus muscle by NE was determined by the methods described in our previous papers.[13,14] As shown in Table I, the potency depended on the substitution at the 2-position in the order: Me > Et > iso-Pr > H. The secondary amine (**1f**) showed only weak activity. The 2-*n*-propyl derivative (**1c**) was substantially devoid of activity. The α-adrenolytic activity of the *N*-allyl derivative of 5,6,7,8-tetrahydrodibenz[*c*,*e*]-azocine has been reported to be more potent than that of the corresponding *N*-methyl derivative.[19] However, the 2-allyl and 2-propargyl derivatives (**1g** and **1h**) showed no potentiating activity.

The 1-methyl derivative (**3a**) of PI-OH (**1a**) showed moderate activity, whereas the 3-methyl compound (**3b**) had significantly decreased activity and the 3-phenyl compound (**3c**) no activity. These facts may indicate that the substituents at C3 interfere with the binding of these compounds to the receptor site of NE uptake.[20]

The effects of substituents on the 4-phenyl group of PI-OH (**1a**) on NE potentiation were examined in detail. Topliss and Martin have proposed[21] an operational scheme for aromatic substitution in drug design, indicating a *para* chloro analogue to be a good first choice. In the present study, the 4-chloro, 4-bromo- and 4-fluorophenyl compounds (**2a**, **2e** and **2f**) were found to be more potent than PI-OH (**1a**) and to be in the order: Cl > Br > F > H. These halogenophenyl compounds exhibited activity even at such a low concentration as 3×10^{-8} M. However, the 3-chloroderivative (**2b**) showed only weak activity, and the 3,4- and 2,4-dichloro compounds (**2c** and **2d**) had almost the same activity as that of PI-OH (**1a**). When an alkyl group was substituted at the *para* or *meta* position as in **2i**, **2j** and **2l**, the activities were greatly decreased. The *m*-methoxy derivative (**2h**) also showed weak activity. On the other hand, the *p*-methoxy and *p*-benzyloxy derivatives (**2g** and **2k**) were almost equipotent activity with PI–OH (**1a**). These findings indicate that substituents bearing atoms with lone-pair electrons at the *para* position of the 4-phenyl group may have high affinity for the NE uptake receptor, and that *para*-chlorine should be a very favorable substituent. The importance of the benzene ring of the isoquinoline skeleton in PI-OH (**1a**) was noted in the previous paper.[14] From the above results and the fact that the 4-cyclohexyl analogue (**5**) is devoid of activity, it is conceivable that the 4-phenyl group in PI-OH (**1a**) is also important for NE potentiation.

The *O*-methylated analogue (**4**) of PI-OH (**1a**) showed a greatly diminished activity. In addition, the desoxy analogue (**6**)[16] of PI-OH (**1a**), a compound having the same skeleton as that of nomifensine, showed high activity (activity ratio 10) at a low concentration of 10^{-6} M. However, the activity of **6** was significantly diminished at higher concentrations. This bell-shaped activity curve presumably results from masking of the potentiation by an inhibitory effect at higher concentrations, since nomifensine is known to have α_1-antagonistic activity besides its agonistic activity.[13] These findings suggest the importance of the β-phenylethanolamine moiety of PI-OH (**1a**), which produces only NE potentiation without any accompanying inhibitory property.

The 4-chlorophenylisoquinolin-4-ol (**2a**) was resolved by HPLC[14] to the enatiomers (*R*)-(+)-**2a** and (*S*)-(−)-**2a**. High enantioselectivity for NE potentiation was noted: the potentiating activity resided exclusively in (*R*)-(+)-**2a**. The *R* enantiomer of **2a** was the most active compound among those tested in this study and its pD_2 value was 7.64 ± 0.07 (activity ratio 25) at 3×10^{-6} M. The *S* enantiomer, (*S*)-(−)-**2a**, revealed neither potentiating nor inhibiting activity in the rat anococcygeus muscle preparation. These results are consistent with the enantioselectivity of PI-OH (**1a**) as reported in the previous paper.[14]

According to the modified Easson–Stedman hypothesis, (*R*)-(−)-epinephrine has highly favorable stereochemical orientation in relation to adrenergic receptor subtypes (α_1, α_2, β_1, and β_2).[22] However, the question as to whether the neuronal uptake pump has absolute steroselectivity for phenethylamines that possess asymmetry at the β-carbon atom has not yet been completely resolved.[22] Recently, Cao *et al.*[20] have proposed the presence of an

TABLE I. Potentiating Activities of PI-OH Analogues (**1a—d**, **1f—h**, **2a—l**, and **3a—c**) and Related Compounds (**4—6**) on the Response of Rat Anococcygeus Muscle to Norepinephrine

No.	$n^{b)}$	pD_2 value (activity ratio)[a]						
		Concentration (M) of test compound						
		0	3×10^{-8}	10^{-7}	3×10^{-7}	10^{-6}	3×10^{-6}	10^{-5}
1a	8	6.37±0.08 (1.0)		6.66±0.06 (2.0)	6.85±0.07 (3.0)	7.18±0.06 (6.5)	7.42±0.05 (11.2)	7.63±0.05 (18.2)
1b	6	6.27±0.06 (1.0)			6.58±0.11 (2.0)	6.81±0.10 (3.5)	7.21±0.07 (8.7)	7.34±0.05 (11.8)
1c	5	6.41±0.06 (1.0)			6.44±0.08 (1.1)	6.47±0.06 (1.1)	6.50±0.08 (1.2)	6.45±0.06 (1.1)
1d	6	6.24±0.011 (1.0)			6.26±0.08 (1.0)	6.47±0.06 (1.7)	6.58±0.07 (2.2)	6.92±0.07 (4.8)
1f	5	6.32±0.04 (1.0)					6.52±0.07 (1.6)	6.74±0.06 (2.6)
1g	4	6.35±0.13 (1.0)			6.40±0.17 (1.1)	6.32±0.09 (0.9)	6.29±0.10 (0.9)	6.27±0.10 (0.8)
1h	4	6.40±0.06 (1.0)			6.45±0.13 (1.1)	6.40±0.10 (1.0)	6.36±0.08 (0.9)	6.35±0.09 (0.9)
(±)-**2a**	4	6.31±0.03 (1.0)	6.73±0.12 (2.6)	7.14±0.08 (6.8)	7.36±0.11 (11.2)	7.55±0.10 (17.4)	7.49±0.11 (15.1)	7.42±0.09 (12.9)
(+)-**2a**	4	6.25±0.05 (1.0)	6.95±0.02 (5.0)	7.20±0.20 (8.9)	7.59±0.08 (21.9)	7.61±0.15 (22.9)	7.64±0.07 (24.6)	7.61±0.03 (22.9)
(−)-**2a**	3	6.36±0.13 (1.0)			6.35±0.14 (1.0)	6.42±0.16 (1.1)	6.39±0.18 (1.1)	6.44±0.20 (1.2)
2b	6	6.39±0.07 (1.0)		6.54±0.09 (1.4)	6.72±0.12 (2.1)	7.10±0.11 (5.1)	7.21±0.10 (6.6)	7.14±0.11 (5.6)
2c	4	6.31±0.012 (1.0)		6.77±0.12 (2.9)	6.92±0.08 (4.1)	7.29±0.09 (9.6)	7.33±0.09 (10.4)	7.32±0.07 (10.2)
2d	4	6.40±0.09 (1.0)		6.84±0.11 (2.8)	6.96±0.12 (3.6)	7.24±0.14 (6.9)	7.38±0.13 (9.6)	7.40±0.13 (10.0)
2e	6	6.36±0.12 (1.0)	6.73±0.09 (2.3)	7.18±0.12 (6.6)	7.37±0.11 (10.2)	7.45±0.10 (12.3)	7.48±0.15 (13.2)	7.44±0.12 (12.0)
2f	6	6.38±0.10 (1.0)	6.73±0.09 (2.2)	6.84±0.09 (2.9)	6.95±0.16 (3.7)	7.30±0.10 (8.3)	7.35±0.18 (9.3)	7.48±0.13 (12.6)
2g	6	6.37±0.08 (1.0)		6.54±0.12 (1.5)	6.65±0.12 (1.9)	7.06±0.16 (4.9)	7.28±0.16 (8.1)	7.36±0.17 (9.8)
2h	6	6.28±0.09 (1.0)				6.46±0.08 (1.5)	6.89±0.16 (4.1)	6.88±0.11 (4.0)
2i	4	6.33±0.15 (1.0)				6.47±0.10 (1.4)	6.61±0.08 (1.9)	6.85±0.08 (3.3)
2j	6	6.17±0.04 (1.0)			6.31±0.07 (1.4)	6.44±0.08 (1.9)	6.72±0.13 (3.5)	7.05±0.11 (7.6)
2k	4	6.36±0.05 (1.0)		6.36±0.05 (1.9)	6.79±0.10 (2.7)	7.00±0.10 (4.4)	7.21±0.12 (7.1)	7.46±0.10 (12.6)
2l	4	6.38±0.16 (1.0)		6.77±0.13 (2.5)	6.88±0.10 (3.2)	7.12±0.10 (5.5)	6.95±0.13 (3.7)	6.66±0.12 (1.9)
3a	6	6.36±0.10 (1.0)			6.59±0.10 (1.7)	6.90±0.09 (3.5)	7.22±0.05 (7.2)	7.35±0.04 (9.8)
3b	6	6.34±0.10 (1.0)				6.48±0.09 (1.4)	6.70±0.12 (2.3)	6.89±0.11 (3.5)
3c	2	6.15 (1.0)			6.18 (1.1)	6.12 (0.9)	6.06 (0.8)	6.05 (0.8)
4	5	6.32±0.06 (1.0)					6.51±0.04 (1.5)	6.81±0.09 (3.1)
5	5	6.42±0.06 (1.0)		6.42±0.10 (1.0)	6.41±0.11 (1.0)	6.41±0.11 (1.0)	6.49±0.14 (1.2)	6.68±0.10 (1.8)
6	6	6.37±0.15 (1.0)	6.83±0.09 (2.9)	7.20±0.04 (6.8)	7.35±0.05 (9.6)	7.37±0.11 (10.0)	7.06±0.09 (4.9)	6.77±0.16 (2.5)

a) Activity ratio is calculated as the antilogarithm of the difference between the pD_2 values for NE obtained in the absence and presence of the test compounds, respectively. *b*) *n* is the number of experiments.

ATP receptor-mediated uptake in addition to the carrier-mediated neuronal amine uptake. The fact that (*R*)-(+)-**1a**[14] and (*R*)-(+)-**2a** showed high enantioselectivities in NE uptake inhibition, as noted above, also suggest that there may be a specific receptor for NE uptake. On the basis of these findings, (*R*)-(+)-**1a** and (*R*)-(+)-**2a** should be valuable tools for analysis of the amine $uptake_1$ mechanism.

Antidepressant activity of the racemic 4-chlorophenyl derivative (**2a**) was evaluated by a forced swimming test in rats according to the method reported by Porsolt *et al.*[23] The results (Table II) indicate that the activity of **2a**

TABLE II. Effects of 4-(4-Chlorophenyl)isoquinolin-4-ol (**2a**) and Desipramine on the Total Duration of Immobility Induced in Rats Forced to Swim for 5 min

Drug	Control	Desipramine	Compound **2a**	
Amount (mg/kg)	—	20	2	5
Duration of immobility (s)	162.1	50.9[a]	59[a]	47.7[a]

a) $p<0.01$.

in terms of the reduction of total duration of immobility was about 10 times that of desipramine. Thus, the 4-chloro derivative (**2a**) appears to be a candidate for a new antidepressant.

Experimental

Chemistry All melting points are given as uncorrected values. Infrared (IR) spectra were taken with a Perkin-Elmer 1720 infrared Fourier transform spectrometer. High-resolution mass spectra (MS) were recorded on a JEOL JMS-D 300 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-FX 200 spectrometer with tetramethylsilane as a standard. Optical rotations were determined with a Union PM-201 polarimeter. CD spectra were recorded on a JASCO J-600 spectropolarimeter. HPLC was run on a Shimadzu LC-6A liquid chromatograph equipped with a chiral stationary phase column (Daicel Chiralcel OJ).

2-Iodo-*N*-*n*-propylbenzylamine (7c) A 0.9 N HCl–MeOH solution (46 ml, 41.4 mmol) and $NaBH_3CN$ (1.00 g, 15.9 mmol) were added to a solution of 2-iodobenzaldehyde (4.81 g, 20.7 mmol) and *n*-propylamine (7.35 g, 124.4 mmol) in absolute MeOH (10 ml) under ice-cooling. The mixture was stirred at room temperature for 48 h. The precipitate was removed by filtration. The filtrate was made acidic with concentrated HCl and evaporated, and the residue was taken up in 50 ml of water. The solution was washed with ether, made basic with concentrated NH_4OH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give **7c** as a pale yellow oil (4.26 g). ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, dd, J=8, 1 Hz, H-3), 7.38 (1H, dd, J=7.5, 2 Hz, H-6), 7.31 (1H, ddd, J=7.5, 7, 1 Hz, H-5), 6.95 (1H, ddd, J=8, 7, 2 Hz, H-4), 3.80 (2H, s, $ArC\underline{H}_2N$), 2.60 (2H, t, J=7.5 Hz, $NC\underline{H}_2CH_2$), 1.64—1.46 (3H, m, $C\underline{H}_2CH_3$ and NH), 0.94 (3H, t, J=7.5 Hz, CH_3). IR (KBr): 3326 cm^{-1}. This free base was converted to the hydrochloride, colorless cubes (3.57 g, 55.3%) (from MeOH–acetone), mp 116—117 °C. *Anal.* Calcd for $C_{10}H_{14}IN\cdot HCl$: C, 38.55; H, 4.85; N, 4.50. Found: C, 38.60; H, 4.84; N, 4.48.

2-Iodo-*N*-isopropylbenzylamine (7d) A 5 N HCl–MeOH solution (8 ml, 40.0 mmol) and $NaBH_3CN$ (1.00 g, 15.9 mmol) were added to a solution of 2-iodobenzaldehyde (4.64 g, 20.0 mmol) and isopropylamine (7.09 g, 120 mmol) in absolute MeOH (28 ml) under ice-cooling. The mixture was stirred at room temperature for 72 h. Work-up in the same way as described for **7c** gave **7d** as a pale yellow oil (4.98 g). ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, dd, J=8, 1 Hz, H-3), 7.38 (1H, dd, J=7.5, 2 Hz, H-6), 7.31 (1H, ddd, J=7.5, 7, 1 Hz, H-5), 6.94 (1H, ddd, J=8, 7, 2 Hz, H-4), 3.80 (2H, s, $ArC\underline{H}_2N$), 2.94—2.76 (1H, m, CH), 1.60 (1H, br s, NH), 1.12 (6H, d, J=6.5 Hz, CH ($C\underline{H}_3)_2$). IR (KBr): 3307 cm^{-1}. This free base was converted to the hydrochloride, colorless cubes (from MeOH–acetone) (4.57 g, 73.4%), mp 202—203 °C. *Anal.* Calcd for $C_{10}H_{14}IN\cdot HCl$: C, 38.55; H, 4.85; N, 4.50. Found: C, 38.37; H, 4.93; N, 4.45.

4-Phenyl-2-*n*-propyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1c) A solution of phenacyl bromide (**8a**) (706 mg, 3.55 mmol) in dioxane (15 ml) was added to a solution of **7c** (1.952 g, 7.09 mmol) in dioxane (15 ml). The mixture was stirred at room temperature for 5 h and evaporated. Benzene (20 ml) was added to the residue and the precipitate formed was removed by filtration. The filtrate was evaporated to give a crude product (1.736 g). The crude product was sujected to flash chromatography on SiO_2 with $CHCl_3$–hexane (5 : 1) to afford the phenacylamine (**9c**) as a pale yellow oil (1.094 g, 78.4%). ^{1}H-NMR ($CDCl_3$) δ: 7.91 (2H, dd, J=8, 1.5 Hz, H-2 and 6), 7.81 (1H, dd, J=8, 1 Hz, H-3′), 7.29 (1H, ddd, J=7.5, 7, 1 Hz, H-5′), 6.93 (1H, ddd, J=8, 7, 2 Hz, H-4′), 3.95 and 3.83 (each 2H, s, $COC\underline{H}_2NC\underline{H}_2Ar$), 2.66 (2H, t, J=7.5 Hz, $NC\underline{H}_2CH_2$), 1.63—1.44 (2H, m, $C\underline{H}_2CH_3$), 0.85 (3H, t, J=7.5 Hz, CH_3). IR (KBr): 1693 cm^{-1}. MS Calcd for $C_{18}H_{20}INO$ (M−1): 392.0511. Found: 392.0503. This was used for the following cyclization reaction without further purification.[24]

Ph_3P (2.787 g, 10.97 mmol), $NiCl_2$ (694 mg, 5.49 mmol) and Zn (359 mg, 5.49 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N_2. Dry oxygen-free dimethyl sulfoxide (DMF) (30 ml) was added through a syringe. The mixture was stirred at 55 °C for 5 min. A solution of **9c** (1.079 g, 2.74 mmol) prepared as above in dry oxygen-free DMF (4 ml) was added and the mixture was stirred at 55—60 °C for 10 h. Then, the mixture was made acidic (pH 2) with 2% HCl and washed with ether (100 ml × 3). The aqueous layer was made basic (pH 9) with concentrated NH_4OH and extracted with $CHCl_3$ (50 ml × 4). The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give a pale brown oil (639 mg). This was subjected to preparative TLC on Al_2O_3 with benzene–$CHCl_3$ (10 : 1) to give pale yellow crystals (470 mg). Recrystallization from MeOH afforded **1c** as colorless pillars (431 mg, 60.0%), mp 63—64 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.47—6.94 (9H, m, ArH), 4.05 and 3.57 (each 1H, d, J=15 Hz, $ArC\underline{H}_2N$), 3.05 and 2.75 (each 1H, d, J=12 Hz, CCH_2N), 2.61 and 2.55 (each 1H, dt, J=12, 7.5 Hz, $NC\underline{H}_2CH_2$), 1.68—1.59 (2H, m, $C\underline{H}_2CH_3$), 0.96 (3H, t, J=7.5 Hz, CH_3). IR (KBr): 3314 cm^{-1}. *Anal.* Calcd for $C_{18}H_{21}NO\cdot 0.5H_2O$: C, 78.22; H, 8.02; N, 5.07. Found: C, 78.22; H, 8.22; N, 4.99. This free base was converted to the hydrochloride, colorless needles (from MeOH), mp 177—178 °C (dec.). *Anal.* Calcd for $C_{18}H_{21}NO\cdot HCl\cdot 0.2H_2O$: C, 70.32; H, 7.34; N, 4.56. Found: C, 70.54; H, 7.44; N, 4.45.

4-Phenyl-2-isopropyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1d) A solution of phenacyl bromide (**8a**) (376 mg, 1.89 mmol) in dioxane (10 ml) was added to a solution of **7d** (1.039 g, 3.78 mmol) in dioxane (10 ml). The mixture was stirred at room temperature for 5 h. Work-up in the same way as described for **9c** gave the phenacylamine (**9d**) as a pale yellow oil (627 mg, 84.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.91 (2H, dd, J=8, 1.5 Hz, H-2 and 6), 7.75 (1H, dd, J=8, 1 Hz, H-3′), 7.57—7.35 (4H, m, H-3, 4, 5 and 6′), 7.27 (1H, ddd, J=7.5, 7, 1 Hz, H-5′), 6.90 (1H, ddd, J=8, 7, 2 Hz, H-4′), 3.91 and 3.75 (each 2H, s, $COC\underline{H}_2NC\underline{H}_2Ar$), 3.16—2.97 (1H, m, CH), 1.13 [6H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$]. IR(KBr): 1697 cm^{-1}. MS Calcd for $C_{18}H_{20}INO(M^+)$: 393.0591. Found: 393.0596.

In the same way as described for **9c**, treatment of a solution of **9d** (523 mg, 1.33 mmol) freshly prepared as above in dry oxygen-free DMF (3 ml) with a solution of Ph_3P (1.349 g, 5.32 mmol), $NiCl_2$ (336 mg, 2.57 mmol) and Zn (174 mg, 2.57 mmol) in dry oxygen-free DMF (25 ml) gave a crude product (301 mg). The crude product was purified by preparative TLC on Al_2O_3 with benzene–$CHCl_3$ (7 : 1) to afford **1d** as a pale yellow oil (209 mg, 62.3%). ^{1}H-NMR ($CDCl_3$) δ: 7.50—6.90 (9H, m, ArH), 3.93 and 3.83 (each 1H, d, J=15 Hz, $ArC\underline{H}_2N$), 2.96 and 2.77 (each 1H, d, J=12 Hz, CCH_2N), 3.08—2.88 (1H, m, CH), 1.13 and 1.11 [6H, each d, J=6.5 Hz, $CH(C\underline{H}_3)_2$]. IR (KBr): 3453 cm^{-1}. The free base was converted to the hydrochloride, colorless needles (from EtOH), mp 184—189 °C (dec.). *Anal.* Calcd for $C_{18}H_{21}NO\cdot HCl$: C, 71.16; H, 7.30; N, 4.61. Found: C, 70.84; H, 7.56; N, 4.52.

4-Phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1f) A 1 N HCl–MeOH solution (1.50 ml) and 20% $Pd(OH)_2$–C (65 mg) were added to a solution of **1e**[16] (472 mg, 1.50 mmol) in MeOH (7 ml) and the mixture was stirred under H_2 and at ambient atmospheric pressure and at room temperature for 3 h. The reaction mixture was filtered and the filtrate was evaporated. H_2O (7 ml) was added and the mixture was made basic with concentrated NH_4OH. The mixture was extracted with $CHCl_3$ (15 ml × 3). The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give an oil (382 mg). This crude product was purified by preparative TLC on SiO_2 with $CHCl_3$–MeOH (25 : 2) to give **1f** as a pale yellow oil (298 mg, 88.4%). ^{1}H-NMR ($CDCl_3$) δ: 7.42—6.94 (9H, m, ArH), 4.09 and 3.97 (each 1H, d, J=15 Hz, $ArC\underline{H}_2N$), 3.18 and 3.07 (each 1H, d, J=12.5 Hz, CCH_2N). IR (KBr): 3062 cm^{-1}. This was converted to the hydrochloride, colorless cubes, mp 195—196 °C (dec.) (lit.[25] mp 230 °C) (from EtOH). *Anal.* Calcd for $C_{15}H_{15}NO\cdot HCl$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.60; H, 6.07; N, 5.32.

2-Allyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1g) A solution of allyl bromide (240 mg, 1.18 mmol) in benzene (1 ml) was added to a mixture of **1f** (88 mg, 0.39 mmol), K_2CO_3 (810 mg, 5.86 mmol) and benzene (5 ml) under stirred at 55 °C. The mixture was stirred at 55—60 °C for 6 h and filtered. The filtrate was washed with H_2O (7 ml × 2), dried over $MgSO_4$ and evaporated to give a crude product (96 mg). This was subjected to preparative TLC on SiO_2 with benzene–acetone (10 : 1) to afford **1g** as colorless plates (85 mg, 81.9%). ^{1}H-NMR ($CDCl_3$) δ:

7.48—6.92 (9H, m, ArH), 5.91 (1H, dddd, J=17, 10, 6.5, 6.5 Hz, CH=), 5.23 (1H, ddd, J=17, 1.5, 1.5 Hz, =CH_2), 5.20 (1H, ddd, J=10, 1.5, 1.5 Hz, =CH_2), 3.96 and 3.53 (each 1H, d, J=15 Hz, ArCH_2N), 3.26 and 3.17 (each 1H, dddd, J=13.5, 6.5, 1.5, 1.5 Hz, NCH_2CH=), 3.04 and 2.67 (each 1H, d, J=12 Hz, CCH_2N). IR (KBr): 3402 and 1644 cm^{-1}. This free base was converted to the hydrochloride, colorless needles (from EtOH), mp 179—181 °C (dec.). *Anal.* Calcd for $C_{18}H_{19}NO \cdot HCl$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.24; H, 6.70; N, 4.65.

4-Phenyl-2-propargyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1h) A solution of propargyl bromide (85 mg, 0.71 mmol) in benzene (1 ml) was added to a mixture of **1f** (31 mg, 0.14 mmol), K_2CO_3 (285 mg, 2.07 mmol) and benzene (2 ml). The mixture was stirred at 55—60 °C for 6 h. Work-up in the same way as described for **1g** gave **1h** as colorless cubes (27 mg, 73.7%). ^{1}H-NMR ($CDCl_3$) δ: 7.47—6.93 (9H, m, ArH), 3.87 and 3.77 (each 1H, d, J=15 Hz, ArCH_2N), 3.52 (2H, d, J=2.5 Hz, CH_2C=), 2.98 and 2.91 (each 1H, d, J=12 Hz, CCH_2N), 2.27 (1H, t, J=2.5 Hz, =CH). IR (KBr): 3280, 3249, 2104 cm^{-1}. This free base was converted to the hydrochloride, colorless needles (from MeOH), mp 202—207 °C (dec.). *Anal.* Calcd for $C_{18}H_{17}NO \cdot HCl \cdot 0.2H_2O$: C, 71.26; H, 6.11; N, 4.62. Found: C, 71.51; H, 6.07; N, 4.47.

4-(2,4-Dichlorophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (2d) A solution of 2,4-dichlorophenacyl bromide (**10d**) (372 mg, 1.39 mmol) in dioxane (5 ml) was added to a solution of **7a** (686 mg, 2.77 mmol) in dioxane (5 ml). The mixture was stirred at room temperature for 3 h. Work-up in the same way as described for **9c** gave **11d** as a plae yellow oil (193 mg, 31.9%). ^{1}H-NMR ($CDCl_3$) δ: 7.81 (1H, d, J=8 Hz, H-3'), 7.41 (1H, d, J=2 Hz, H-3), 7.34 (1H, d, J=7.5 Hz, H-6), 7.25 (1H, dd, J=7.5, 2 Hz, H-5), 6.95 (1H, m, H-4'), 3.80 and 3.70 (each 2H, s, $COCH_2NCH_2Ar$), 2.39 (3H, s, NCH_3). IR (KBr): 1698 cm^{-1}. MS Calcd for $C_{16}H_{14}Cl_2INO$ (M^+): 432.9499. Found: 432.9459.

n-BuLi (0.32 ml of 1.6 M solution in hexane, 0.52 mmol) was added to a solution of **11d** (173 mg, 0.40 mmol) in THF (4 ml) under N_2 at −78 °C. The mixture was stirred at −78 °C for 10 min and warmed up to room temperature. Then, H_2O (20 ml) was added and the mixture was extracted with ether. The extract was dried over $MgSO_4$ and evaporated to give an oil (157 mg). The oil was purified by preparative TLC on SiO_2 with $CHCl_3$–ethyl acetate (10 : 1) to afford **2d** as a pale yellow oil (71.4 mg, 58.0%). ^{1}H-NMR ($CDCl_3$) δ: 8.20 (1H, d, J=8.5 Hz, H-6'), 7.35 (1H, dd, J=8.5, 2 Hz, H-5'), 7.27 (1H, d, J=2 Hz, H-3'), 7.22—6.81 (4H, m, ArH), 3.41 and 3.34 (each 1H, d, J=15 Hz, ArCH_2N), 3.31 and 2.76 (each 1H, d, J=12 Hz, CCH_2N), 2.38 (3H, s, NCH_3). IR (KBr): 3168 cm^{-1}. This free base was converted to the hydrochloride, colorless needles (from EtOH), mp 209—210.5 °C (dec.). *Anal.* Calcd for $C_{16}H_{15}Cl_2NO \cdot HCl \cdot 0.2H_2O$: C, 55.04; H, 4.76; N, 4.01. Found: C, 55.07; H, 4.42; N, 3.91.

4-(4-Trifluoromethylphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (2i) A solution of 4-trifluoromethylphenacyl bromide (**10i**) (404 mg, 1.51 mmol) in dioxane (5 ml) was added to a solution of **7a** (747 mg, 3.02 mmol) in dioxane (5 ml). The mixture was stirred at room temperature for 3 h. Work-up in the same way as described for **9c** gave **11i** as a pale yellow oil (377 mg, 57.7%). ^{1}H-NMR ($CDCl_3$) δ: 8.05 (2H, d, J=8 Hz, H-2 and 6), 7.85 (1H, dd, J=8, 1 Hz, H-3'), 7.67 (2H, d, J=8 Hz, H-3 and 5), 7.40 (1H, dd, J=7.5, 2 Hz, H-6'), 7.31 (1H, ddd, J=7.5, 7.5, 1 Hz, H-5'), 6.97 (1H, ddd, J=8, 7.5, 2 Hz, H-4'), 3.84 and 3.73 (each 2H, s, $COCH_2NCH_2Ar$), 2.41 (3H, s, NCH_3). IR (KBr): 1692 cm^{-1}. MS Calcd for $C_{17}H_{15}F_3INO$ (M^+): 433.0147. Found: 433.0118.

n-BuLi (0.66 ml of 1.6 M solution in hexane, 1.05 mmol) was added to a solution of **11i** (350 mg, 0.81 mmol) in THF (4 ml) under N_2 at −78 °C. The mixture was stirred at −78 °C for 10 min. Work-up in the same way as described for **2d** gave **2i** as a pale brown oil (162 mg, 65.2%). ^{1}H-NMR ($CDCl_3$) δ: 7.56 (4H, s, H-2', 3', 5' and 6'), 7.27—6.87 (4H, m, H-5, 6, 7 and 8), 3.25 (2H, s, ArCH_2N), 2.93 and 2.57 (each 1H, d, J=12 Hz, CCH_2N), 2.32 (3H, s, NCH_3). IR (KBr): 3162 cm^{-1}. This free base was converted to the hydrochloride, colorless needles (from EtOH), mp 207—210 °C (dec.). *Anal.* Calcd for $C_{17}H_{16}F_3NO \cdot HCl$: C, 59.40; H, 4.98; N, 4.07. Found: C, 59.01; H, 4.63; N, 4.16.

4-(4-Benzyloxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (2k) 4-Benzyloxyphenacyl bromide (**10k**) (980 mg, 3.21 mmol) was added to a solution of **7a** (1.587 g, 6.43 mmol) in dioxane (20 ml). The mixture was stirred at room temperature for 3 h. Work-up in the same way as described for **9c** gave **11k** as a pale yellow oil (1.440 g, 95.1%). ^{1}H-NMR ($CDCl_3$) δ: 7.96 (2H, d, J=9 Hz, H-2 and 6), 7.84 (1H, dd, J=7.5, 1 Hz, H-3'), 7.46 (1H, dd, J=7.5, 2 Hz, H-6'), 7.31 (1H, ddd, J=7.5, 7.5, 1 Hz, H-5'), 6.97 (2H, d, J=9 Hz, H-3 and 5), 7.01—6.91 (1H, m, H-4'), 5.12 (2H, s, ArCH_2O), 3.83 and 3.75 (each 2H, s, $COCH_2NCH_2Ar$), 2.41 (3H, s, NCH_3). IR (KBr): 1676 cm^{-1}. MS Calcd for $C_{23}H_{22}INO_2$ (M^+): 471.0696. Found: 471.0706.

n-BuLi (0.89 ml of 1.6 M solution in hexane, 1.43 mmol) was added to a solution of **11k** (519 mg, 1.10 mmol) in THF (4 ml) under N_2 at −78 °C and the mixture was stirred for 10 min. Work-up in the same way as described for **2d** gave **2k** as a pale brown oil (183 mg, 48.1%). ^{1}H-NMR ($CDCl_3$) δ: 7.37 (2H, d, J=9 Hz, H-2' and 6'), 5.07 (2H, s, ArCH_2O), 3.88 and 3.46 (each 1H, d, J=15 Hz, ArCH_2N), 2.90 and 2.66 (each 1H, d, J=12 Hz, CCH_2N), 2.45 (3H, s, NCH_3). IR (KBr): 3320 cm^{-1}. This free base was converted to the hydrochloride, colorless cubes (from MeOH), mp 183.5—185 °C (dec.). *Anal.* Calcd for $C_{23}H_{23}NO_2 \cdot HCl \cdot 0.25H_2O$: C, 71.49; H, 6.39; N, 3.62. Found: C, 71.13; H, 6.41; N, 3.66.

2-Methyl-4-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-4-ol (2l) A solution of 4-methylphenacyl bromide (**10l**) (747 mg, 3.51 mmol) in dioxane (10 ml) was added to a solution of **7a** (1.733 g, 7.01 mmol) in dioxane (10 ml). The mixture was stirred at room temperature for 30 min. Work-up in the same way as described for **9c** gave **11l** (1.067 g, 80.7%). ^{1}H-NMR ($CDCl_3$) δ: 7.87 (2H, d, J=8 Hz, H-2 and 6), 7.85 (1H, dd, J=7.5, 1.5 Hz, H-3'), 7.48 (1H, dd, J=7.5, 2 Hz, H-6'), 7.31 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-5'), 7.22 (2H, d, J=8 Hz, H-3 and 5), 6.96 (1H, ddd, J=7.5, 7.5, 2 Hz, H-4'), 3.88 and 3.76 (each 2H, s, $COCH_2NCH_2Ar$), 2.42 and 2.40 (each 3H, s, NCH_3 and ArCH_3). MS Calcd for $C_{17}H_{18}INO$ (M^+): 379.0351. Found: 379.0382.

n-BuLi (0.6 ml of 1.6 M solution in hexane, 0.96 mmol) was added to a solution of **11l** (284 mg, 0.784 mmol) in THF (5 ml) under N_2 at −78 °C and the mixture was stirred for 10 min. Work-up in the same way as described for **2d** gave **2l** as a pale brown oil (115 mg, 60.8%). ^{1}H-NMR ($CDCl_3$) δ: 7.35 (2H, d, J=8 Hz, H-2' and 6'), 7.12 (2H, d, J=8 Hz, H-3' and 5'), 3.85 and 3.33 (each 1H, d, J=15 Hz, ArCH_2N), 2.93 and 2.63 (each 1H, d, J=12 Hz, CCH_2N), 2.34 and 2.32 (each 3H, s, NCH_3 and ArCH_3). This free base was converted to the hydrochloride, colorless needles (from MeOH–acetone), mp 180—185 °C (dec.). *Anal.* Calcd for $C_{17}H_{19}NO \cdot HCl \cdot 0.33H_2O$: C, 69.03; H, 7.04; N, 4.74. Found: C, 68.91; H, 7.01; N, 4.72.

α-(2-Iodophenyl)-*N*-methylethylamine (7f) 2-Iodophenyl methyl ketone (6.432 g, 26.2 mmol) and $NaBH_3CN$ (1.643 g, 52.4 mmol) were added to a mixture of CH_3NH_2 (16.21 g of 30% MeOH solution, 157.2 mmol) and 1 N HCl–MeOH (52.3 ml, 52.3 mmol) under N_2. The mixture was stirred at room temperature for 18 h. The precipitate formed was removed by filtration and the filtrate was evaporated. The residue was taken up in H_2O (80 ml) and the mixture was made acidic (pH 2) with concentrated HCl. The aqueous layer was washed with ether and made basic (pH 9) with solid KOH. The mixture was extracted with ether. The extract was dried over $MgSO_4$ and evaporated to give **7f** as a pale yellow oil (5.050 g). ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, dd, J=8, 1 Hz, H-3), 6.93 (1H, m, H-4), 3.96 (1H, q, J=6.5 Hz, CH), 2.31 (3H, s, NCH_3), 1.63 (1H, s, NH), 1.29 (3H, d, J=6.5 Hz, $CHCH_3$). IR (CCl_4): 3350 cm^{-1}. This free base was converted to the hydrochloride, colorless prisms (from MeOH–acetone), mp 187—189 °C. *Anal.* Calcd for $C_9H_{12}IN \cdot HCl$: C, 36.33; H, 4.40; N, 4.71. Found: C, 36.38; H, 4.43; N, 4.63.

1,2-Dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (3a) A solution of phenacyl bromide (**8a**) (884 mg, 4.44 mmol) in dioxane (15 ml) was added to a solution of **7f** (2.319 g, 8.89 mmol) in dixane (15 ml) and the mixture was stirred at room temperature for 19 h. Work-up in the same way as described for **9c** gave **12a** as a pale yellow oil (1.406 g, 83.5%). ^{1}H-NMR ($CDCl_3$) δ: 7.91—7.81 (3H, m, H-2, 6 and 3'), 6.94 (1H, m, H-4'), 4.07 (1H, q, J=6.5 Hz, CH), 3.90 and 3.78 (each 1H, d, J=16.5 Hz, ArCH_2N), 2.39 (3H, s, NCH_3), 1.34 (3H, d, J=6.5 Hz, $CHCH_3$). IR (CCl_4): 1700 cm^{-1}. MS Calcd for $C_{17}H_{18}INO$ (M^+): 379.0434. Found 379.0394.

n-BuLi (1.3 ml of 1.6 M solution in hexane, 2.03 mmol) was added a solution of **12a** (591 mg, 1.56 mmol) in tetrahydrofuran (THF) (4 ml) under N_2 at −78 °C. The mixture was stirred for 10 min. Work-up in the same way as described for **2d** gave a crude product (406 mg), which was subjected to flash chromatography on SiO_2 with $CHCl_3$–acetone (5 : 1) to give **3a** as colorless prisms (145 mg, 36.6%) (from EtOH), mp 132—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.95 (1H, dd, J=7.5, 2 Hz, H-5), 4.10 (1H, q, J=7 Hz, ArCHN), 3.25 and 2.71 (each 1H, d, J=12 Hz, CCH_2N), 2.54 (3H, s, NCH_3), 1.35 (3H, d, J=7 Hz, $CHCH_3$). MS Calcd for $C_{17}H_{19}NO$ (M^+): 253.1466. Found: 253.1506. *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found; C, 80.48; H, 7.74; N,

5.46. This free base was converted to the hydrochloride, colorless pillars, mp 193—196 °C (dec.). *Anal.* Calcd for $C_{17}H_{19}NO \cdot HCl \cdot 0.75H_2O$: C, 70.46; H, 6.96; N, 4.83. Found: C, 70.10; H, 7.00; N, 4.80.

4-Methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (4) KH (29 mg of 0.35% dispersion in oil, 0.25 mmol) was placed in a two-necked flask under N_2 and washed with dry pentane (3 ml × 2). Dry THF (2 ml) was added and the mixture was cooled at 0 °C. A solution of **1a** (30 mg, 0.13 mmol) and CH_3I (0.015 ml, 0.25 mmol) in dry THF (2 ml) was added over 2 min with a syringe. MeOH (0.5 ml) was added and the mixture was evaporated to give a crude product (81 mg). The crude product was purified by preparative TLC on SiO_2 with $CHCl_3$–actone (3 : 1) to afford **4** as a pale yellow oil (24.9 mg, 78.4%). ^{1}H-NMR ($CDCl_3$) δ: 7.42—7.08 (9H, m, ArH), 3.85 (and 3.47 (each 1H, d, J=15 Hz, $ArC\underline{H}_2N$), 3.24 (3H, s, OCH_3), 3.09 and 2.59 (each 1H, d, J=12 Hz, CCH_2N), 2.40 (3H, s, NCH_3). IR (KBr): 2937, 1447, 1076 cm^{-1}. MS Calcd for $C_{17}H_{19}NO$ (M−1): 252.1386. Found: 252.1368. This oil was converted to the acidic styphnate,[26] yellow cubes (from acetone), mp 176—179 °C (dec.). *Anal.* Calcd for $C_{17}H_{19}NO \cdot C_6H_3N_3O_8$: C, 55.42; H, 4.45; N, 11.24. Found: C, 55.21; H, 4.24; N, 10.92.

Resolution of (±)-4-(4-Chlorophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol (2a) (±)-**2a** (115 mg) was submitted to semi-preparative HPLC with a hexane–2-propanol (25 : 1) mixture at a flow rate of 4 ml/min to give two fractions (detected at 220 nm). The first fraction at 8.8 min retention time afforded the (+)-enantiomer (39.6 mg) as a white solid, $[\alpha]_D^{23}$ +50.0° (c=0.76, methanol). CD (c=0.00505, methanol) $[\theta]^{23}$ (nm): 0 (232), −26000 (224) (negative maximum), 0 (217), +32000 (205) (positive maximum). IR (KBr): 3181, 2786, 1491, 1459 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.39 (2H, d, J=9 Hz, H-3′ and 5′), 7.29 (2H, d, J=9 Hz, H-2′ and 6′), 6.93 (1H, dd, J=8, 1.5 Hz, H-5), 3.70 and 3.43 (each 1H, d, J=15 Hz, $ArC\underline{H}_2N$), 2.96 and 2.66 (each 1H, d, J=12 Hz, CCH_2N), 2.45 (3H, s, NCH_3). This free base was converted to the hydrochloride of (+)-**2a**, colorless needles (from EtOH), mp 203.5—204 °C (dec.). *Anal.* Calcd for $C_{16}H_{16}ClNO \cdot HCl$: C, 61.95; H, 5.52, N, 4.52. Found: C, 61.61; H, 5.54; N, 4.42.

The second fraction at 12.0 min retention time gave the (−)-enantiomer (34.9 mg) as a white solid, $[\alpha]_D^{23}$ −50.1° (c=0.74, methanol). CD (c=0.00505, methanol) $[\theta]^{23}$ (nm): 0 (232), +26000 (224) (positive maximum), 0 (217), −32000 (205) (negative maximum). The IR and ^{1}H-NMR spectra of this (−)-enantiomer were identical with those of the (+)-enantiomer. This free base was converted to the hydrochloride of (−)-**2a**, colorless needles (from EtOH), mp 204—205 °C (dec.). *Anal.* Calcd for $C_{16}H_{16}ClNO \cdot HCl \cdot 0.33H_2O$: C, 60.77; H, 5.63; N, 4.43. Found: C, 60.94; H, 5.49; N, 4.41.

Pharmacology The method used for evaluating these compounds has been reported in our previous papers.[13,14] The isolated rat anococcygeus muscle was used for the assay of potentiating activity of tetrahydroisoquinolin-4-ols on the response to NE, which was evaluated from the shift in the concentration–response curves for NE. The potency of drugs for the potentiation of NE was expressed as the activity ratio, which was determined as the antilogarithm of the difference between the pD_2 values for NE (negative logarithm of the molar concentration of the agonist producing 50% of the maximum response) in the presence and absence of the test compounds.

Forced Swimming Test A behavioral screening test of the racemic 4-chlorophenyl derivative (**2a**) as an antidepressant was carried out according to the method reported by Porsolt *et al.*[23] Ten male Wistar rats were used as each group. Rats were individually forced to swim inside vertical stainless steel cylinders (height, 40 cm; diameter, 18 cm) containing 17 cm of water maintained at 25 °C. After 15 min in the water they were removed and received an intraperitoneal injection of a drug. After 23 h, the drug was again administered. They were replaced in the cylinder 1 h later and the total duration of immobility was measured during a 5 min test.

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