# *trans*-2-Aryl-*N*,*N*-dipropylcyclopropylamines: Synthesis and Interactions with 5-$HT_{1A}$ Receptors

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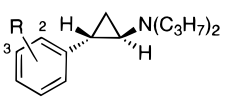
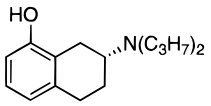
Twelve *N*,*N*-dipropyl-substituted derivatives of *trans*-2-arylcyclopropylamine have been prepared and assayed for their ability to displace [$^3$H]-8-OH-DPAT from rat brain 5-$HT_{1A}$ receptors. The new derivatives include phenyl (**7a**), bromo- (**7b**) and fluorophenyl (**7c**−**e**), 2-methoxy-5-fluorophenyl (**7h**), and 2-hydroxy-5-fluorophenyl (**7l**) as well as trifluoromethylphenyl (**7f**) and 2,3-dichlorophenyl (**7g**) analogues. In the present series of compounds, electron-withdrawing substituents in the phenyl ring appear to decrease the affinity for 5-$HT_{1A}$ receptors. In contrast, electron-rich aryl groups, such as 2- or 3-thienyl (**7j** and **7k**, respectively), provide compounds with high affinity. The additional bulk produced by the aromatic moiety in the 2-benzothienyl derivative **7i** appears to be detrimental to 5-$HT_{1A}$ receptor affinity. The racemic mixtures of the interesting **7j** and **7l** were resolved into the enantiomers; **7j** and **7l** exhibited a high enantiomeric 5-$HT_{1A}$ receptor affinity ratio (75-fold and 100-fold, respectively). The enantiomers of **7j** and **7l** were evaluated *in vivo* by use of biochemical and behavioral tests in rats. Compound (1*R*,2*R*)-**7j** behaved as a partial agonist whereas (1*R*,2*S*)-**7l** appeared as an efficacious 5-$HT_{1A}$ receptor agonist, stimulating both autoreceptors and postsynaptic receptors.

## Introduction

The putative involvement of serotonergic 5-$HT_{1A}$ receptors in anxiety and depression has generated a considerable interest in the medicinal chemistry of selective 5-$HT_{1A}$ receptor agonists and antagonists.[1] A large number of 2-aminotetralin and arylpiperazine derivatives display high affinity and selectivity for the 5-$HT_{1A}$ receptors.[2] The 2-arylcyclopropylamine derivatives constitute another structural class of 5-$HT_{1A}$ ligands that has been much less investigated. However, *trans*-cyclopropylamines **1** and **2** have been identified as potent and selective 5-$HT_{1A}$ receptor agonists.[3] In contrast to the prototypal 5-$HT_{1A}$ receptor agonist 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT, **3**),[4] which exhibits a low stereoselectivity in its interactions with 5-$HT_{1A}$ receptors, phenylcyclopropylamine derivative **1** appears to be highly stereoselective; the affinity and potency of (1*R*,2*S*)-**1** is much higher than that of the antipode.[3,5]




(1*R*,2*S*)-**1**: R= 2-OH
(1*R*,2*S*)-**2**: R= 3-OH




(*R*)-**3**

Our previous study of structure−activity relationships (SAR) of *trans*-2-arylcyclopropylamine derivatives[3] was focused on variations of the phenolic substitution pattern and of the alkyl groups on the amino group. In the present study we have prepared a series of 12 racemic derivatives (**7a**−**l**) in which the *N*,*N*-dipropylcyclopropylamine moiety has been kept constant and in which the aromatic part has been varied. We have also prepared the enantiomers of the 5-fluoro-2-methoxyphenyl (**7h**), 5-fluoro-2-hydroxyphenyl (**7l**), and 2-thienyl (**7j**) derivatives. The compounds were studied for their ability to displace [$^3$H]-8-OH-DPAT from 5-$HT_{1A}$ receptors. In addition, four selected derivatives were evaluated *in vivo* by use of biochemical and behavioral studies in rats.

## Chemistry

The synthesis of the test compounds is described in Scheme 1; *trans* arylated methyl acrylates **4** were prepared from the corresponding aryl iodides by a palladium-catalyzed coupling with methyl acrylate under phase transfer conditions.[6]

4-Fluoro-2-iodoanisole is not commercially available. Attempts to prepare the compound regioselectively failed; we never achieved a regiospecific formation of an anion in the 2-position of 4-fluoroanisole and the 2- and 3-halogenated regioisomers were nonseparable. The best regioselectivity was accomplished at room temperature, but the yield was unacceptably low at this temperature. Consequently, an alternative synthetic route was chosen:[7a] 4-Fluoroanisole was chloromethylated in the 2-position with dimethoxymethane in a hydrochloric acid−sulfuric acid mixture, and the resulting intermediate was treated with hexamethylenetetraamine and acetic acid to form 4-fluoro-2-methoxybenzaldehyde which was converted into the corresponding *trans*-phenylpropenoate (**4h**) by a Knoevenagel condensation with malonic acid followed by esterification with methanol (Scheme 2).

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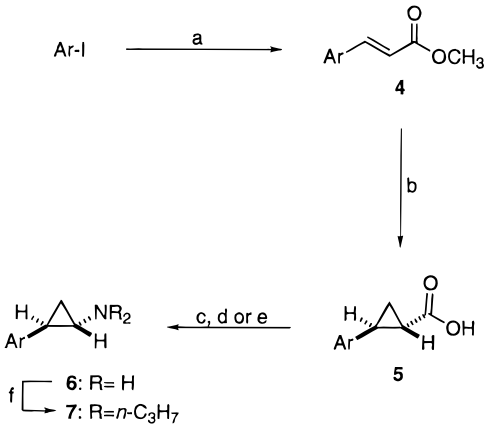
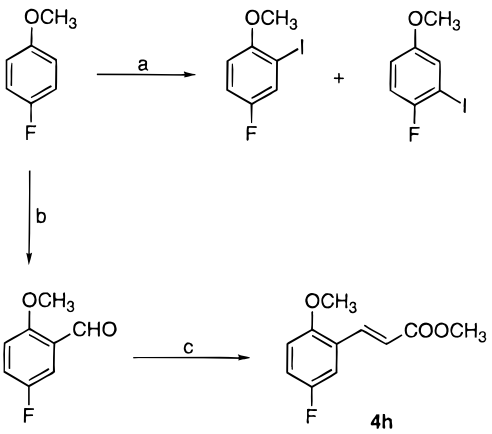
**Scheme 1**[a]




[a] Reagents: (a) methyl acrylate, $Pd(OAc)_2$, $NBu_4Cl$, $K_2CO_3$, DMF (method I); (b) (i) $CH_2N_2$, $Pd(OAc)_2$, (ii) NaOH, $H_2O$, MeOH (method III); (c) DPPA, $NEt_3$, *t*-BuOH (method V); (d) (i) $NEt_3$, EtOCOCl, acetone, (ii) $NaN_3$, (iii) *t*-BuOH, (iv) HCl (method VI); (e) (i) $NEt_3$, EtOCOCl, acetone, (ii) $NaN_3$, (iii) $TMS(CH_2)_2OH$, (iv) $NBu_4F$, THF (method VII); (f) PrI, $K_2CO_3$, acetonitrile (method VIII).

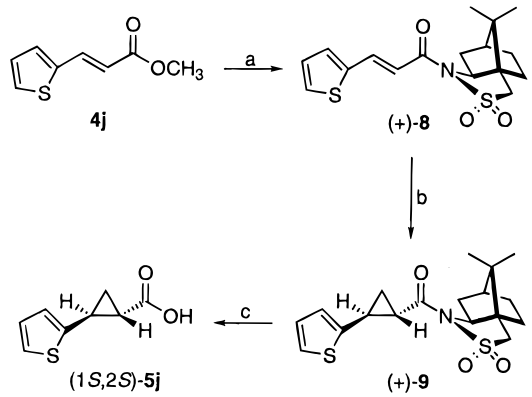
**Scheme 2**[a]




[a] Reagents: (a) (i) *n*-BuLi, THF, −78 → −25 °C, (ii) $I_2$, −78 °C → room temperature; (b) (i) concentrated HCl/concentrated $H_2SO_4$, 70 °C, (ii) hexamethylenetetramine, 50% aqueous HOAc, reflux; (c) (i) malonic acid, piperidine/pyridine, room temperature → 60 °C, (ii) Δ (100 °C), (iii) catalytic $H_2SO_4$, MeOH, reflux.

The arylated methyl acrylate derivatives were cyclopropanated with diazomethane in the presence of 0.005 equiv of palladium(II) acetate.[8] Higher concentrations of the catalyst often led to precipitation of palladium(0) with accompanying termination of the reaction. Alkaline hydrolysis gave the desired *trans*-arylcyclopropanecarboxylic acids **5** (Scheme 1). These acids were transformed to the corresponding primary amines by Curtius rearrangements; the one-pot procedure with diphenyl phosphorazidate[9] worked well in many cases but occasionally produced a complex reaction mixture. Therefore, an alternative method was used for most of the compounds that involved preparation of a mixed anhydride which was treated with sodium azide. The resulting acyl azides were transformed into *tert*-butyl carbamates via the the corresponding isocyanates. These carbamates were hydrolyzed with 1 M hydrochloric acid. However, when the aryl moiety was acid sensitive we prepared the 2-(trimethylsilyl)ethyl carbamate, which was hydrolyzed with tetrabutylammonium fluoride.[10] Due to decomposition of the aryl moiety, we were not able to isolate the desired product

**Scheme 3**[a]




[a] Reagents: (a) (i) NaOH, MeOH, $H_2O$, (ii) $C_2O_2Cl_2$, (iii) L-(+)-camphorsultam sodium salt; (b) $CH_2N_2$, $Pd(OAc)_2$; (c) (i) $Ti(i\text{-}PrO)_4$, BzOH, (ii) 2 M NaOH, MeOH, THF (method IV).

from the hydrolysis (tetrabutylammonium fluoride or iodotrimethylsilane[11]) of the carbamate function in the 2-furylcyclopropyl derivative.

The *trans* stereochemistry of the primary amines (**6**) was confirmed by analysis of vicinal proton−proton coupling constants of the cyclopropyl moiety ($J_{H1-H2} \sim$ 3.5−3.8 Hz). Compounds **6** were *N*,*N*-dipropylated by treatment with 1-iodopropane to afford the corresponding tertiary amines (**7**). Methoxy derivative **7h** was *O*-demethylated by treatment with hydrobromic acid to form the phenol **7l**.

In order to obtain (1*S*,2*R*)-**7l** and (1*S*,2*S*)-**7j**, we prepared the (+)-enoyl sultams from L-(+)-camphorsultam and the methyl acrylate derivatives **4h** and **4j** (see Scheme 3; the D-(−)-camphorsultam was used in the preparation of the antipodes). The enoyl sultams were cyclopropanated, and the products were recrystallized to provide the corresponding cyclopropanoyl derivatives of high diastereomeric purities.[7] The camphorsultam moiety of the diastereoisomers was removed by a two-step procedure involving (a) treatment with titanium(IV) isopropoxide in benzyl alcohol and (b) base-promoted hydrolysis of the resulting benzyl ester, thus providing the enantiomers of **5h** and **5j**. Test compounds were prepared from the enantiomers of **5h** and **5j** according to methods described above.

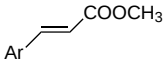
Physical data of the new compounds are presented in Tables 1 and 2.

## Pharmacology

**Affinity for 5-$HT_{1A}$ Receptors *in Vitro*.** The affinities of the *N*,*N*-dipropylcyclopropylamine derivatives for rat hippocampal and cortical 5-$HT_{1A}$ receptors were determined in competition studies with [$^3$H]-8-OH-DPAT. In addition, the structurally related and previously reported[3] enantiomers of **1**, **2**, and **10** were evaluated in the same assay for comparison. The $K_i$ values are reported in Table 3.

***In Vivo* Biochemistry.** The rationale for the *in vivo* biochemical experimental protocol is based on the well-established phenomenon of (auto)receptor-mediated feedback inhibition of presynaptic monoaminergic neurones.[12−15] Thus, the synthesis rate of the catecholamines dopamine (DA) and norepinephrine (NE) is inhibited by agonists via an action at DA receptors and α-adrenoceptors, respectively. Similarly, the synthesis rate of serotonin (5-HT) is inhibited by 5-HT

**Table 1.** Physical Data of Some Substituted Methyl Propenoates




| compd | Ar | prepn[a] method | yield, % | mp, °C | bp, °C/mmHg | formula |
|---|---|---|---|---|---|---|
| **4b** | 2-BrPh | I | 80 | oil[b] | | $C_{10}H_9BrO_2$ |
| **4c** | 2-FPh | I | 84 | | 122−123/9.5[c,d] | $C_{10}H_9FO_2$ |
| **4d** | 3-FPh | I | 73 | | 68−70/0.05[c,d] | $C_{10}H_9FO_2 \cdot {}^1/_8H_2O$ |
| **4e** | 4-FPh | I | 92 | | 114−116/4.5[c,d] | $C_{10}H_9FO_2$ |
| **4f** | 2-$CF_3$Ph | I | 78 | | 66−68/0.1[c] | $C_{11}H_9F_3O_2$ |
| **4g** | 2,3-$(Cl)_2$Ph | I | 88 | 69−71 | | $C_{10}H_8Cl_2O_2$ |
| **4h** | 5-F,2-$OCH_3$Ph | II | 94 | 43−44 | | $C_{11}H_{11}FO_3$ |
| **4i** | benzothienyl | I | 75 | 124−125.5[e] | | $C_{12}H_{10}O_2S$ |
| **4j** | 2-thienyl | I | 96 | 46−47[f] | | $C_8H_8O_2S$ |
| **4k** | 3-thienyl | I | 50 | | 70−72/0.08[c,g] | $C_8H_8O_2S \cdot {}^1/_8H_2O$ |

[a] See Experimental Section. [b] Reference 30. [c] Purified by distillation. [d] Reference 31. [e] Reference 32. [f] Reference 33. [g] Reference 34.

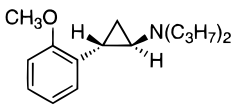
receptor agonists. The accumulation of 3,4-dihydroxyphenylalanine (DOPA), following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD1015; 100 mg/kg sc), was used as an index of the DA synthesis rate in the DA-rich parts (limbic forebrain, striatum) and of the NE synthesis rate in the remaining NE-predominated portions (mainly cortex). The accumulation of 5-hydroxytryptophan (5-HTP) following decarboxylase inhibition was taken as an indicator of the 5-HT synthesis rate in all three brain parts (Figure 1). Reserpine-pretreated rats (5 mg/kg, 18−20 h before) were used throughout this study. Reserpine depletes central monoamine stores, thereby facilitating the assessment of direct receptor agonist properties of the test compounds, both with regard to biochemical and behavioral effects.[16]

The (1*R*,2*R*)-enantiomer of **7j** and the (1*R*,2*S*)-enantiomer of **7l** decreased the cerebral 5-HT synthesis rate by about 50% from control values at the highest doses tested (35 $\mu$mol/kg sc) (Figure 1). This is similar to the maximum 5-HT synthesis reduction elicited by (1*R*,2*S*)-**1**,[3] and the reference 5-$HT_{1A}$ receptor agonist **3**.[4] A rough graphical approximation of the doses required to produce a half-maximal suppression of the 5-HT synthesis indicates that (1*R*,2*S*)-**7l**—the 5-fluorinated derivative of (1*R*,2*S*)-**1**—and the thienyl analogue (1*R*,2*R*)-**7j** display similar potency (~1.5−3 $\mu$mol/kg), both being about 5−10 times less potent than (1*R*,2*S*)-**1** (cf. ref 3). None of the compounds tested caused any significant change in rat brain DOPA accumulation (data not shown). This was true in both DA-rich (limbic forebrain, striatum) and NA-predominated (cortex) brain areas, and suggests lack of potent DA and NA α-receptor stimulatory properties, respectively.

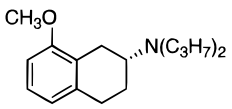
**5-HT Syndrome and Gross Behavioral Observations.** Stimulation of postsynaptic 5-$HT_{1A}$ receptors by means of, for example, administration of **3** results in a clear-cut motor behavioral syndrome, the "5-HT syndrome", in rats. Flattened body posture, forepaw treading, and hindlimb abduction are the most prominent features of this syndrome.[4c,17] The ability of the test drugs to elicit putative postsynaptic 5-$HT_{1A}$ receptor agonist properties was thus assessed by rating the occurrence and intensity of these behavioral components in the reserpinized rats (Table 4).[16] The gross behavior of the animals was observed in their home cages. Immediately after the scoring session the rats were injected with NSD1015 and subsequently used for determination of brain 5-HT and catecholamine synthesis rates (cf. above). (1*S*,2*S*)-**7j** and (1*R*,2*S*)-**1** both induced a clear-cut 5-HT behavioral syndrome, qualitatively similar to that seen after the reference 5-$HT_{1A}$ receptor agonist **3**. In contrast, the effects of (1*R*,2*R*)-**7j** were at best mild, even at the highest dose tested (35 $\mu$mol/kg sc; Table 4). (1*S*,2*R*)-**7l** failed to induce any appreciable behavioral change under these conditions.

## Discussion

The previously prepared (1*R*,2*S*)-enantiomers of 2- and 3-hydroxy derivatives **1** and **2** had 177- and 29-fold higher 5-$HT_{1A}$ receptor affinity, respectively, than the (1*S*,2*R*)-antipodes (Table 3). This is consistent with earlier studies of the *in vivo* 5-$HT_{1A}$ receptor agonist properties of these derivatives.[3] The 2-methoxyphenyl derivative (1*R*,2*S*)-**10** was only about 3-fold less potent than the phenolic analogue (1*R*,2*S*)-**1**. A similar low-affinity ratio has been reported between the 8-hydroxy and 8-methoxy derivatives of 2-(dipropylamino)tetralin (**3** and **11**, respectively).[18] Additional comparisons with




(1*R*,2*S*)-**10**

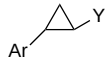



(*R*)-**11**

the 2-aminotetralin series can be made: In studies of C8-substituted 2-(dipropylamino)tetralin derivatives it has been demonstrated that most of the affinity for 5-$HT_{1A}$ receptors is retained when the C8-substituent is replaced by a hydrogen.[18] A similar trend was observed in the present study since phenyl derivative **7a** is about 5-fold less potent than the 2-hydroxyphenyl analogue (1*R*,2*S*)-**1** (Table 3). These findings point to similarities in the SAR of the two series and indicates that the modes of binding of the 2-aminotetralin and arylcyclopropylamine derivatives to the 5-$HT_{1A}$ receptors are similar (compare the SAR discussion in refs 19 and 20).

When the affinities of the halogen-substituted derivatives are compared with that of the phenyl derivative **7a**, it is apparent that halogen substitution in the phenyl ring does not affect (2-Br, **7b**), decreases (2-F, 3-F, or 4-F; **7c**, **7d**, or **7e**, respectively), or abolishes (2,3-$Cl_2$; **7g**) the affinity for 5-$HT_{1A}$ receptors (Table 3). Introduction of the strongly electron withdrawing trifluoromethyl group in the C2-position of the phenyl moiety, affording **7f**, also abolished affinity. These data indicate that the introduction of electron-withdrawing substituents in the phenyl ring is detrimental for affinity. In contrast, hydroxyl groups, which enhance

**Table 2.** Physical Data of Cyclopropyl Compounds




| compd | Ar | Y | prepn meth | yield, % | mp, °C | recrystn solvents[a] | formula |
|---|---|---|---|---|---|---|---|
| **5a** | Ph | COOH | III[b] | 91 | 89.5−90.5[c] | NR[d] | $C_{10}H_{10}O_2$ |
| **5b** | 2-BrPh | COOH | III | 75 | 106−107.5 | NR | $C_{10}H_9BrO_2$ |
| **5c** | 2-FPh | COOH | III | 92 | oil | | $C_{10}H_9FO_2 \cdot {}^1/_8H_2O$ |
| **5d** | 3-FPh | COOH | III | 90 | 80−81 | NR | $C_{10}H_9FO_2$ |
| **5e** | 4-FPh | COOH | III | 94 | 110−112 | NR | $C_{10}H_9FO_2$ |
| **5f** | 2-$CF_3$Ph | COOH | III | 69 | 117−118.5 | F | $C_{11}H_9F_3O_2$ |
| **5g** | 2,3-$(Cl)_2$Ph | COOH | III | 63 | 129.5−130.5 | NR | $C_{10}H_8Cl_2O_2$ |
| **5h** | 5-F,2-$OCH_3$Ph | COOH | III | 89 | 165.5−166.5 | NR | $C_{11}H_{11}FO_3$ |
| (1*S*,2*S*)-**5h** | 5-F,2-$OCH_3$Ph[e] | COOH | IV | 93 | 125.5−126 | NR | $C_{11}H_{11}FO_3$ |
| (1*R*,2*R*)-**5h** | 5-F,2-$OCH_3$Ph[f] | COOH | IV | 92 | 125.5−126 | NR | $C_{11}H_{11}FO_3$ |
| **5i** | benzothienyl | COOH | III | 84 | 165.5−167[g] | C | $C_{12}H_{10}O_2S$ |
| **5j** | 2-thienyl | COOH | III | 87 | 46−48[h] | NR | $C_8H_8O_2S$ |
| (1*S*,2*S*)-**5j** | 2-thienyl[i] | COOH | IV | 60 | oil | | $C_8H_8O_2S$ |
| (1*R*,2*R*)-**5j** | 2-thienyl[j] | COOH | IV | 78 | oil | | $C_8H_8O_2S$ |
| **5k** | 3-thienyl | COOH | III | 91 | 73−75 | NR | $C_8H_8O_2S$ |
| **6a** | Ph | $NH_2$ | V | 45 | 154−156[c] | A | $C_9H_{11}N \cdot HCl$ |
| **6b** | 2-BrPh | $NH_2$ | VI | 45 | 172−174 | A | $C_9H_{10}BrN \cdot HCl$ |
| **6c** | 2-FPh | $NH_2$ | V | 40 | 130−133[k] | A | $C_9H_{10}FN \cdot HCl$ |
| **6d** | 3-FPh | $NH_2$ | VI | 85 | 181−184[k] | A | $C_9H_{10}FN \cdot HCl$ |
| **6e** | 4-FPh | $NH_2$ | VI | 68 | 190−192[k,l] | *m* | $C_9H_{10}FN \cdot HCl$ |
| **6f** | 2-$CF_3$Ph | $NH_2$ | VI | 63 | 177−179 | A | $C_{10}H_{10}F_3N \cdot HCl$ |
| **6g** | 2,3-$(Cl)_2$Ph | $NH_2$ | V | 43 | 193−195 | A | $C_9H_9Cl_2N \cdot HCl \cdot {}^1/_4H_2O$ |
| **6h** | 5-F,2-$OCH_3$Ph | $NH_2$ | VI | 58 | 201.5−203.5 | B | $C_{10}H_{12}FNO \cdot HCl$ |
| (1*S*,2*R*)-**6h** | 5-F,2-$OCH_3$Ph[n] | $NH_2$ | VI | 58 | 213.5−216 | A | $C_{10}H_{12}FNO \cdot HCl$ |
| (1*R*,2*S*)-**6h** | 5-F,2-$OCH_3$Ph[o] | $NH_2$ | VI | 59 | 215−218 | A | $C_{10}H_{12}FNO \cdot HCl$ |
| **6i** | benzothienyl | $NH_2$ | VI | 82 | 190[g,l] | A | $C_{11}H_{11}NS \cdot C_2H_2O_4 \cdot {}^1/_4H_2O$ |
| **6j** | 2-thienyl | $NH_2$ | VII | 36 | 174−175[g,l] | A | $C_7H_9NS \cdot {}^1/_2C_2O_4H_2$ |
| (1*S*,2*S*)-**6j** | 2-thienyl[p] | $NH_2$ | VII | 58 | 178−180 | A | $C_7H_9NS \cdot {}^1/_2C_2O_4H_2$ |
| (1*R*,2*R*)-**6j** | 2-thienyl[q] | $NH_2$ | VII | 49 | 207−210[l] | A | $C_7H_9NS \cdot C_2O_4H_2$ |
| **6k** | 3-thienyl | $NH_2$ | VII | 35 | 171−172[l] | A | $C_7H_9NS \cdot C_2O_4H_2$ |
| **7a** | Ph | N(*n*-$C_3H_7)_2$ | VIII | 56 | 154−155 | A | $C_{15}H_{23}N \cdot HCl$ |
| **7b** | 2-BrPh | N(*n*-$C_3H_7)_2$ | VIII | 75 | 148.5−150.5 | A | $C_{15}H_{22}BrN \cdot HCl$ |
| **7c** | 2-FPh | N(*n*-$C_3H_7)_2$ | VIII | 41 | 93−94 | D | $C_{15}H_{22}FN \cdot HCl$ |
| **7d** | 3-FPh | N(*n*-$C_3H_7)_2$ | VIII | 52 | 148−151 | E | $C_{16}H_{23}N \cdot HCl$ |
| **7e** | 4-FPh | N(*n*-$C_3H_7)_2$ | VIII | 63 | 117−119 | D | $C_{16}H_{23}N \cdot HCl$ |
| **7f** | 2-$CF_3$Ph | N(*n*-$C_3H_7)_2$ | VIII | 33 | 130−132 | A | $C_{16}H_{22}F_3N \cdot HCl$ |
| **7g** | 2,3-$(Cl)_2$Ph | N(*n*-$C_3H_7)_2$ | VIII | 74 | 141−143 | A | $C_{15}H_{21}Cl_2N \cdot HCl$ |
| **7h** | 5-F,2-$OCH_3$Ph | N(*n*-$C_3H_7)_2$ | VIII | 75 | 154.5−156 | A | $C_{16}H_{24}FNO \cdot HCl$ |
| (1*S*,2*R*)-**7h** | 5-F,2-$OCH_3$Ph[r] | N(*n*-$C_3H_7)_2$ | VIII | 42 | 163−165 | A | $C_{16}H_{24}FNO \cdot HCl$ |
| (1*R*,2*S*)-**7h** | 5-F,2-$OCH_3$Ph[s] | N(*n*-$C_3H_7)_2$ | VIII | 48 | 163.5−165 | A | $C_{16}H_{24}FNO \cdot HCl$ |
| **7i** | benzothienyl | N(*n*-$C_3H_7)_2$ | VIII | 41 | 132−133.5 | A | $C_{17}H_{23}NS \cdot HCl \cdot {}^1/_4H_2O$ |
| **7j** | 2-thienyl | N(*n*-$C_3H_7)_2$ | VIII | 94 | 83−85 | A | $C_{13}H_{21}NS \cdot C_2O_4H_2 \cdot {}^1/_4H_2O$ |
| (1*S*,2*S*)-**7j** | 2-thienyl[t] | N(*n*-$C_3H_7)_2$ | VIII | 56 | 172−175[l] | A | $C_{13}H_{21}NS \cdot HCl \cdot {}^1/_8H_2O$ |
| (1*R*,2*R*)-**7j** | 2-thienyl[u] | N(*n*-$C_3H_7)_2$ | VIII | 80 | 170−172[l] | A | $C_{13}H_{21}NS \cdot HCl \cdot {}^1/_4H_2O$ |
| **7k** | 3-thienyl | N(*n*-$C_3H_7)_2$ | VIII | 68 | 150−52 | A | $C_{13}H_{21}NS \cdot HCl$ |
| **7l** | 5-F,2-OHPh | N(*n*-$C_3H_7)_2$ | IX | 65 | 167.5−169 | A | $C_{15}H_{22}FNO \cdot HCl$ |
| (1*S*,2*R*)-**7l** | 5-F,2-OHPh[v] | N(*n*-$C_3H_7)_2$ | IX | 52 | 169−172 | A | $C_{15}H_{22}FNO \cdot HCl$ |
| (1*R*,2*S*)-**7l** | 5-F,2-OHPh[w] | N(*n*-$C_3H_7)_2$ | IX | 58 | 170−174 | A | $C_{15}H_{22}FNO \cdot HCl$ |

[a] A = methanol/ether, B = ethanol/ether, C = toluene, D = ether (after several days at −25 °C), E = 2-propanol/ether, *F* = ether. [b] Prepared from the commercially available methyl cinnamate. [c] Reference 35. [d] Not recrystallized due to high initial purity. [e] $[\alpha]^{22}_D$ = +211 (*c* = 1.0, $CH_2Cl_2$). [f] $[\alpha]^{22}_D$ = −212 (*c* = 1.0, $CH_2Cl_2$). [g] Reference 36. [h] Reference 37. [i] $[\alpha]^{22}_D$ = +328 (*c* = 1.0, $CH_2Cl_2$). [j] $[\alpha]^{22}_D$ = −326 (*c* = 1.1, $CH_2Cl_2$). [k] Reference 38. [l] Decomposed. [m] Not recrystallized, decomposed on attempt to recrystallize from methanol/ether. [n] $[\alpha]^{22}_D$ = +42.0 (*c* = 1.0, MeOH). [o] $[\alpha]^{22}_D$ = −41.3 (*c* = 1.0, MeOH). [p] $[\alpha]^{22}_D$ = +77.4 (*c* = 0.6, MeOH). [q] $[\alpha]^{22}_D$ = −57.0 (*c* = 0.9, MeOH), $[\alpha]^{22}_D$ = −58.8 (*c* = 0.5, MeOH). [r] $[\alpha]^{22}_D$ = +8.9 (*c* = 1.0, MeOH). [s] $[\alpha]^{22}_D$ = −9.4 (*c* = 1.0, MeOH). [t] $[\alpha]^{22}_D$ = +75.2 (*c* = 1.0, MeOH). [u] $[\alpha]^{22}_D$ = −76.3 (*c* = 1.1, MeOH). [v] $[\alpha]^{22}_D$ = +6.8 (*c* = 1.0, MeOH). [w] $[\alpha]^{22}_D$ = −7.8 (*c* = 1.0, MeOH).

the electron density of the aromatic ring, appear to be beneficial for 5-$HT_{1A}$ receptor affinity (cf. above).

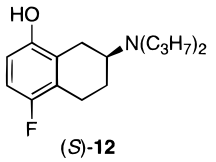
Three compounds with electron-rich heteroaromatic rings, 2-thienyl (**7j**), 3-thienyl (**7k**), and 2-benzothienyl (**7i**), were synthesized and tested as potential bioisosteres of the potent phenolic derivatives **1** and **2** (Table 3). The 2-thienyl derivative **7j** proved to be a potent 5-$HT_{1A}$ receptor ligand, the affinity being 2−3-fold less than that of the phenolic analogues **1** and **2**. The affinity of the 3-thienyl analogue **7k** was slightly lower. It thus appears that the 2- and 3-thienyl rings constitute good isosteric replacements for the 2- and 3-hydroxyphenyl moieties in **1** and **2**. The 2-benzothienyl derivative **7i** was inactive, most likely due to the steric bulk of the fused phenyl moiety.

Because of the high affinity of racemic **7j**, we synthesized and tested the enantiomers. As might have been predicted on the basis of previously observed stereoselectivities in the phenylcyclopropylamine series,[3,5] **7j** exhibited a large enantiomeric affinity ratio, the affinity of the (1*R*,2*R*)-enantiomer being 75-fold higher than that of the antipode. In the *ex vivo* biochemical experiments, (1*R*,2*R*)-**7j** behaved as a full 5-$HT_{1A}$ receptor agonist but of slightly lower potency than (1*R*,2*S*)-**1**. In contrast, the antipode, (1*S*,2*S*)-**7j**, was unable to reduce the 5-HTP levels even at the highest dose level (35 $\mu$mol/kg) (Figure 1). It is noteworthy that neither enantiomer of **7j** induced a clear-cut 5-HT behavioral syndrome (Table 4) in the reserpinized rats. Thus, the high 5-$HT_{1A}$ receptor affinity of **7j** (Table 2) was accompanied

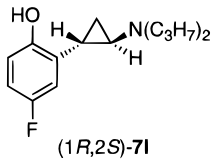
**Table 3.** Affinities for 5-$HT_{1A}$ Receptors Defined by the Displacement of [$^3$H]-8-OH-DPAT

| compd | $K_i$, nM | range | $n_H$ |
|---|---|---|---|
| **7a** | 24 | (21−28) | 0.88 |
| **7b** | 22 | (20−23) | 0.87 |
| **7c** | 59 | (48−77) | 0.94 |
| **7d** | 100 | (85−130) | 0.74 |
| **7e** | 76 | (63−95) | 0.83 |
| **7f** | >1000 | | |
| **7g** | >300 | | |
| **7h** | 140 | (89−280) | 0.52 |
| (1*S*,2*R*)-**7h** | 199 | (174−224) | 0.90 |
| (1*R*,2*S*)-**7h** | 60 | (39−87) | 0.80 |
| **7i** | >1000 | | |
| **7j** | 13 | (12−14) | 0.94 |
| (1*S*,2*S*)-**7j** | 820 | (710−980) | 1.00 |
| (1*R*,2*R*)-**7j** | 11 | (10−13) | 0.96 |
| **7k** | 21 | (19−23) | 0.93 |
| **7l** | 99 | (78−140) | 0.84 |
| (1*S*,2*R*)-**7l** | 348 | (184−503) | 0.90 |
| (1*R*,2*S*)-**7l** | 3.2 | (2.7−3.6) | 0.88 |
| (1*S*,2*R*)-**1** | 140 | (100−230) | 0.90 |
| (1*R*,2*S*)-**1** | 4.9 | (4.6−5.2) | 0.97 |
| (1*S*,2*R*)-**2** | 460 | (240−760) | 0.70 |
| (1*R*,2*S*)-**2** | 2.6 | (2.2−3.2) | 0.80 |
| (1*S*,2*R*)-**10** | 230 | (160−430) | 0.90 |
| (1*R*,2*S*)-**10** | 17 | (16−20) | 0.75 |

by potent agonist properties in the *ex vivo* biochemical model, but low apparent efficacy (if any) in the behavioral test model, reflecting, respectively, the ability to activate synthesis controlling 5-$HT_{1A}$ autoreceptors and postsynaptic 5-$HT_{1A}$ receptors mediating the 5-HT behavioral syndrome in reserpinized rats. These data are consistent with a characterization of (1*R*,2*R*)-**7j** as a partial 5-$HT_{1A}$ receptor agonist. Thus, the isosteric replacement of the hydroxyphenyl moiety of (1*S*,2*R*)-**1** with a 2-thienyl ring appears to result in a considerable loss in efficacy, manifested under the present conditions only at the level of postsynaptic 5-$HT_{1A}$ receptors, likely due to differences in apparent receptor reserve (cf. ref 21). In contrast, most of the affinity is retained.



(*S*)-**12**



(1*R*,2*S*)-**7l**

Introduction of a C5-fluoro substituent in 2-aminotetralin derivative **3**, producing **12** (UH-301),[22] reduces mainly efficacy but also affinity. Thus, (*R*)-**12** is a partial 5-$HT_{1A}$ receptor agonist whereas (*R*)-**3** is a full agonist, and (*S*)-**12** is a 5-$HT_{1A}$ receptor antagonist whereas (*S*)-**3** is a partial agonist.[5] Similar effects were not observed when a C5-fluoro substituent was introduced in the cyclopropylamine-derived agonist (1*R*,2*S*)-**1**; (1*R*,2*S*)-**7l** had about the same affinity as (1*R*,2*S*)-**1** and displayed clear-cut *in vivo* biochemical (Figure 1) as well as behavioral (Table 4) agonist activity. (1*S*,2*R*)-**7l**, on the other hand, was 100-fold less potent than the antipode in terms of affinity and only mildly affected 5-HTP accumulation at the highest dose tested (35 $\mu$mol/kg sc). Similarly, (1*S*,2*R*)-**7l** failed to produce a full-blown 5-HT behavioral syndrome.

## Experimental Section

**Chemistry. General Comments.** Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. $^1$H NMR spectra were recorded on a JEOL JNM-EX270 spectrometer at 270 MHz, and $^{13}$C NMR spectra were recorded on a JEOL FX 90Q spectrometer at 22.5 MHz, except where noted. NMR spectra were referenced to internal tetramethylsilane. GLC analysis was performed on a Shimadzu GC14A equipped with a FID detector and a HP-1 column (50 m × 0.32 mm). Mass spectral analysis was performed on a Hewlett-Packard mass spectrometer HP 5971A MSD connected to a gas chromatograph HP GC 5890 Series 2, equipped with a HP-1 column (25 m × 0.2 mm). Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. The elemental analyses (C, H, and N), which were performed by Micro Kemi AB, Uppsala, Sweden, were within 0.4% of the theoretical values. TLC analysis was carried out on aluminum sheets precoated with silica gel $F_{254}$ (0.2 mm) or on $Al_2O_3$ 60 $F_{254}$ neutral (Typ E), E. Merck, and was visualized with UV light and/or $I_2$. All reactions except the cyclopropanations were performed under nitrogen.

**2-Iodobenzothiophene.**[23] Benzothiophene (10 g, 75 mmol) was dissolved in ether (100 mL). The solution was cooled to 0 °C, and butyllithium (1.6 M in hexane, 49 mL, 78 mmol) was added. After 3.5 h the solution was cooled to −50 °C, iodine (18.9 g, 75 mmol) was added, and the reaction temperature was slowly increased to room temperature. Saturated aqueous $NH_4Cl$ (50 mL) and saturated aqueous $Na_2S_2O_3$ (70 mL) were added to the mixture. The organic layer was separated, washed with $H_2O$ (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by distillation (bp 153−156 °C/14 mmHg). The resulting oil was dissolved in hexane. The solution was treated with charcoal, filtered, and concentrated to afford 8.31 g (43%) of pure 2-iodobenzothiophene as an oil: $^1$H NMR (acetone-$d_6$, 90 MHz) $\delta$ 7.96−7.77 (m, 2 H), 7.71 (s, 1 H), 7.44−7.23 (m, 2 H); $^{13}$C NMR (acetone-$d_6$) $\delta$ 145.0, 141.8, 134.9, 125.4, 125.3, 123.2, 122.1, 79.2.

Below are examples of the methods described in Scheme 1:

**Methyl *trans*-3-(2-Bromophenyl)propenoate (4b). Method I.** A mixture of 2-bromoiodobenzene (7.0 g, 24.7 mmol), methyl acrylate (2.8 mL, 31.9 mmol), tetrabutylammonium chloride (6.9 g, 24.7 mmol), $Pd(OAc)_2$ (0.11 g, 0.5 mmol), and finely grounded $K_2CO_3$ (8.55 g, 62 mmol) in DMF (26 mL) was stirred at 50 °C for 19 h. Petroleum ether (150 mL) and brine (40 mL) were added, and the mixture was filtered under suction. The filtrate was collected, and the aqueous layer was extracted with petroleum ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica column (ether/petroleum ether, 1:4) to afford 4.8 g of pure **4b**: $^1$H NMR ($CDCl_3$, 90 MHz) $\delta$ 8.06 (d, $J$ = 16.0 Hz, 1 H), 7.66−7.55 (m, 2 H), 7.41−7.10 (m, 2 H), 6.38 (d, $J$ = 16.0 Hz, 1 H), 3.82 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.7, 143.1, 134.4, 133.4, 131.2, 127.7 (2 C's), 125.3, 120.6, 51.8.

**Methyl *trans*-3-(5-Fluoro-2-methoxyphenyl)propenoate (4h). Method II.** Concentrated $H_2SO_4$ (3 mL) was added to a solution of *trans*-3-(5-fluoro-2-methoxyphenyl)propenoic acid[7a] (6.0 g, 30.6 mmol) in MeOH (150 mL). The solution was heated to reflux for 5 h. Saturated aqueous $Na_2CO_3$ was added to the resulting solution until neutral pH. The solution was filtered and concentrated. The residue was partitioned between ether (100 mL) and $H_2O$ (150 mL). The organic layer was washed with $H_2O$ (100 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica column eluted with ether/petroleum ether (1:4) to afford **4h** as a white solid.

***trans*-2-(2-Fluorophenyl)cyclopropanecarboxylic Acid (5c). Method III.** Diazomethane (*CAUTION*)[24] was prepared as previously described;[24] a solution of *N*-methyl-*N*-nitroso-4-toluenesulfonamide (Diazogen, 5.95 g, 27.8 mmol) in ether (60 mL) was slowly added to a heated (70 °C oil bath) mixture of KOH (4.67 g, 83.3 mmol), ether (10 mL), $H_2O$ (50 mL), and 2-(2-ethoxyethoxy)ethanol (50 mL). The resulting ether solution of diazomethane was continuously distilled into a stirred, cooled (−10 °C) solution of **4c** (0.50 g, 2.8 mmol) and $Pd(OAc)_2$ (3.1 mg, 0.0014 mmol) in $CH_2Cl_2$/ether (1:2; 75 mL). The reaction was quenched by addition of a few milliliters of HOAc after 1.5 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$ (2 × 3 mL), dried ($MgSO_4$), filtered, and

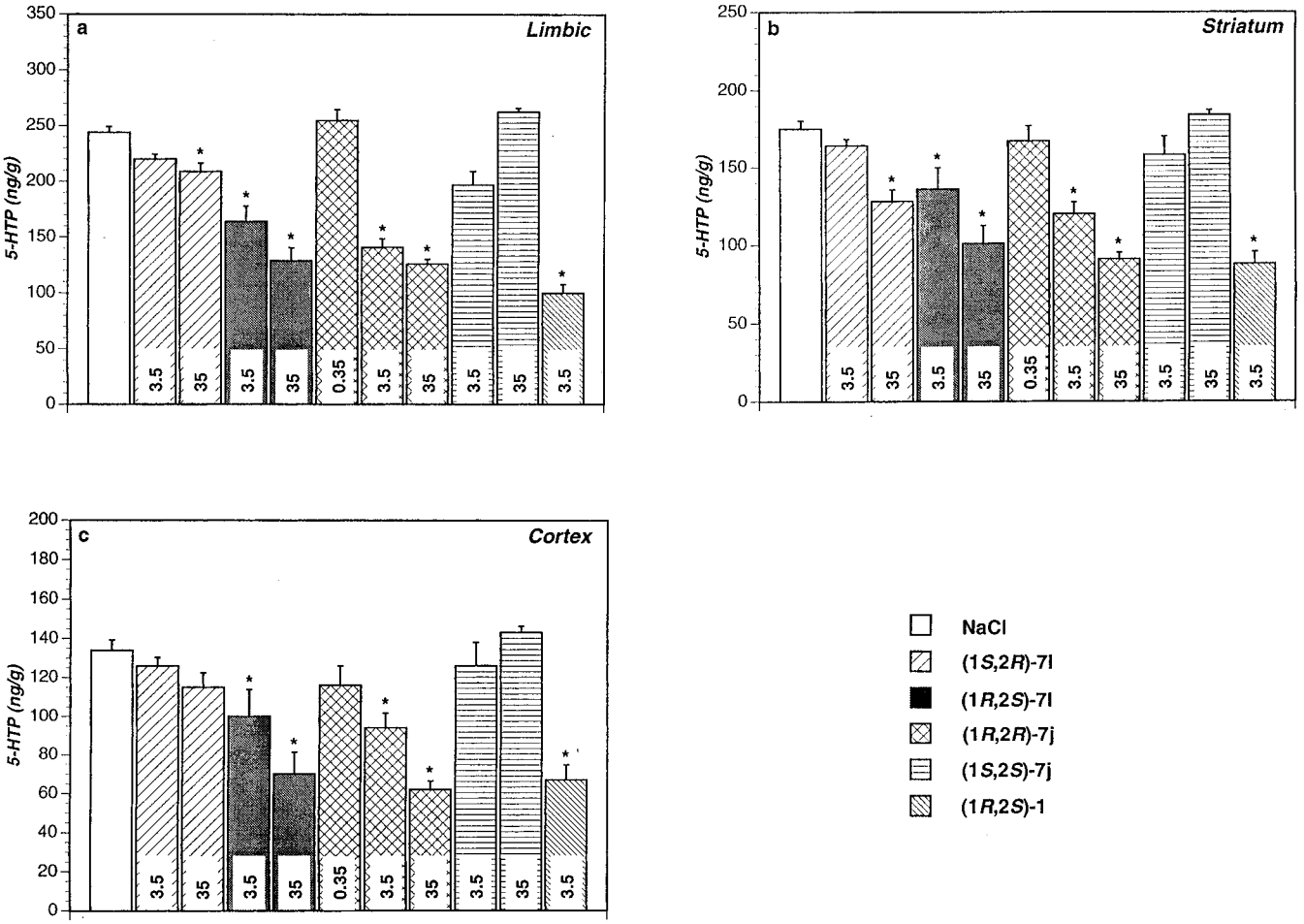



**Figure 1.** Effect of (1*R*,2*R*)-**7j**, (1*S*,2*S*)-**7j**, (1*R*,2*S*)−**7l**, (1*S*,2*R*)-**7l**, and (1*R*,2*S*)-**1** on cerebral 5-HT synthesis in rats. Reserpin-pretreated rats (5 mg/kg sc, 18−20 h before the experiment) were given 0.35, 3.5, or 35 μmol/kg sc of (1*R*,2*R*)-**7j**, (1*S*,2*S*)-**7j**, (1*R*,2*S*)-**7l**, (1*S*,2*R*)-**7l**, or (1*R*,2*S*)-**1** 60 min, and NSD1015 (100 mg/kg sc) 30 min before death; controls received NaCl and NSD1015 at corresponding time intervals. Shown are the 5-HTP contents (ng/g tissue) in limbic forebrain (a), striatal (b), and cortical (c) brain tissue samples, means ± SEM of two to seven observations. Vertical figures inside the bars depict doses of the test compounds (0.35−35 μmol/kg sc). *$p \leq 0.05$ vs corresponding NaCl control values.

**Table 4.** 5-HT Behavioral Effects of (1*R*,2*R*)-**7j**, (1*S*,2*S*)-**7j**, (1*R*,2*S*)-**7l**, (1*S*,2*R*)-**7l**, and (1*R*,2*S*)-**1** in Reserpinized Rats[a]

| | dose, μmol/kg sc | | | |
|---|---|---|---|---|
| treatment | 0 | 0.35 | 3.5 | 35 |
| control | 0 (0−0)<br>*7* | | | |
| (1*R*,2*R*)-**7j** | | 0 (0−0)<br>*2* | 0 (0−0)<br>*3* | 1 (0−1)<br>*3* |
| (1*S*,2*S*)-**7j** | | | 0 (0−0)<br>*3* | 0 (0−0)<br>*4* |
| (1*R*,2*S*)-**7l** | | | 0 (0−0)<br>*3* | 4 (3−5)<br>*4* |
| (1*S*,2*R*)-**7l** | | | 1 (1−2)<br>*5* | 0 (0−0)<br>*3* |
| (1*R*,2*S*)-**1** | | | 4 (2−5)<br>*3* | |

[a] Shown are the summed "5-HT behavioral syndrome" scores (median, range in brackets; *n* observations) obtained in a 60-s rating session, starting 30 min after administration of the test compounds (0.35−35 μmol/kg sc) in reserpine-pretreated rats (5 mg/kg sc, 18−20 h before experiment).

concentrated. The crude product was purified on a silica column eluted with ether/petroleum ether (1:6). The resulting ester was dissolved in MeOH (10 mL), and 2 M aqueous NaOH (5 mL) was added. The solution was stirred at room temperature for 2 h. The MeOH was evaporated, and the remaining solution was diluted with $H_2O$ (15 mL), washed with ether (20 mL), acidified with 5 M aqueous HCl, and extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford pure **5c**: $^1$H NMR ($CDCl_3$) $\delta$ 7.24−7.16 (m, 1 H), 7.10−6.95 (m, 3 H), 2.75 (ddd, $J_1 = 4.1$ Hz, $J_2 = 7.0$ Hz, $J_3 = 9.5$ Hz, 1 H), 1.95 (ddd, $J_1 = 4.1$ Hz, $J_2 = 4.8$ Hz, $J_3 = 8.3$ Hz, 1 H), 1.67 (ddd, $J_1 = 4.8$ Hz, $J_2 = 4.7$ Hz, $J_3 = 9.5$ Hz, 1 H), 1.45 (ddd, $J_1 = 4.7$ Hz, $J_2 = 7.0$ Hz, $J_3 = 8.3$ Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 180.1, 161.7 (d, $J = 246.4$ Hz), 128.2 (d, $J = 8.4$ Hz), 127.0 (d, $J = 4.2$ Hz), 126.1, 124.1 (d, $J = 3.5$ Hz), 115.4 (d, $J = 21.6$ Hz), 22.7 (d, $J = 1.4$ Hz), 20.8 (d, $J = 4.9$ Hz), 16.2.

**(1*S*,2*S*)-*trans*-2-(2-Thienyl)cyclopropanecarboxylic Acid [(1*S*,2*S*)-5j]. Method IV.** Titanium isopropoxide (6.0 mL, 21 mmol) was added to a solution of (+)-**9**[8a] (7.41 g, 21 mmol) in benzyl alcohol (40 mL). The solution was heated (150 °C, oil bath) for 45 min and then allowed to cool to room temperature. The solution was concentrated and the residue was purified on a silica column eluted with ether/petroleum ether (1:9), yielding 3.62 g of a mixture of the benzyl and the isopropyl esters. The mixture was dissolved in MeOH (30 mL), and 2 M aqueous NaOH (30 mL) was added. The resulting solution was stirred at room temperature for 6 h and finally heated to 40 °C (oil bath) for 20 min in order to dissolve the remaining substrate. The solution was concentrated, and the residue was washed with $CH_2Cl_2$ (3 × 30 mL), EtOAc (3 × 30 mL), and ether (3 × 30 mL), acidified with 5 M aqueous HCl, extracted with $CH_2Cl_2$ (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated to yield 2.11 g (60%) of (1*S*,2*S*)-**5j**: $^1$H NMR ($CDCl_3$) $\delta$ 7.11 (dd, $J_1 = 1.3$ Hz, $J_2 = 5.1$ Hz, 1 H), 6.91 (dd, $J_1 = 3.6$ Hz, $J_2 = 5.0$ Hz, 1 H), 6.84 (m, 1 H), 2.78 (ddd, $J_1 = 4.0$ Hz, $J_2 = 6.6$ Hz, $J_3 = 9.2$ Hz, 1 H), 1.94 (ddd, $J_1 = 4.0$ Hz, $J_2 = 5.2$ Hz, $J_3 = 8.4$ Hz, 1 H), 1.69 (ddd, $J_1 = 4.6$ Hz, $J_2 = 5.2$ Hz, $J_3 = 9.2$ Hz, 1 H), 1.42 (ddd, $J_1 = 4.6$ Hz, $J_2 = 6.6$ Hz, $J_3$

= 8.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 179.5, 143.4, 126.9, 124.1, 123.4, 24.8, 22.3, 18.3.

**(1*R*,2*R*)-*trans*-2-(2-Thienyl)cyclopropanecarboxylic Acid [(1*R*,2*R*)-5*j*].** The acid (1*R*,2*R*)-**5j** was prepared from (−)-**9**[7a] (6.62 g, 24 mmol) yielding 3.08 g (78%) of pure carboxylic acid.

***trans*-2-(2,3-Dichlorophenyl)cyclopropylamine (6g). Method V.** Diphenyl phosphorazidate (1.93 mL, 9.0 mmol) and triethylamine (1.25 mL, 12 mmol) was added to a solution of **5g** (2.00 g, 8.2 mmol) in dry *t*-BuOH (20 mL). The resulting solution was stirred at 90 °C (bath temperature) for 42 h and was then concentrated. The residue was partitioned between 10% aqueous $Na_2CO_3$ (40 mL) and ether (4 × 40 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified on a silica column eluted with ether/petroleum ether (1:4). The resulting *tert*-butyl carbamate was treated with 1 M aqueous HCl (50 mL) at 100 °C overnight. The solution was washed with ether (3 × 40 mL), and saturated aqueous $K_2CO_3$ was added to pH about 10. The mixture was extracted with EtOAc (3 × 70 mL). The combined organic layers were dried ($K_2CO_3$), filtered, and concentrated. The resulting primary amine was converted into the hydrochloride and recrystallized to afford **6g**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 7.46 (d, $J$ = 7.9 Hz, 1 H), 7.27 (dd, $J_1 = J_2$ = 7.9 Hz, 1 H), 7.12 (d, $J$ = 7.9 Hz, 1 H), 2.86 (ddd, $J_1$ = 3.8 Hz, $J_2$ = 4.6 Hz, $J_3$ = 7.9 Hz, 1 H), 2.64 (ddd, $J_1$ = 3.8 Hz, $J_2$ = 6.6 Hz, $J_3$ = 10.2 Hz, 1 H), 1.51 (ddd, $J_1$ = 4.6 Hz, $J_2$ = 6.6 Hz, $J_3$ = 10.2 Hz, 1 H), 1.41 (ddd, $J_1$ = 6.6 Hz, $J_2$ = 6.6 Hz, $J_3$ = 7.9 Hz, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 139.6, 134.3, 133.9, 130.2, 128.9, 127.4, 31.6, 21.8, 13.1.

***trans*-2-(5-Fluoro-2-methoxyphenyl)cyclopropylamine (6h). Method VI.** A mixture of **5h** (4.6 g, 21.9 mmol), triethylamine (4.27 mL, 30.6 mmol), and ethyl chloroformate (3.14 mL, 32.8 mmol) in dry acetone (150 mL) was stirred at −10 °C, and a solution of $NaN_3$ (2.42 g, 37.2 mmol) in $H_2O$ (10 mL) was added after 2.5 h. The stirring was discontinued after an additional 2 h. The resulting suspension was poured into cold $H_2O$ (220 mL) and was extracted with toluene (4 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to about 50% of the volume to remove remaining traces of $H_2O$. The resulting solution was heated (90 °C bath temperature) until the evolution of nitrogen ceased (about 3 h), and the solution was concentrated. The resulting isocyanate was dissolved in dry *t*-BuOH (50 mL), and the solution was refluxed for 23 h. The reaction mixture was concentrated, and the crude *tert*-butyl carbamate was purified on a silica column eluted with ethyl acetate/hexane (1:3). The carbamate was hydrolyzed by use of 1 M aqueous HCl (200 mL) at 100 °C (both temperature) for 15 h. The solution was washed with ether (3 × 100 mL), alkalinized with saturated aqueous $K_2CO_3$, and extracted with EtOAc (4 × 200 mL). The combined organic layers were dried ($K_2CO_3$), filtered, and concentrated. The oily primary amine was converted into the hydrochloride and recrystallized to afford pure **6h**·HCl: $^1$H NMR ($CD_3OD$) $\delta$ 6.95−6.93 (m, 2 H), 6.74 (d, $J$ = 9.0 Hz, 1 H), 3.86 (s, 1 H), 2.79 (ddd, $J_1$ = 3.6 Hz, $J_2$ = 4.2 Hz, $J_3$ = 7.8 Hz, 1 H), 2.53 (ddd, $J_1$ = 3.6 Hz, $J_2$ = 6.9 Hz, $J_3$ = 10.1 Hz, 1 H), 1.38 (ddd, $J_1$ = 4.2 Hz, $J_2$ = 6.7 Hz, $J_3$ = 10.1 Hz, 1 H), 1.32 (ddd, $J_1$ = 6.9 Hz, $J_2$ = 6.7 Hz, $J_3$ = 7.8 Hz, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 158.3 (d, $J$ = 237 Hz), 155.8 (d, $J$ = 2.1 Hz), 129.6 (d, $J$ = 7.7 Hz), 114.6 (d, $J$ = 23.0 Hz).

**(1*R*,2*R*)-*trans*-2-(2-Thienyl)cyclopropylamine [(1*R*,2*R*)-6j]. Method VII.** Ethyl chloroformate (2.3 mL, 24 mmol) was added to a cooled solution (−10 °C) of (1*R*,2*R*)-**5j** (2.9 g, 17 mmol) and triethylamine (2.9 mL, 21 mmol) in dry acetone (100 mL). After 2 h, a solution of $NaN_3$ (1.68 g, 26 mmol) in $H_2O$ (5 mL) was added to the stirred solution. The stirring was discontinued after 1 h, and $H_2O$ (100 mL) was added. The solution was concentrated, and the remaining $H_2O$ solution was extracted with ether (4 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in toluene (150 mL). The solution was concentrated to about half the volume in order to remove remaining traces of $H_2O$ and was then heated (90 °C bath temperature) until the evolution of $N_2$ ceased (2 h). The volatiles were evaporated *in vacuo*. The resulting isocyanate was dissolved in dry 2-(trimethylsilyl)ethanol (5 mL), and the solution was heated to 60 °C (bath temperature) for 14 h. The crude carbamate was purified on a silica column eluted with ether/petroleum ether (1:2). The purified carbamate was treated with tetrabutylammonium fluoride (1 M solution in THF, 19 mL, 19 mmol) at 50 °C for 19 h. $H_2O$ (50 mL) was added, and the stirring was discontinued after an additional 15 min. The mixture was concentrated, and the remaining water solution was acidified with 1 M aqueous HCl, washed with $CH_2Cl_2$ (50 mL), alkalinized [$Na_2CO_3$(s)], and extracted with $EtOAc_3$ (3 × 100 mL). The combined organic layers were dried ($K_2CO_3$) and concentrated. The crude primary amine was converted into the oxalate and recrystallized to afford (1*R*,2*R*)-**6j**·$C_2O_4H_2$: $^1$H NMR ($CD_3OD$) $\delta$ 7.17 (dd, $J_1$ = 1.3 Hz, $J_2$ = 5.1 Hz, 1 H), 6.91−6.83 (m, 2 H), 2.74 (ddd, $J_1$ = 3.5 Hz, $J_2$ = 4.4 Hz, $J_3$ = 7.9 Hz, 1 H), 2.47 (dddd, $J_1$ = 0.75 Hz, $J_2$ = 3.5 Hz, $J_3$ = 6.4 Hz, $J_4$ = 9.9 Hz, 1 H), 1.40 (ddd, $J_1$ = 4.4 Hz, $J_2$ = 6.6 Hz, $J_3$ = 9.9 Hz, 1 H), 1.22 (ddd, $J_1$ = 6.4 Hz, $J_2$ = 6.6 Hz, $J_3$ = 7.9 Hz, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 166.7, 143.2, 128.0, 125.3, 124.8, 32.6, 17.8, 14.7.

***trans*-2-(5-Fluoro-2-methoxyphenyl)-*N*,*N*-dipropylcyclopropylamine (7h). Method VIII.** A mixture of **6h**·HCl (0.5 g, 2.3 mmol), 1-iodopropane (0.54 mL, 5.5 mmol), and finely ground $K_2CO_3$ (1.14 g, 8.3 mmol) in MeCN (10 mL) was stirred at room temperature for 4 days. Ether (15 mL) was added, and insoluble material was removed by filtration. The filtrate was concentrated, and the residue was chromatographed on an alumina column eluted with ether/petroleum ether (1:16). The resulting tertiary amine was converted into the hydrochloride and recrystallized to afford **7h**·HCl as a white solid: $^1$H NMR ($CD_3OD$, 90 MHz) $\delta$ 7.00−6.92 (m, 2 H), 6.75 (d, $J$ = 9.4 Hz, 1 H), 3.88 (s, 1 H), 3.39−3.20 (m, 4 H), 3.00−2.64 (m, 2 H), 1.97−1.50 (m, 6 H), 1.03 (dd, $J_1$ = 7.2 Hz, $J_2$ = 7.2 Hz, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 158.4 (d, $J$ = 237 Hz), 155.8 (d, $J$ = 2.1 Hz), 128.7 (d, $J$ = 7.7 Hz), 115.0 (d, $J$ = 23.0 Hz), 114.3 (d, $J$ = 24.4 Hz), 112.6 (d, $J$ = 8.4 Hz), 57.7 (2 C's), 56.5, 46.0, 18.5 (3 C's), 12.7, 11.5 (2C's).

***trans*-2-(5-Fluoro-2-hydroxyphenyl)-*N*,*N*-dipropylcyclopropylamine (71). Method IX.** A stirred solution of **7h**·HCl (0.15 g, 0.50 mmol) in 48% aqueous HBr (10 mL) was heated for 2 h (120 °C bath temperature). The solution was concentrated, and the residue was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and ether (20 mL). The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic layers were dried ($Na_2SO_4$, filtered, and concentrated. The crude **71** was converted into the hydrochloride and recrystallized to afford **71**·HCl as a white solid: $^1$H NMR ($CD_3OD$, 90 MHz) $\delta$ 6.85−6.60 (m, 3 H), 3.42−3.23 (m, 4 H), 3.00−2.61 (m, 2 H), 1.98−1.50 (m, 6 H), 1.02 (dd, $J_1$ = 7.2 Hz, $J_2$ = 7.2 Hz, 6 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 157.7 (d, $J$ = 235 Hz), 153.6 (d, $J$ = 1.4 Hz), 126.4 (d, $J$ = 7.7 Hz), 116.4 (d, $J$ = 8.3 Hz), 115.0 (d, $J$ = 23.0 Hz), 114,2 (d, $J$ = 24.3 Hz), 57.6 (2 C's), 45.8, 18.8, 18.4 (2 C's), 12.5, 11.3 (2 C's).

**Pharmacology. Animals.** Male Sprague-Dawley rats (B & K Universal, Sollentuna, Sweden), weighing 250−300 g, were used throughout the studies. The rats were housed five/cage under standardized environmental conditions (temperature 22−23 °C; humidity 55−60%; 14/10 light/dark cycle, lights on at 6 am; rat chow and tap water allowed *ad lib*) for at least 1 week after the arrival until used in the experiments. Reserpine pretreatment (5 mg/kg, sc) was given to all animals 18−20 h before start of the experiments (cf. below).

**Drugs.** The compounds to be tested were dissolved in physiological (0.9%, w/v) saline immediately before use, occasionally with the addition of a few drops of glacial HOAc and/or moderate heating to obtain complete dissolution. Reserpine (Ciba, Basel, Switzerland) was dissolved in a few drops of glacial HOAc and made up to volume with 5.5% glucose (w/v). All drugs, including reserpine and NSD1015 (Sigma, St. Louis, MO), were subcutaneously injected into the neck region, in a volume of 5 mL/kg.

**Biochemistry.** The biochemical experiments, including brain dissections and HPLC determinations (electrochemical detection) of tissue contents of DOPA and 5-HTP, were carried out essentially according to methods detailed elsewhere.[25,26] Empirically, the maximum decrease of cerebral 5-HTP values

obtained with a direct-acting 5-$HT_{1A}$ receptor agonist (*e.g.*, **3**) is about 50% from control values under conditions equivalent to those used in the present experiments (see ref 4c).

**Behavior.** The occurrence and intensity of flattened body posture, forepaw treading, and hindlimb abduction was scored for 60 s at the 30-min time point following test drug administration, using an intensity-based rating scale, where 0 = absent, 1 = equivocal, 2 = definite, and 3 = intense;[27] *i.e*, the maximum summed score for the total set of behavioral items was 9. For reference, a dose of 0.1 $\mu$mol/kg (sc) of (*R*)-**3** which causes a near-maximal postsynaptic 5-$HT_{1A}$ behavioral activation yields summed scores 8−9 using this approach under similar conditions (cf. ref 27). Observations of other effects of the drugs on behavior were also simultaneously noted, though not quantified.

**Statistics.** The biochemical data are expressed in percent of the corresponding control values, means ± SEM. One-way ANOVA, followed by Fisher's protected least-significant-difference test (PLSD), was used for statistical comparisons of drug-treated groups with controls. The behavioral data are expressed as medians (range). Probability levels ≤5% were considered statistically significant.

**5-$HT_{1A}$ Receptor Binding Assay.** Male Sprague−Dawley rats (weighing about 200 g) were decapitated, and the cortex and hippocampus were dissected. The tissues (600−900 mg) from each rat were immediately homogenized in 15 mL of ice-cold 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5, with an Ultra Turrax (Janke and Kunkel, Staufen, FRG) for 10 s. After centrifugation for 12.5 min at 17000 rpm (39800*g*) in a Beckman centrifuge with a chilled JA-17 rotor (Beckman, Paulo Alto, CA), the pellets were resuspended in the same buffer, and homogenization and centrifugation were repeated. The pellets from at least six rats were again suspended in the buffer, pooled, homogenized, and stored on ice for 1−4 h. The tissue homogenate was diluted to 10 mg/1.25 mL with the buffer, incubated for 10 min at 37 °C, and supplied with 10 $\mu$M pargylin (Sigma, St. Louis, MO) followed by reincubation for 10 min.

Incubation mixtures (2 mL) contained 1−300 nM test compound (diluted in 50 mM Tris-HCl containing 5.7 mM ascorbic acid, pH 7.5), 2 nM [$^3$H]-8-OH-DPAT ([$^3$H]-8-hydroxy-2-(dipropylamino)tetralin hydrobromide), 31.60 Ci/mmol, New England Nuclear, Dreieich, Germany, and Research Biochemicals, Wayland, MA), 5 mg/mL tissue homogenate in 50 mM Tris-HCl buffer containing 4.0 mM $CaCl_2$ and 5.7 mM ascorbic acid, pH 7.5. Binding experiments were started by the addition of tissue homogenate followed by incubation at 37 °C for 10 min. The incubation mixtures were filtered through Whatman GF/B glass filters with a Brandel Cell Harvester (Gaithersburg, MD). The filters were washed twice with 5 mL of ice-cold 50 mM Tris-HCl buffer, pH 7.5, and counted with 5 mL of Packard Ultima Gold in a Beckman LS 3801 scintillation counter. Nonspecific binding was measured by the addition of 10 $\mu$M 5-HT·HCl to the reaction mixture. The binding data were processed by nonlinear least squares computer analysis.[28] A $K_d$ value of 1.4 nM for 8-OH-DPAT binding was obtained from the saturation experiments and was used to calculate the $K_i$ values. The range of $K_i$ was calculated from the inverse of the standard error of the estimate of $K_i$. Four of the compounds in Table 4 [(1*S*,2*R*)-**7h**, (1*R*,2*S*)-**7h**, (1*S*,2*R*)-**7l**, and (1*R*,2*S*)-**7l**] were assayed for 5-$HT_{1A}$ binding using a slightly modified procedure.[29]

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**Supporting Information Available:** Selected $^1$H NMR chemical shifts and coupling constants of **6a**−**k** (1 page). Ordering information is given on any current masthead page.

## References

(1) Schreiber, R.; DeVry, J. 5-$HT_{1A}$ Receptor Ligands in Animal Models of Anxiety, Impulsivity and Depression—Multiple Mechanisms of Action, *Prog. Neuro-Psych. Biol. Psych.* **1993**, *17*, 87−104.

(2) (a) Glennon, R. A.; Westkaemper, R. B.; Bartyzel, P. Medicinal Chemistry of Serotonergic Agents. In *Serotonin Receptor Subtypes*; Peroutka, S. J., Ed.; Wiley-Liss: New York, 1991; pp 19−64. (b) Arvidsson, L.-E.; Hacksell, U.; Glennon, R. A. Recent Advances in Central 5-Hydroxytryptamine Receptor Agonists and Antagonists. *Prog. Drug Res.* **1986**, *30*, 365-471. (c) Hacksell, U.; Mellin, C.; Hillver, S.-E.; Björk, L.; Cornfield, L. J.; Nelson, D. N.; Lewander, T. 8-OH-DPAT-Derived 5-$HT_{1A}$-Receptor Agonists and Antagonists. In *Trends in Medicinal Chemistry '90*; Sarel, S., Mechoulam, R., Agranat, I., Eds.; Blackwell: London, 1992; pp 113−120.

(3) Arvidsson, L.-E.; Johansson, A. M.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Magnusson, T.; Carlsson, A.; Lindberg, P.; Andersson, B.; Sanchez, D.; Wikström, H.; Sundell, S. *N*,*N*-Dialkylated Monophenolic *trans*-2-Phenylcyclopropylamines: Novel Central 5-Hydroxytryptamine Receptor Agonists. *J. Med. Chem.* **1988**, *31*, 92−99.

(4) (a) Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Hjorth, S. Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H. 8-Hydroxy-2-(dipropylamino)tetralin, A New Centrally Acting 5-Hydroxytryptamine Receptor Agonist. *J. Med. Chem.* **1981**, *24*, 921−923. (b) Arvidsson, L.-E.; Hacksell, U.; Johansson, A. M.; Nilsson, J. L. G.; Lindberg, P.; Sanchez, D.; Wikström, H.; Svensson, K.; Hjorth, S.; Carlsson, A. 8-Hydroxy-2-(alkylamino)-tetralins and Related Compounds as Central 5-Hydroxytryptamine Receptor Agonists. *J. Med. Chem.* **1984**, *27*, 45−51. (c) Hjorth, S.; Carlsson, A.; Lindberg, P.; Sanchez, D.; Wikström, H.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G. 8-Hydroxy-2-(di-n-propylamino)tetralin, 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT-receptor stimulating activity. *J. Neural Transm.* **1982**, *55*, 169−188.

(5) Cornfield, L. J.; Lambert, G.; Arvidsson, L.-E.; Mellin, C.; Vallgårda, J.; Hacksell, U.; Nelson, D. L. Intrinsic Activity of Enantiomers of 8-Hydroxy-2-(di-n-propylamino)tetralin and its Analogs at 5-Hydroxytryptamine$_{1A}$ Receptors That Are Negatively Coupled to Adenylate Cyclase. *Mol. Pharmacol.* **1991**, *39*, 780−787.

(6) Jeffery, T. Highly Stereospecific Palladium-Catalysed Vinylation of Vinylic Halides Under Solid-liquide Phase Transfer Conditions. *Tetrahedron Lett.* **1985**, *26*, 2667−2670.

(7) (a) Vallgårda, J.; Appelberg, U.; Csöregh, I.; Hacksell, U. Stereoselectivity and Generality of the Palladium-Catalysed Cyclopropanation of α,β-Unsaturated Carboxylic Acids Derivatized with Oppolzer's Sultam. *J. Chem. Soc., Perkin Trans. 1* **1994**, 461−470. (b) Vallgårda, J.; Hacksell, U. Stereoselective Palladium-Catalyzed Cyclopropanation of α,β-Unsaturated Carboxylic acids Derivatized with Oppolzer's Sultam. *Tetrahedron Lett.* **1991**, *32*, 5625−5628; 7136.

(8) Paulissen, R.; Hubert, A. J.; Teyssie, Ph. Transition Metal Catalysed Cyclopropanation of Olefins. *Tetrahedron Lett.* **1972**, *15*, 1465−1466.

(9) Shioiri, T.; Ninomiya, K.; Yamada, S. Diphenylphosphoryl Azide. A New Convenient Reagent for a Modified Curtius Reaction and for the Peptide Synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

(10) (a) Carpino, L. A.; Tsao, A. C. Convenient Source of 'Naked' Fluoride: Tetra-*n*-butylammonium Chloride and Potassium Fluoride Dihydrate. *J. Chem. Soc., Chem. Commun.* **1979**, 514−515. (b) Capson, T. L.; Thompson, M. D.; Dixit, V. M.; Gaughan, R. G.; Poulte, C. D. Synthesis of Ammonium Analogues of Carbocationic Intermediates in the Conversion of Presqualene Diphosphate to Squalene. *J. Org. Chem.* **1988**, *53*, 5903−5908.

(11) Jung, M. E.; Lyster, M. A. Conversion of Alkyl Carbamates into Amines *via* Treatment with Trimethylsilyl Iodide. *J. Chem. Soc., Chem. Commun.* **1978**, 315−316.

(12) Andén, N.-E.; Carlsson, A.; Häggendal, J. Adrenergic mechanisms. *Annu. Rev. Pharmacol.* **1969**, *9*, 119−134.

(13) Aghajanian, G. K. Feedback regulation of central monoaminergic neurons: evidence from single cell recording studies. In *Essays in neurochemistry and neuropharmacology*; Youdim, M. B. H., Lovenberg, W., Sharman, D. F., Lagnado, J. R., Eds.; John Wiley & Sons: New York, 1978; pp 2−32.

(14) Hjorth, S.; Magnusson, T. The 5-$HT_{1A}$ agonist 8-OH-DPAT preferentially activates cell body 5-HT autoreceptors in rat brain *in vivo*. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *338*, 463−471.

(15) Neckers, L. M.; Neff, N. H.; Wyatt, R. J. Increased Serotonin turnover in corpus striatum following an injection of kainic acid: evidence for neuronal feedback regulation of synthesis. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *306*, 173−177.

(16) It was suggested by one of the referees that the *in vivo* effects of the arylcyclopropylamine derivatives studied herein might be primarily due to monoamine oxidase B (MAO B) inhibition and not due to 5-$HT_{1A}$ receptor interactions. Although this possibility cannot be unambiguously excluded for the novel compounds, a number of factors support the notion that MAO B inhibition is irrelevant: (i) MAO inhibitors like tranylcypromine significantly reduce 5-HIAA levels to about 80−90% of control levels. In contrast, the 5-HIAA decrease induced by the compounds studied herein does not exceed 20% of controls. (ii) The DOPAC levels are only affected by one of the novel compounds and the reduction amounts to only about 40% of the control values. (iii) The *in vivo* effects of the lead compounds for the present study, (1*R*,2*S*)-**1** and (1*R*,2*S*)-**2**, have been demonstrated to be unrelated to indirect effects, such as MAO inhibition, because their *in vivo* effects persisted after the combined treatment with the monoamine depletor reserpine and the 5-HT synthesis inhibitor H 22/54 (ref 3). It is very unlikely that the structural changes introduced in the novel compounds would enhance their ability to inhibit MAO B. (iv) Although primary amines may be good MAO-inhibitors, this activity is normally reduced or lost in the tertiary amino analogues.

(17) Tricklebank, M.; Forler, C.; Fozard, J. R. The involvement of subtypes of the 5-$HT_1$ receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-*n*-propylamino)-tetralin in the rat. *Eur. J. Pharmacol.* **1985**, *106*, 271−282.

(18) (a) Liu, Y.; Svensson, B. E.; Yu, H.; Cortizo, L.; Ross, S. B.; Lewander, T.; Hacksell, U. C8-Substituted Derivatives of 2-(Dipropylamino)tetralin: Palladium-Catalyzed Synthesis and Interactions with 5-$HT_{1A}$ Receptors. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 257−262. (b) Liu, Y.; Yu, H.; Svensson, B. E.; Cortizo, L.; Lewander, T.; Hacksell, U. Derivatives of 2-(Dipropylamino)tetralin: Effects of the C8-Substituent on the Interaction with 5-$HT_{1A}$ Receptors. *J. Med. Chem.* **1993**, *36*, 4221−4229.

(19) Arvidsson, L.-E.; Karlén, A.; Norinder, U.; Kenne, L.; Sundell, S.; Hacksell, U. Structural Factors of Importance for 5-Hydroxytryptaminergic Activity. Conformational Preferences and Electrostatic Potentials of 8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and Some Related Agents. *J. Med. Chem.* **1988**, *31*, 212−221.

(20) Mellin, C.; Vallgårda, J.; Nelson, D. L.; Björk, L.; Yu, H.; Andén, N.-E.; Csöregh, I.; Arvidsson, L.-E.; Hacksell, U. A 3-D Model for 5-$HT_{1A}$-Receptor Agonists Based on Stereoselective Methyl-Substituted and Conformationally Restricted Analogues 8-Hydroxy-2-(dipropylamino)tetralin. *J. Med. Chem.* **1991**, *34*, 497−510.

(21) Yocca, D.; Iben, L.; Meller, E. Lack of Apparent Receptor Reserve at Postsynaptic 5-Hydroxytryptamine$_{1A}$ Receptors Negatively Coupled to Adenylyl Cyclase Activity in Rat Hippocampal Membranes. *Mol. Pharmacol.* **1992**, *41*, 1066−1072.

(22) (a) Hillver, S.-E.; Björk, L.; Li, Y.-L.; Svensson, B.; Ross, S.; Andén, N.-E.; Hacksell, U. (*S*)-5-Fluoro-8-hydroxy-2-(dipropylamino)tetralin: A Putative 5-$HT_{1A}$-Receptor Antagonist. *J. Med. Chem.* **1990**, *33*, 1541−1544. (b) Björk, L.; Cornfield, L. J.; Nelson, D. L.; Hillver, S.-E.; Andén, N.-E.; Lewander, T.; Hacksell, U. Pharmacology of the Novel 5-Hydroxytryptamine$_{1A}$ Receptor Antagonist (*S*)-5-Fluoro-8-hydroxy-2-(dipropylamino)-tetralin: Inhibition of (*R*)-8-Hydroxy-2-(dipropylamino)tetralin-Induced Effects. *J. Pharmacol. Exp. Ther.* **1991**, *258*, 58−65.

(23) Gaertner, R. Bromination, Iodination and Phenylation of Thianaphthenes. *J. Am. Chem. Soc.* **1952**, *74*, 4950−4951.

(24) Black, T. H. The Preparation and Reactions of Diazomethane. *Aldrichimica Acta* **1983**, *16*, 3−10.

(25) Carlsson, A.; Lindquist, M. Effect of ethanol on the hydroxylation of tyrosine and tryptophan in rat brain in vivo. *J. Pharm. Pharmacol.* **1973**, *25*, 437−440.

(26) Shum, A.; Sole, M. J.; van Loon, G. R. Simultaneous measurement of 5-hydroxytryptophan and L-dihydroxyphenylalanine by high performance liquid chromatography with electrochemical detection. Measurement of serotonin and catecholamine turnover in discrete brain regions. *J. Chromatogr.* **1982**, *228*, 123−130.

(27) Hjorth, S.; Sharp, T. Mixed agonist/antagonist properties of NAN-190 at 5-$HT_{1A}$ receptors: Behavioural and *in vivo* brain microdialysis studies. *Life Sci.* **1990**, *46*, 955−963.

(28) Munson, P. J.; Rodbard, D. LIGAND: A Versatile Computerized Approach for Characterization of Ligand-Binding Systems. *Anal. Biochem.* **1980**, *107*, 220−239.

(29) Jackson, D. M.; Mohell, N.; Georgiev, J.; Bengtsson, A.; Larsson, L.-G.; Magnusson, O.; Ross, S. B. Time course of bromocriptine induced excitation in the rat: behavioural and biochemical studies. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1995**, *351*, 146−155.

(30) Buckle, D. R. Arachidonic Acid Analogues, Processes for Their Preparation and Their Use in Medicine. European Patent 0109 225 A1, 1983.

(31) Beck, M.; Jaunich, S.; Frahm, A. W. Synthese Kernfluorierter Stereomerer 3-Oxo-5-phenyl-1-cyclopentancarbonsäuren. (Stereochemistry of 3-oxo-5-phenyl-cyclopentanecarboxylic acids, IX: Synthesis of stereoisomeric 5-(fluorophenyl)-3-oxocyclopentanecarboxylic acids.) *Arch. Pharm.* **1986**, *319*, 29−37.

(32) Collins, R. J.; Brown, E. V. Heterocyclic Analogs of the Estrogenic Steroid Hormones. I. Synthesis of a Thiophene Analog of 3-Desoxyisoequilenin. *J. Am. Chem. Soc.* **1957**, *79*, 1103−1107.

(33) Gregory, B.; Hinz, W.; Jones, R. A.; Arques, J. S. Utilisation of $^{13}C$ N.M.R. Spectroscopy for the Identification of E- and Z-α,β-Unsaturated Esters, Ketones and Nitriles *J. Chem. Res. Miniprint* **1984**, 2801−2809.

(34) Satonaka, A. 1H-NMR Data for Methyl *trans*-β-(2-,4-, and 5-Substituted-3-thienyl)acrylates. *Magn. Reson. Chem.* **1986**, *24*, 265−267.

(35) Burger, A.; Yost, W. Arylcyclopropylamines. I. 2-Phenylcyclopropylamine. *J. Am. Chem. Soc.* **1948**, *70*, 2198−2201.

(36) Kaiser, C.; Lester, B. M.; Zirkle, C. L.; Burger, A.; Davis, C. S.; Delia, T. J.; Zirngibl, L. 2-Substituted Cyclopropylamines. I. Derivatives and Analogs of 2-Phenylcyclopropylamine. *J. Med. Pharm. Chem.* **1962**, *5*, 1243−1265.

(37) McFarland, J. W. On the Isomers of 2-(2-Thienyl)- and 2-Phenylcyclopropanecarboxylic Acid. *J. Org. Chem.* **1965**, *30*, 3298−3301.

(38) Kang, G. I.; Hong, S. K. Quantitative Structure-Activity Relationship in MAO-Inhibitory 2-Phenylcyclopropylamines: Insight into the Topography of MAO-A and MAO-B. *Arch. Pharm. Res.* **1990**, *13*, 82−96.

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