aromatic H), 7.82 (d of d, 1, J = 3 and 8 Hz, CHCCO).

1-Morpholino-2-(*o*-phenoxyphenyl)-1-ethanethione (8c). A mixture of *o*-phenoxyacetophenone (**7c**; 17.5 g, 82.5 mmol), morpholine (14.2 g, 0.163 mol), and sulfur (3.8 g, 0.12 g-atom) was boiled for 6 h. The reaction mixture was diluted with water, and this mixture was extracted with ether. The ether solution was filtered and extracted with 1 N hydrochloric acid and dried (Na_2SO_4). Evaporation of the ether left a residual oil, which on standing partially crystallized, mp 87–93 °C. Repeated recrystallization of this solid from isopropyl ether–ethanol (2:1) gave **8c** (7.18 g, 28%): mp 105–106 °C; ^{1}H NMR δ 3.50 (m, 2, morpholino H), 3.70 (m, 2, morpholino H), 3.72 (m, 2, morpholino H), 4.32 (s, 2, C-2 H), 4.36 (m, 2, morpholino H), 6.76–7.40 (m, 8, aromatic H), 7.56 (d of d, 1, J = 2 and 7 Hz, C*H*CCH$_2$). Anal. ($C_{18}H_{19}NO_2S$) C, H, N.

2-Morpholinobenzo[*b*]thiophene (9). 1-Morpholino-2-(*o*-phenoxyphenyl)-1-ethanethione (**8c**; 0.99 g, 3.2 mmol) was added with stirring to polyphosphoric acid ($H_6P_4O_{15}$; 10 mL) at 90–100 °C, and the mixture was stirred for 2 h. After the mixture was cooled, water was added, and the mixture was extracted with ether. The ether solution was extracted with saturated sodium carbonate and dried (Na_2SO_4). After the ether was evaporated, recrystallization of the solid residue from toluene gave **9** (0.63 g, 91%): mp 177–178 °C (lit.[13] mp 175 °C); ^{1}H NMR δ 3.12 (m, 4, morpholino H), 3.75 (m, 4, morpholino H), 6.08 (s, 1, C-3 H), 6.84–7.52 (m, 4, aromatic H). Anal. ($C_{12}H_{13}NOS$) C, H, N, S.

Biological Activity. Brain tissue and other materials for biological testing were as reported earlier.[4] Displacements of [^{3}H]clozapine from specific muscarinic and nonmuscarinic binding sites in rat forebrain and [^{3}H]spiroperidol from specific binding sites in rat caudate nuclei by the clozapine analogues were determined as described previously.[4]

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2-Amino-4,7-dimethoxyindan Derivatives: Synthesis and Assessment of Dopaminergic and Cardiovascular Actions

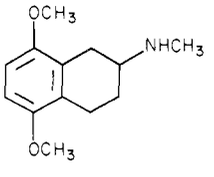
R. D. Sindelar,† J. Mott,† C. F. Barfknecht,† S. P. Arneric,*,‡ J. R. Flynn,‡ J. P. Long,‡ and R. K. Bhatnagar‡

Division of Medicinal Chemistry and Natural Products, College of Pharmacy, and Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242. *Received August 25, 1981*

N-Alkylated derivatives of 2-amino-4,7-dimethoxyindan were prepared for evaluation of central and peripheral dopaminergic activity using biochemical and behavioral tests in the rat and cardiovascular responses in the cat. 2-(Di-*n*-propylamino)-4,7-dimethoxyindan (**4e**) demonstrated equal activity with apomorphine to activate peripheral presynaptic dopamine receptors. Central pre- and postsynaptic dopamine receptors were also activated with **4e**. In contrast to the intense long-acting sympathomimetic actions previously reported for the 2-amino-5,8-dimethoxytetralins, these compounds produced weak, transient effects in heart rate and blood pressure. The majority of 2-amino-4,7-dimethoxyindan derivatives tested are weak or inactive pre- and postsynaptic dopamine receptor agonists.

Various researchers have prepared an extensive series of 2-amino-1,2,3,4-tetrahydronaphthalenes (2-aminotetralins) as restricted conformers of compounds containing the β-phenethylamine skeleton. These efforts have been useful in studying the structure–activity relationships of substances related to lysergic acid diethylamide (LSD), the psychotomimetic phenylisopropylamines, and dopamine.[1-6] In 1976 Rusterholz and co-workers[7] reported the synthesis and pharmacological testing of several compounds as potential inhibitors of prolactin release, among them certain 2-amino-5,8-dimethoxytetralins.

Of particular interest is *N*-methyl-2-amino-5,8-dimethoxytetralin (1). Although compound 1 is ineffective as an



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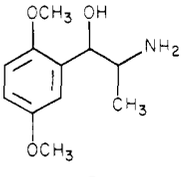

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inhibitor of prolactin release, it has the ability to inhibit several apomorphine-induced responses,[8] which suggests that it may interact with some dopamine receptor mediated responses. An interesting action of the 2-amino-5,8-dimethoxytetralins that Rusterholtz and co-workers reported is the ability of these derivatives to block apomorphine-induced emesis in dogs. Cardiovascular testing demonstrated that compound 1 also produces prolonged hypertension in dogs which is the result of postsynaptic α-receptor stimulation.[9] Inspection of the chemical structures shows that the pressor agent methoxamine (2) and compound 1 are structurally related. Other 2-amino-5,8-dimethoxytetralin derivatives also appear to interact with α receptors in the periphery[4] and in the CNS.[10]

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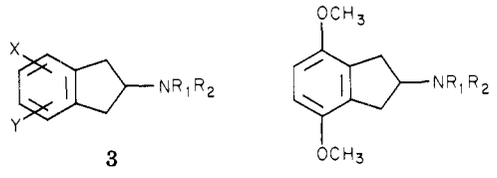
Table I. Neural and Cardiovascular Properties of 2-Amino-4,7-dimethoxyindan Derivatives in the Cat

compd	N	inhibn of rt cardioaccelerator nerves: ID_{50}, μmol/kg (95% CI)	$\overline{BP}$, %Δ (±SEM)	$\overline{HR}$, bpm (±SEM)
Apo[d]	6	0.103[b]		
1				
4a	3	1.55[a]	+6.3 ± 6.3	0 ± 0
4b	3	1.23[a]	+28.1 ± 8.9	+2.5 ± 1.4
4c	3	1.16[a]	+51.8 ± 14.0*[c]	+3.2 ± 3.5
4d	3	1.10[a]	+0.7 ± 6.4	−3.2 ± 2.1
4e	6	0.107[b] (0.2-0.38)	−16.6 ± 8.0	−6.4 ± 2.8
4f	3	1.10[a]	+3.8 ± 3.8	0 ± 0

[a] No significant activity shown at the specified dose (micromoles per kilogram). [b] Responses were antagonized by haloperidol. [c] An asterisk indicates the value is significantly different from saline control; $p < 0.05$. [d] Apo = apomorphine.

Some of the most active dopamine receptor agonists known are certain catechol-containing 2-aminotetralins, which are more potent than apomorphine in inducing central dopaminergic activation in rats.[11] However, monohydroxy derivatives are also potent emetics in dogs.[12] Cannon and co-workers[6] found that 2-aminoindan derivatives are comparable in potency to apomorphine in inducing central dopaminergic activation but much less active than apomorphine as emetics in dogs. The most potent central dopamine receptor stimulating activity is associated with the 5-hydroxy group in the 2-aminotetralin[12] and the 4-hydroxy group in the 2-aminoindan[13] derivatives.

Due to the interesting pharmacological effects attributed to the 2-amino-5,8-dimethoxytetralins and decreased emetic liability associated with the 2-aminoindans, it became desirable to synthesize a series of 2-amino-4,7-dimethoxyindans (**4a–f**) to further study the structural requirements for these effects. Congener **4a** has been previously reported;[14] however, only preliminary pharmacological testing results have appeared in the literature. This report will be concerned with our synthesis of **4a–f** and their pharmacological evaluation.



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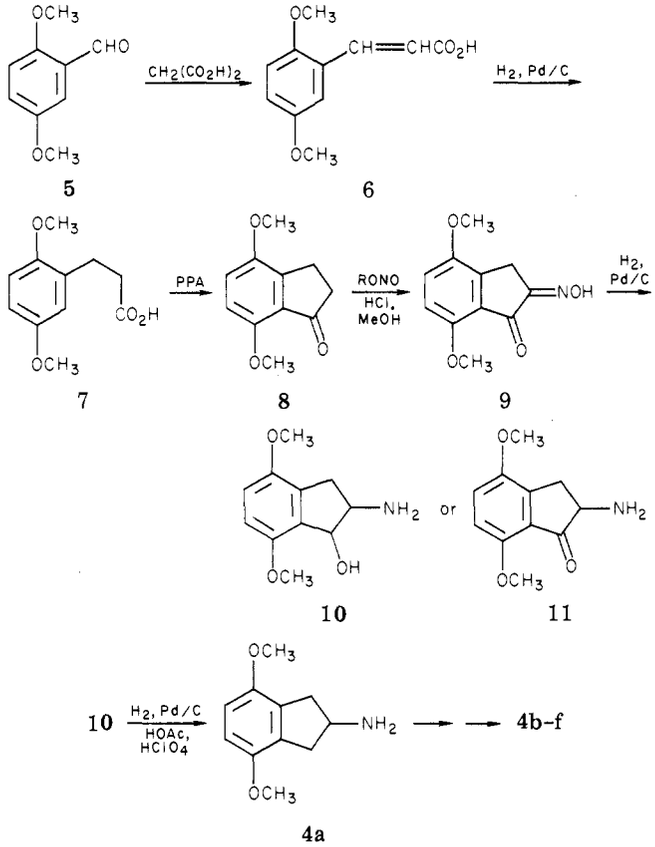
4a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$
d, $R_1 = H$; $R_2 = CH_2CH_2CH_3$
e, $R_1 = R_2 = CH_2CH_2CH_3$
f, $R_1 = H$; $R_2 = CH(CH_3)_2$

Chemistry. The preparation of compounds **4a–f** was accomplished by either of two synthetic routes. The ability to prepare the N-substituted and N,N-disubstituted congeners **4b-f** was contingent on an efficient synthesis of the primary amine analogue **4a**. One route (Scheme I) to **4a** is a modification of the procedure developed by Coutts and Malicky[14] and is also similar to a synthesis of related indan amino alcohols by Heinzelmann and co-workers.[15] Scheme II outlines a precedented[13] alternative route to **4a** which, while having one more step than the route shown in Scheme I, provides a general and reasonably convenient pathway to β-phenethylamine derivatives.

Scheme I



Scheme II

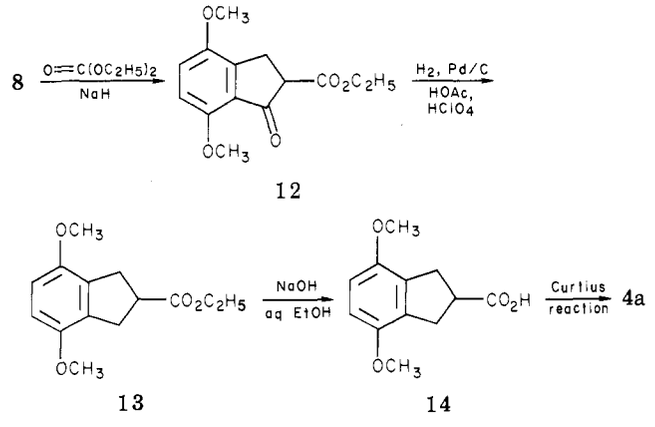


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Table II. Central Nervous System Effects of 2-Amino-4,7-dimethoxyindan Derivatives

compd	rat rotation: potency[c] ratio to Apo (95% CI)	rat CNS transmitter synth[b]: Dopa (caudate)	rat CNS transmitter synth[b]: 5-HTP (olf tub.)
Apo[g]	1.0	18.3*[d]	NT
1	3.9[a]	103.8	33.2*[c]
4a	8.7[a]	94.4	109.7
4b	8.2[a]	67.9*	94.7
4c	0.019[h] (estimated)	NT	NT
4d	7.4[a]	79.1	104.7
4e	0.13 (0.024-0.27)	31.8*[c,d]	51.5*[c]
4f	NT	NT	NT

[a] No significant activity shown at the specified dose (micromoles per kilogram). [b] Compounds were screened at 4.0 mg/kg hydrochloride salt, sc (n = 3-4). Data are expressed as percent of control. [c] An asterisk indicates the value is significantly different from saline control; $p < 0.05$. [d] Responses were antagonized by haloperidol, 1.0 mg/kg ip, 15-min pretreatment. [e] The dose of apomorphine that produces half the maximal response in rotation behavior is 2 μmol/kg sc. [f] NT = not tested. [g] Apo = apomorphine.

Literature procedures were generally closely followed. Any modifications of the known methods are noted under Experimental Section.

Pharmacology Results

The cardioaccelerator nerve inhibitory actions and cardiovascular properties of **4a–f** are shown in Table I. The increasing sympathomimetic responses seen with **4a–c** appear to be dependent upon methylation of the nitrogen substituent. The maximal sympathomimetic responses occured 1–6 min following intravenous administration. Pressor responses were transient (2–5 min) and were much shorter acting than that observed with 1 (refer to ref 9). *N*-Propyl and *N*-isopropyl derivatives (**4d–f**) did not significantly alter basal blood pressure or heart rate. The *N,N*-di-*n*-dipropyl derivative, **4e**, exhibited inhibition of the positive chronotropic response induced with stimulation of the right cardioaccelerator nerve. Inhibition was maximal within 2 min and was effective 15–30 min. The calculated ED_{50} values for **4e** and apomorphine were equivalent. Prior administration of haloperidol, 100 μg/kg iv, blocked the neuronal inhibitory effects of **4e** and apomorphine.

In rats with unilateral lesions of the substantia nigra, this series of compounds showed little activity with respect to postsynaptic DA receptor stimulation. The rationale behind the use of this model has been given previously.[16,17] Only compounds **4c** and **4e** induced stereotypy following sc administration. Doses are specified in Table II that did not produce significant rotational behavior. Compound **4e** showed weak contralateral rotational behavior. The results with **4c** were inconsistent from animal to animal, and so only an estimate of its potency was made. Both compounds **4c** and **4e** exhibited continuous sniffing, licking, gnawing, and hyperactive behavior that resembled apomorphine-induced stereotypy. Rotational response was not a potent effect, but the effect seen had a duration of action of approximately 2–6 h, which is 2–4 times longer than that produced by apomorphine. Stereotyped behavior and hyperactivity apeared at doses lower than those producing rotational responses. Pretreatment with pimozide (0.25 mg/kg ip, 2 h prior) blocked the hyperactivity and stereotypy of **4e** (data not shown).

In mice, these compounds inhibited spontaneous locomotor activity (see Figure 1). Significant attenuation of locomotor activity was evident within 10 min postadministration and began to return to control activity within 1 h. These results parallel those found for 1 and the corresponding 2-AT derivatives.[10] Only **4a** and **4f** lacked any significant ability to inhibit locomotor activity at the specified doses. The potency did not follow a clear structure–activity relationship.

These compounds weakly displaced specific [^{3}H]-spiroperidol binding in calf caudate homogenates. There was a statistically significant correlation when IC_{50}'s for inhibiting [^{3}H]spiroperidol were correlated to the ED_{50}'s for inhibiting locomotor activity in mice (see Figure 1). Again, no apparent structure–activity relationships were demonstrated.

Another evaluation of CNS actions of these compounds is to monitor alteration in CNS transmitter synthesis. Walters and Roth[18] developed a model whereby inhibition of striatal Dopa accumulation is shown to be strongly correlated with the ability of a compound to stimulate presynaptic dopamine receptors. Similar autoregulatory mechanisms seem to exist for 5-HT neurons.[19] Because relatively dense innervation of DA neurons and 5-HT neurons can be found in the caudate nucleus and olfactory tubercle, respectively, data for Dopa and 5-HTP accumulation are reported for these brain regions.

Compounds **4b**, **4e**, and apomorphine significantly inhibited the accumulation of Dopa in the caudate nucleus, $p < 0.05$ (see Table II). The other compounds did not significantly alter Dopa accumulations. Only **4e** and 1 significantly decreased the accumulation of 5-HTP, $p < 0.05$. An explanation for the lack of any apparent SAR may be attributed to the screening procedure using one dose at one specific time point. The other compounds may be active at higher concentrations.

Pharmacology Discussion

With one exception, **4e**, the 2-amino-4,7-dimethoxyindans we investigated are weak or inactive dopamine receptor agonists when compared to apomorphine. The central[20] and peripheral (present investigation) presynaptic dopamine receptor agonist actions of **4e** have demonstrated a potency equal to or greater than apomorphine. The long-acting sympathomimetic actions of the 2-amino-5,8-dimethoxytetralin derivatives are not observed with the 2-amino-4,7-dimethoxyindans.

Previous reports[4,5,9] demonstrated that 2-amino-5,8-dimethoxytetralin derivatives lacking an hydroxyl group bioisosteric with the β-hydroxy group of methoxamine (**2**) produced long-acting sympathomimetic actions. Cheng and co-workers[4] (and unpublished observations) demonstrated that 2-amino-4,7-dimethoxyindan derivatives probably stimulate peripheral postsynaptic α receptors directly. In vitro findings suggested that the 2-amino-4,7-dimethoxyindan structure is much less potent in ac-

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tivating α receptors than is the 2-amino-5,8-dimethoxytetralin structure.[4] This is consistent with the weak sympathomimetic actions observed in this investigation.

Recently, dopaminergic effects of nonhydroxylated semirigid analogues of apomorphine (including some 2-aminoindans) have been reported.[21] McDermed et al.[11] demonstrated that 2-(di-*n*-propylamino)-5,6-dimethoxytetralin has equivalent potency to apomorphine in inducing stereotyped behavior yet is significantly less emetic than apomorphine. However, Costall et all.[23] reported that while central injection of the 5,6- and 6,7-dihydroxy derivatives of 2-(di-*n*-propylamino)tetralin are able to induce hyperactivity and stereotyped biting, the dimethoxy derivatives are inactive. Hacksell et al.[12] demonstrated that there is little difference in potency between 2-(di-*n*-propylamino)-5-hydroxytetralin and 2-(di-*n*-propylamino)-5-methoxytetralin in interacting with negative feedback systems to reduce Dopa accumulation. This may be a significant pharmacological finding, since 2-(di-*n*-propylamino)-5-hydroxytetralin is nearly equipotent to the 5,6-dihydroxy derivative in producing central dopaminergic activation.[24] While the most potent central dopamine receptor stimulating activity in the 2-aminotetralin derivatives is associated with the 5-hydroxy group,[12] the most potent central dopamine receptor stimulating activity in the 2-aminoindan derivatives is associated with the 4-hydroxy group.[13] Both the 4-hydroxy group in the 2-aminoindan analogues and the 5-hydroxy group of the 2-aminotetralins are bioisoteric with the "meta" hydroxy group of dopamine. The meta hydroxy is thought to be of considerable importance in agonist–receptor interactions.[25] However, significant central dopaminergic activity is observed with 2-(di-*n*-propylamino)indan and other related N-alkylated derivatives.[21,22] The possibility that the unsubstituted or methoxy analogues are hydroxylated or O-demethylated to exert dopamine receptor agonist actions has not been excluded. Previous reports demonstrate that structurally related compounds, such as amphetamine, are readily hydroxylated,[26] and 4-methyl-2,5-dimethoxyphenylisopropylamine is O-demethylated.[27]

2-(Di-*n*-propylamino)- and 2-(di-*n*-methylamino)-4,7-dimethoxyindan (**4e** and **4c**, respectively) demonstrated central dopamine receptor stimulating activity, as characterized by rat rotational behavior, apomorphine-like stereotypies in rats, inhibition of locomotor activity in mice, and competitive inhibition of [^{3}H]spiroperidol binding to calf caudate membrane preparations. It appears that **4c** has a lower potency than **4e** in inhibiting Dopa accumulation, in activating dopamine receptors, and in inducing rotational behavior (see Tables I and II), yet **4c** is more potent than **4e** in inhibiting locomotor activity in mice and in inhibiting [^{3}H]spiroperidol binding (see Figure 1).

Data from more intensive investigation of **4e** indicate that this compound may interact with central dopamine receptors more potently than indicated by the screening procedure. Following subcutaneous administration, **4e** dose-dependently inhibited the accumulation of Dopa in the caudate nucleus (ED_{50} = 0.15 μmol/kg) and the olfactory tubercle (ED_{50} = 0.93 μmol/kg).[20] Apomorphine had an ED_{50} of 1.0 and 0.93 μmol/kg for inhibition of Dopa accumulation in the caudate nucleus and olfactory tubercle, respectively. Unlike apomorphine or any of the 2-aminotetralins or 2-aminoindans reported by Hacksell et al.,[12,13] **4e** demonstrated a preferential inhibition of Dopa accumulation in the nigrostriatal vs. the mesolimbic dopamine systems. It is unclear what structural feature may impart this selectivity in activity. Other dopamine-receptor mediated behaviors (i.e., inhibition of food intake) are also activated more potently with **4e** than with apomorphine and appear to be a direct action of the compound.[28] Nearly all dopamine-receptor agonist activity is lost with the 2-(di-*n*-propylamino)-5,6-dimethoxyindan derivative.[28]

The ability of **4e** or **1** to inhibit 5-HTP accumulation can be explained with the recent report of Arvidsson et al.[29] These authors reported that 5,6-dihydroxy or 7-hydroxy derivatives of 2-(di-*n*-propylamino)tetralin selectively inhibit Dopa accumulation, whereas the 8-hydroxy derivative selectively inhibits 5-HTP accumulations. Compounds **4e** and **1** have both of the necessary positions occupied, albeit with methoxy substitutions. With either **4e** or **1**, the dimethoxy groups and the amine group coincide approximately with the indole amino group, the 5-hydroxy group, and the side-chain amino group of serotonin, respectively.

The 2-amino-4,7-dimethoxyindan moiety demonstrates interesting biological interactions with dopamine-related systems. In most, but not all, cases these analogues show very weak dopaminergic activity. The significant correlation between inhibitory effects on locomotor activity and inhibition of [^{3}H]spiroperidol binding indicates that these derivatives possess some inherent agonist–receptor interactions that warrant further investigation.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded with a Varian Associates T-60 or EM-360A spectrophotometer using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 267 grating infrared spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

Rat Rotational Behavior. Male Sprague–Dawley rats (Biolabs) were unilaterally lesioned in the substantia nigra (AP, 2.4; LM, 1,8; V, 7.0) following injection of 6-hydroxydopamine hydrobromide (6 μg in 3 μl, see ref 12). Experimental compounds were screened at 2 mg/kg (HCl salt dissolved in saline, sc), and the rotational behavior was observed and quantified for at least 1 h. Contralateral circling responses were recorded automatically and expressed as turns per hour. Dose–response curves were generated for active compounds using four to five animals, and a potency ratio to apomorphine with 95% confidence interval (CI) was calculated for the 60 min following compound administration.

Cat Cardiovascular Nerve Stimulation. Cats (2–4 kg) of either sex were anesthetized with pentobarbital sodium, 30 mg/kg ip. All animals were intubated with an endotracheal tube and artificially ventilated with a Harvard respirator. Arterial blood pressure was measured from a femoral artery catheter by a Statham P23AA pressure transducer, and heart rate was monitored with a Beckman cardiotachometer. After bilateral vagotomy,

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the right postganglionic cardioaccelerator nerves were isolated and attached to bipolar electrodes. Stimulation parameters were 2 Hz with 5-ms pulse duration and a supramaximal voltage of 20–25 V. Test compounds were dissolved in saline and administered in a bolus, iv, via a femoral catheter. All animals were pretreated with atropine sulfate, 0.2 mg/kg iv.

Mice Motor Activity. Male Swiss-Webster mice (Biolabs), 20–40 g, were housed in groups of nine and allowed free access to standard lab chow and water. Lighting was on a 12 h (6:00 on/18:00 off) schedule. Experiments were performed in a quiet, well-lighted room. Locomotor activity was monitored and recorded with a selective activity meter (Columbus Instruments, Model S) set at 25 mA. Three to four groups of three mice were injected sc with test compound and placed in a plastic (18 × 25 × 15 cm) cage, which was placed on the activity meter and covered with a clear Plexiglas sheet with ventilation holes. Counts of activity were recorded each minute for 1 h. Inhibitory responses during the period 15–40 min postinjection were found to produce maximal effects. These data were summed for statistical analysis to determine, by probit analysis,[30] the ED_{50} for inhibition of exploratory activity as compared to saline control mice. Control motor activity, which was used as 100% in calculating percent reduction, was 470 ± 20 (counts/25 min ± SEM).

Transmiter Synthesis Measurement. The in vivo model developed by Carlsson and co-workers[31,32] was used to quantify two indexes of dopamine (DA) and serotonin (5-HT) synthesis in the CNS and Dopa and 5-HTP accumulation, respectively. This model has been recently modified to evaluate presynaptic dopamine receptor activity.[18] Test compounds were screened at 4.0 mg/kg sc and were administered 30 min prior to an ip injection of γ-butyrolactone (GBL, 750 mg/kg, in distilled water). Apomorphine was administered 5 min prior to GBL, 4.0 mg/kg sc. Control animals received saline plus GBL. Five minutes after GBL administration, animals received 100 mg/kg, ip, of the aromatic L-amino acid decarboxylase inhibitor *m*-hydroxybenzylhydrazine dihydrochloride (NSD 1015; prepared in saline). All compounds were administered in a volume of 2.0 mL/kg. Thirty minutes following NSD 1015 treatment, the rats were decapitated. Samples of the caudate nucleus and olfactory tubercle were dissected and were analyzed by high-performance liquid chromatography with electrochemical detection as described by Arneric and co-workers.[33] Data were analyzed with a one-way analysis of variance. Treatment differences were detected by a two-tailed Dunnett's procedure. The 0.05 level of probability was used as the criterion for statistical significance. Data are expressed as percent of vehicle control, which was 3.58 ± 0.21 ng/mg wet weight of Dopa in the caudate nucleus and 439 ± 26 pg/mg wet weight of 5-HTP in the olfactory tubercle (mean ± SEM).

[^{3}H]Spiroperidol Binding. The binding studies were carried out on total particulate homogenates of calf caudate according to the published procedures of Seeman and co-workers.[34] Competitive binding curves were constructed using a wide concentration range of the test compounds (10^{-8}–10^{-3} M) to compete with the [^{3}H]spiroperidol. Each sample concentration was assayed in triplicate, and the binding curves were replicated 2–5 times for each compound. IC_{50}'s were determined using probit analysis.[37]

2,3-Dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4a·HCl). The procedures of Coutts and Malicky[14] and Heinzelmann[15] were followed, with the exception of the transformation of **10** into **4a**. In a procedure based on that of Cannon eet al.,[6] 21.1 g (0.086 mol) of **10**·HCl in 600 mL of glacial acetic acid and 20 mL of 70% perchloric acid was hydrogenated over 2.0 g of 10% Pd/C at ambient temperature (27 h, 310 kPa pressure). The catalyst was filtered, and the filtrate was treated with 40 g of solid KOAc. After thorough mixing, the solid was filtered and the filtrate was evaporated. The syrupy residue was dissolved in H_2O, basified with 2.5 M NaOH, and extracted with Et_2O. The Et_2O was evaporated, and the salt was formed with Et_2O–HCl. Recrystallization from EtOH–Et_2O yielded 15.5 g (79%), mp 246–247 °C (lit.[14] 245–247 °C).

***N*-(2,3-Dihydro-4,7-dimethoxy-2-1*H*-indenyl)trifluoroacetamide.** Compound **4a** (1.0 g, 0.005 mol) was stirred under a N_2 atmosphere at 10 °C in 300 mL of trifluoroacetic anhydride for 20 min, allowed to warm up to room temperature, and then stirred for 10 min. Excess trifluoroacetic anhydride was removed under reduced pressure to give a white solid. The solid was dissolved in 15 mL of Et_2O and precipitated with 75 mL of hexane to afford pure white solid: yield 1.4 g (98%); mp 162–163 °C. Anal. ($C_{13}H_{14}F_3NO_3$) C, H, N.

***N*-Methyl-2,3-dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4b·HCl).** Following the procedure of Johnstone et al.,[35] a mixture of *N*-(2,3-dihydro-4,7-dimethoxy-2-1*H*-indenyl)trifluoroacetamide (0.50 g, 0.0025 mol) and iodomethane (1.47 g, 0.010 mol) was warmed to reflux in 20 mL of dry acetone. Powdered KOH (0.57 g, 0.010 mol) was added, and the reaction mixture was heated under reflux for 5 min. The excess iodomethane and acetone were removed under vaccum, and 2 mL of H_2O was added. After refluxing for 10 min, the solution was extracted with Et_2O, and the Et_2O was evaporated. The residue was dissolved in dry Et_2O and treated with Et_2O–HCl. The HCl salt was recrystallized from 2-PrOH–Et_2O to give **4b**·HCl: yield 0.38 g (63%); mp 237–238 °C dec. Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

***N*,*N*-Dimethyl-2,3-dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4c·HCl).** A solution of 2.0 g (0.01 mol) of **4a**·HCl, 5 mL of 37% formaldehyde, and 5 mL of 95% EtOH was allowed to stand for 15 min. An additional 10 ml of 95% EtOH, 1 mL of glacial acetic acid, and 0.15 g of PtO_2 were added. The mixture was shaken under 310 kPa of hydrogen until hydrogen uptake ceased. The catalyst was filtered and the filtrate was evaporated. The residue was treated with 5 mL of 0.25 N NaOH and extracted with Et_2O. The Et_2O was evaporated, and the resulting viscous oil was treated with 3 mL of phenyl isocyanate.[36] The mixture was allowed to stand for 16 h, dissolved in 75 mL of MeOH, heated on a steam bath for 15 min, and azeotroped under reduced pressure with benzene. A benzene solution of the residue was filtered and extracted with 2.5 N HCl. The pooled HCl extracts were made basic with 1 N KOH and extracted with Et_2O. The Et_2O extract was evaporated to dryness and treated with Et_2O–HCl to give 2.3 g (97%) of **4c**·HCl. Recrystallization from 2-PrOH–Et_2O gave the analytical sample: mp 219–220 °C dec. Anal. ($C_{13}H_{20}ClNO_2$) C, H, N.

***N*-(2,3-Dihydro-4,7-dimethoxy-2-1*H*-indenyl)propionamide.** Compound **4a**·HCl (0.43 g, 0.002 mol) was stirred at room temperature with 5 mL (5.1 g, 0.04 mol) of propionic anhydride and 10 mL of pyridine for 2 h. The reaction was diluted with H_2O and extracted with EtOAc. The extract was washed with 2 N HCl and H_2O. Following evaporation of the solvent, the residue was recrystallized from 2-PrOH–hexane: yield 0.30 g (64%); mp 175–176.5 °C. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

***N*-Propyl-2,3-dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4d·HCl).** To a solution 1.1 mL of 3.5 M sodium bis(2-methoxyethoxy)aluminum hydride in 15 mL of benzene was added dropwise with stirring under an N_2 atmosphere 0.29 g (0.0012 mol) of *N*-(2,3-dihydro-4,7-dimethoxy-2-1*H*-indenyl)-propionamide in 30 mL of benzene. After refluxing for 24 h, the reaction mixture was decomposed with 1 mL of H_2O. The benzene layer was separated and evaporated to a clear, viscous oil. Treatment of this oil with Et_2O–HCl and recrystallization of the resulting salt from 2-PrOH–Et_2O gave 0.25 g (75%) of **4d**·HCl: mp 209–210 °C dec. Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

***N*,*N*-Dipropyl-2,3-dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4e·HCl).** Using the method of Marchini et al. (procedure B),[37] sodium borohydride (8.1 g, 0.21 mol) was

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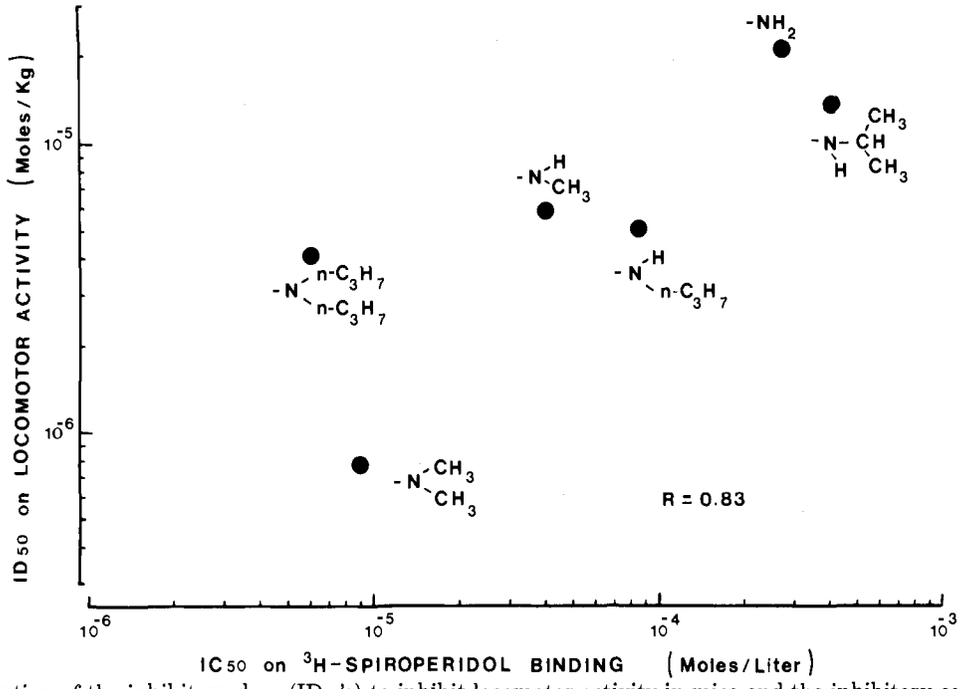

Figure 1. Correlation of the inhibitory dose (ID_{50}'s) to inhibit locomotor activity in mice and the inhibitory concentration (IC_{50}'s) to competitively inhibit [^{3}H]spiroperidol binding to calf caudate membrane preparations using various N-alkylated derivatives of 2-amino-4,7-dimethoxyindan. The nitrogen substitution of each compound is indicated in the figure.

added in small portions to 51.3 g (0.70 mol) of propionic acid in 75 mL of dry benzene maintained at 5–10 °C under an N_2 atmosphere. When hydrogen evolution had ceased, compound **4a** (2.7 g, 0.04 mol) in 10 mL of benzene was added, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, the mixture was treated with 2 N NaOH until the aqueous phase was strongly basic. The organic layer was separated, dried (Na_2SO_4), and evaporated. The residue was treated with 3 mL of phenyl isocyanate and worked up as described for **4c**. The resulting solid was dissolved in Et_2O, treated with Et_2O–HCl, and recrystallized from BuOH: yield 3.0 g (69%); mp 193–194 °C dec. Anal. ($C_{17}H_{28}ClNO_2$) C, H, N.

***N*-Isopropyl-2,3-dihydro-4,7-dimethoxy-1*H*-inden-2-amine Hydrochloride (4f·HCl).** Compound **4a** (1.75 g, 0.009 mol) and acetone (2.5 g, 0.045 mol) were hydrogenated in 50 mL of absolute EtOH over 0.07 g of PtO_2 at room temperature and an initial pressure of 310 kPa. The theoretical amount of hydrogen was absorbed in 3 h. The reduction mixture was filtered, and the solvent was removed under reduced pressure. The residue was treated with Et_2O: yield 1.6 g (64%); mp 221–222 °C dec. Anal. ($C_{14}H_{22}ClNO_2$) C, H, N.

2-Carbethoxy-2,3-dihydro-4,7-dimethoxy-1*H*-inden-1-one (12). The procedure used was a modification of known methods.[38-40] To a suspension of 1.01 g of NaH (1.80 g, 56% mineral oil dispersion of NaH, 0.042 mol) in 50 mL of dry diglyme was added a warm solution of 3.7 mL (3.61 g, 0.031 mol) of diethyl carbonate and 3.88 g (0.020 mol) of **8** in a mixture of 25 mL of dry diglyme and 65 mL of dry benzene at a steady dropwise rate. The mixture was stirred at room temperature under an N_2 atmosphere for 17 h. The excess base was decomposed by the addition of H_2O and then dilute HCl. The phases were separated, and the aqueous phase was extracted twice with EtOAc. The benzene and EtOAc phases were combined, washed extensively with H_2O, dried ($MgSO_4$), and evaporated to a dark red oil. The oil was chromatographed on 250 g of silica gel, using benzene–EtOAc (9:1) to elute the desired fraction: yield 4.15 g (78%) as an oil, which solidified on standing. An analytical sample was obtained by recrystallization of the solid from MeOH–H_2O, mp 93–95 °C. Anal. ($C_{14}H_{16}O_5$) C, H.

2,3-Dihydro-4,7-dimethoxy-1*H*-indene-2-carboxylic Acid (14). Following the method of Martin et al.,[41] a solution of 7.40 g (0.028 mol) of **12** in 100 mL of glacial acetic acid containing 2 mL of 70% perchloric acid was hydrogenated over 2 g of 10% Pd/C with an initial hydrogen pressure of 345 kPa. Hydrogen absorption was complete in 2 h. The reaction mixture was treated with excess KOAc, stirred, and filtered. The filtrate was diluted with H_2O and extracted twice with Et_2O. The pooled extracts were washed with three portions of fresh H_2O, dried ($MgSO_4$), and evaporated to a brown oil, using toluene to aazeotrope residual acetic acid. Obtained was 6.68 g (95%) of crude ester **13**. Due to the gradual decomposition of **13** under distillation conditions, the crude material was used in the next reaction without further purification.

A mixture of 2.66 g (0.011 mol) of **13** in 50 mL of 1:1 EtOH–H_2O containing 5.1 g of KOH (85% pure, 4.34 g, 0.078 mol) was stirred at room temperature for 5 h. The reaction mixture was poured into 100 g of ice containing 30 mL of concentrated HCl, stirred, and filtered. The solid was dissolved in aqueous KOH, filtered, acidified with ice–HCl, and filtered again. After air-drying there was obtained 1.12 g (48%) of **14**. The analytical sample was obtained by recrystallization from MeOH–H_2O to give near-white crystals, mp 170–172 °C. Anal. ($C_{12}H_{14}O_4$) C, H.

2,3-Dihydro-4,7-dimethoxy-1*H*-inden-2-amine (4a) via a Modified Curtius Reaction. The procedure of Weinstock[42] was used with some modification. Compound **14** (2.44 g, 0.011 mol) was dissolved in a mixture of 40 mL of acetone and 7 mL of H_2O. An ice–MeOH bath was used to maintain the solution at or below 0 °C, and 1.3 g (0.013 mol) of triethylamine in 23 mL of acetone was added. A solution of 1.7 g (0.016 mol) of ethyl chloroformate in 8 mL of acetone was added slowly, and the resulting mixture was stirred at 0 °C for 30 min. A solution of 1.08 g (0.017 mol) of sodium azide in 4 mL of H_2O was added dropwise, and stirring was continued for 90 min (0 °C). The reaction was diluted with brine and extracted twice with toluene. The combined extracts were washed with H_2O, dried ($MgSO_4$), and filtered. The toluene solution of the acyl azide was boiled for 1 h to effect rearrangement to the isocyanate (solution volume was reduced to one-third). When the solution had cooled, it was added dropwise to 25 mL of 20% HCl maintained at 80 °C. After the addition was complete, the mixture was refluxed with vigorous stirring for 2 h. The

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mixture was cooled and diluted with H_2O, and the phases were separated. The aqueous phase was extracted once with Et_2O, and the Et_2O phase was added to the toluene phase. The combined toluene-Et_2O phases were washed once with 2 N HCl, and the aqueous phases were combined. The aqueous solution was decolorized with charcoal, filtered, and evaporated to dryness. The residue was recrystallized from MeOH-Et_2O: yield 1.40 g (56%); mp 244-245 °C.

Antiallergics: 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones

J. P. Yevich,* D. L. Temple, Jr., R. R. Covington, D. A. Owens, R. J. Seidehamel, and K. W. Dungan

Bristol-Meyers Pharmaceutical Research and Development Division, Evansville, Indiana 47721. *Received September 17, 1981*

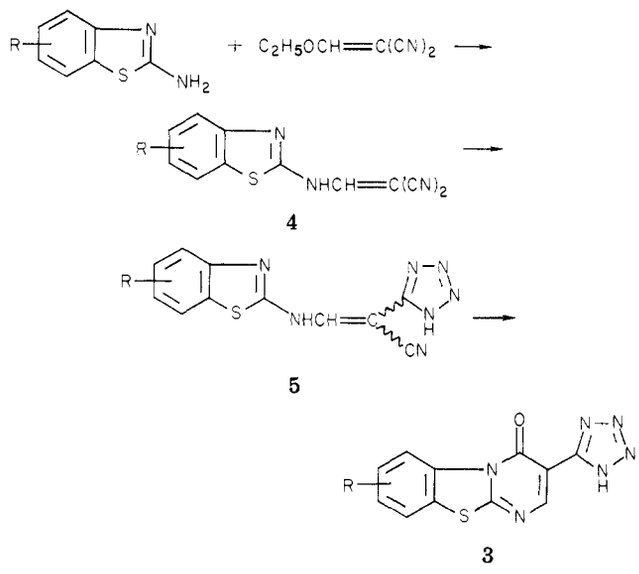
A short series of the title compounds was prepared and evaluated for both antiallergic and bronchodilator activity. Members of the series exhibit good oral activity in the rat PCA test, the most potent being the parent compound, 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one, and its 8-chloro derivative. The latter two compounds are considerably more potent than either disodium chromoglycate or theophylline as antiallergic agents and also show significant bronchodilator activity.

The various types of drug therapy available for bronchial asthma include bronchodilators, antiallergy agents, anticholinergics, steroids, and prostaglandins.[1] Of these agents, bronchodilators, including both β-agonists and nonadrenergics such as theophylline, have long been the primary drugs of choice. Although they are quite efficacious, the use of these agents is often limited by the patient's intolerance of their potentially severe side effects.

While the advent of disodium chromoglycate (DSCG) has afforded an alternative to bronchodilator therapy, this drug has not fulfilled initial expectations. As an antiallergic agent, DSCG appears to act mainly by inhibiting the release of various chemical mediators of anaphylaxis from mast cells. Recently, however, at least some of its effects have been attributed to inhibition of reflex mechanisms, reduction of bronchial hyperactivity, and other nonimmunologic modes of action.[2-5] In addition to its lack of oral absorption, which necessitates topical administration, DSCG lacks the broad efficacy of bronchodilators and as a prophylactic drug can prevent, but not alleviate, an asthmatic attack.

Recent work in our laboratories has focused on the development of superior agents acting as either bronchodilators, as mediator release inhibitors, or by a combination of these mechanisms. We have previously reported a series of thieno[2,3-*d*]pyrimidine-5-carboxylic acid derivatives as orally active mediator release inhibitors having no bronchodilator component.[6] Subsequently, we have described 4-substituted imidazo[1,2-*a*]purin-9-ones as bronchodilators having greater potency and fewer side-effect liabilities than theophylline in animal models.[7] Members of this series also show significant antiallergic activity.

Scheme I



Oral antiallergic activity has been reported for various other molecules containing a pyrimidine ring, including the 2-aryl-8-azapurinones 1[8-10] and the 6-oxo-2-phenylpyrimidine-5-carboxylic acids 2.[11] The activity of such compounds is greatly enhanced by the introduction of *o*-alkoxy groups on the aryl ring, an observation which has been further corroborated by unpublished studies of several structurally analogous series of fused pyrimidines in our laboratories. It has been suggested that the substituent effect may be attributable to intramolecular hydrogen bonding between the alkoxy oxygen and the proton of the pyrimidinone ring NH moiety.[9] Such bonding should stabilize a conformation of these molecules in which the aryl and heterocyclic rings are coplanar and which may be

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