4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A Novel Class of Compounds with Central Dopamine Agonist Properties

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The design, synthesis, and pharmacological properties of a novel type of 4-(1,2,5,6-tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamine with dopaminergic properties are described. In particular, 4-(1,2,5,6-tetrahydro-1-propyl-3-pyridinyl)-2-thiazolamine (**4c**, PD 118440) and its allyl analogue (**4i**, PD 120697) have been identified as orally active dopamine (DA) agonists with pronounced central nervous system effects in tests that include [^{3}H]-haloperidol and [^{3}H]-*N*-propylnorapomorphine binding, inhibition of striatal DA synthesis, inhibition of DA neuronal firing, inhibition of spontaneous locomotor activity, and reversal of reserpine-induced depression in rats. The DA autoreceptor selectivity of these heterocyclic analogues of 3-(1-propyl-3-piperidinyl)phenol (3-PPP) was also evaluated. In this series, DA agonist activity was found to be highly dependent on the size of the *N*-alkyl substituent, the saturation level of the six-membered ring, and the mode of attachment of the 2-aminothiazole ring.

Early reports indicated that (±)-3-(1-propyl-3-piperidinyl)phenol [(±)-3-PPP, **1**] was highly selective for presynaptic brain dopamine (DA) receptors (DA autoreceptors).[1] Further evaluation of the pure enantiomers indicated that both compounds are indeed presynaptic DA agonists at low doses; however, at high doses the (+)-isomer is also a postsynaptic agonist, while the (−)-isomer is a postsynaptic antagonist.[2] Both compounds have gained wide acceptance as useful research tools. However, their clinical potential, i.e. as antischizophrenic or antiparkinsonian agents, may be limited by their relatively low oral bioavailability and their short duration of action.[3] These properties can be attributed to the presence of a phenol moiety in the 3-PPP structure which provides a likely site for metabolism as well as for conjugation and excretion.

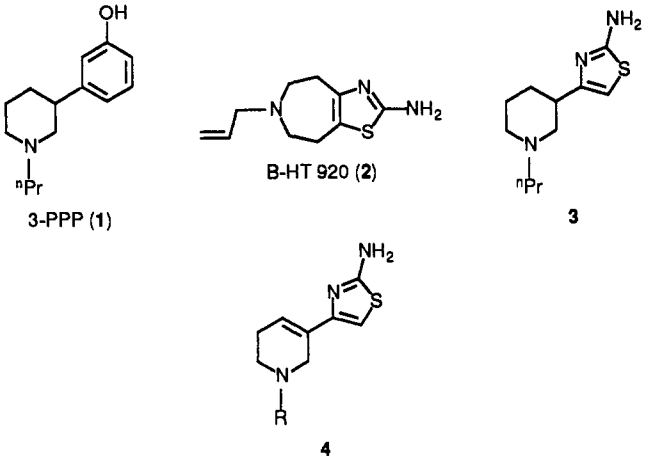
Several examples can be found in the literature of successful replacements of the phenol or catechol moieties by heterocyclic bioisosteres.[4] Thus, a heterocyclic analogue of 3-PPP might retain some of its unique pharmacological actions while having improved oral bioavailability and duration of action. The structure of B-HT 920 (**2**),[5] another DA agonist which has been reported to be selective for DA autoreceptors, suggested the 2-aminothiazolyl moiety as a potential replacement for the phenol ring of 3-PPP.

This paper describes the synthesis of compound **3**, the 2-amino-4-thiazolyl analogue of 3-PPP, and its evaluation for dopaminergic activity. In addition, we describe the structre–activity relationship (SAR) of a series of compounds of generic structure **4**, which were designed with the help of a molecular modeling program using **3** as the starting point.[6]

Chemistry

The synthesis of **3** is outlined in Scheme I. Alkylation of ethyl nipecotate (**5**) with 1-bromopropane in ethanol gave amino ester **6** in 83% yield. Hydrolysis of **6** with lithium hydroxide provided the corresponding acid as its lithium salt, which was subsequently treated with methyllithium to give amino ketone **7** in 59% yield. The neat reaction of **7** with 2 equiv of thiourea and 1 equiv of iodine at 100 °C gave the desired aminothiazole **3**.

4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines **4a–l** were prepared according to the sequence of reactions described in Scheme II. Aminothiazoles **10a,b** were prepared from 3-acetylpyridine (**8**) according to the method of Taurins and Blaga.[7] Alkylation of **10a,b** with a variety of alkyl halides took place exclusively at the pyridine nitrogen to yield quaternary salts **11a–l** in nearly quantitative yield. Reduction of these salts with excess sodium borohydride yielded the desired target compounds **4a–l** (see Table I) in yields ranging from 30 to 89%. No



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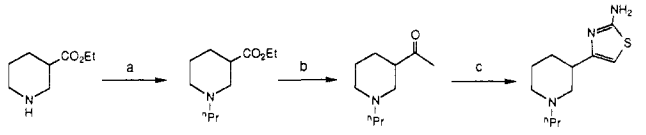
Scheme I[a]



5 6 7 3

[a] (a) ^{n}PrBr, $NaHCO_3$, EtOH; (b) (i) LiOH, EtOH; (ii) MeLi, THF; (c) thiourea, I_2, 100 °C.

Table I. Physical Properties of Target Compounds

no.	R_1	R_2	formula[a]	% yield	mp,[b] °C
3			$C_{11}H_{19}N_3S \cdot 2HCl$	50	243–248
4a	H	CH_3	$C_9H_{13}N_3S \cdot 2HCl \cdot 0.5H_2O$	50	272 dec
4b	H	C_2H_5	$C_{10}H_{15}N_3S$	49	116–120
4c	H	$^nC_3H_7$	$C_{11}H_{17}N_3S$	50	121–123
4d	H	$^nC_4H_9$	$C_{12}H_{19}N_3S \cdot 2HCl$	45	239–240
4e	H	$^nC_5H_{11}$	$C_{13}H_{21}N_3S \cdot 2HBr$	56	246–247
4f	H	$^nC_6H_{13}$	$C_{14}H_{23}N_3S \cdot 2HCl$[c]	30	200–202
4g	H	$^nC_7H_{15}$	$C_{15}H_{25}N_3S \cdot 2HCl$	35	191–193
4h	H	$^iC_5H_{11}$	$C_{13}H_{21}N_3S \cdot 2HCl$	40	204
4i	H	$CH_2{=}CHCH_2$	$C_{11}H_{15}N_3S$	30	129–132
4j	H	$PhCH_2CH_2$	$C_{16}H_{19}N_3S \cdot 2HCl \cdot H_2O$[d]	50	209–211
4k	CH_3	$^nC_3H_7$	$C_{12}H_{19}N_3S$	64	138 dec
4l	CH_3	$^nC_4H_9$	$C_{13}H_{21}N_3S \cdot 2HCl$	57	245–248
16			$C_{11}H_{17}N_3S \cdot 0.2H_2O$	50	130–132
18			$C_{12}H_{18}N_2S \cdot 2HCl \cdot H_2O$	89	200–204

[a] Elemental analysis for C, H, N were within 0.4% of the calculated values unless otherwise indicated. The NMR, IR, and mass spectra of all compounds were consistent with their assigned structure. [b] In general, free bases were obtained from medium-pressure liquid chromatography as oils that solidified upon trituration with ether. Unless otherwise indicated, salts were recrystallized from ethanol/ethyl acetate. [c] N: calc, 12.42; found, 13.05. [d] N: Calc, 11.16; found, 11.90.

tetrahydropyridine regioisomers of **4a–l** were detectable by NMR in the crude reaction mixtures.[8]

The synthesis of **16**, the 2-amino-5-thiazolyl isomer of **4c**, is described in Scheme III. In order to prepare the key intermediate **15**, the hydrochloride salt of aldoxime **14**[9] was used as a more stable masked form of the required 3-pyridylacetaldehyde. Reaction of **14** with thiourea and iodine provided a low yield of crude aminothiazole **15**, which was quaternized with 1-bromopropane and reduced with sodium borohydride to give **16**, the "reversed" analogue of **4c**.

Compound **18** was prepared according to Scheme IV. Reaction of bromo ketone **9** with thioacetamide gave **17** in 78% yield. Compound **17** was alkylated with 1-bromopropane and reduced with sodium borohydride to give **18** in 89% yield.

Results and Discussion

The dopaminergic properties of the target compounds were evaluated in the following manner. Their in vitro affinity for DA D_2 receptors in rat striatal membranes was measured with the DA agonist [^{3}H]-*N*-propylnorapomorphine ([^{3}H]NPA)[10] and the DA antagonist [^{3}H]-haloperidol ([^{3}H]HPD)[11] as ligands. The DA agonist activity of selected compounds on DA autoreceptors was established by their ability to inhibit the spontaneous firing of DA neurons in the substantia nigra of anesthetized rats[12] and by their ability to reverse the γ-butyrolactone (GBL) induced increase in the rate of dihydroxyphenylalanine (DOPA) synthesis (an indirect measure of the rate of DA synthesis) in the rat corpus striatum, a major brain DA projection area.[13] Inhibition of exploratory locomotor activity in mice and rats was used as a behavioral index of DA autoreceptor activation[14] and/or postsynaptic DA antagonism.[15] As part of this test, compounds were tested for their ability to impair motor coordination, since previous studies have indicated that DA autoreceptor agonists and postsynaptic DA antagonists reduce locomotor activity at doses that do not produce ataxia.[15,16] Increases in locomotor activity in normal and DA depleted (reserpine-pretreated) rats were used as a measure of postsynaptic DA agonist activity.[17]

The initial target, compound **3**, was found to be a very weak DA agonist. Even though it had moderate activity in the behavioral tests (Table II), its weak binding affinity and weak potency in inhibiting brain DA synthesis prompted us to undertake conformational analyses aimed at understanding its weak activity. MAXIMIN,[18a] the molecular mechanics procedure available in the SYBYL molecular modeling package,[18b] was used to determine the energy requirements for rotation around the bond joining both rings in **3**. These calculations indicated that while all possible relative orientations of the two rings are very close in energy content, the lowest energy conformation is "orthogonal". In this conformation, the thiazole ring eclipses the hydrogen at the 3-position of the piperidine ring, analogous to the results obtained for 3-PPP.[19] The highest energy conformations of **3** are the ones where the thiazole ring eclipses one edge of the piperidine ring, but they are only about 1 kcal/mol above the orthogonal conformation. Extensive work on DA agonists has established the strict requirement for near coplanarity of the side chain amine nitrogen atom and the aromatic ring in order to achieve DA agonist activity.[17b,19b,c,20,21] For an optimal fit at the DA receptor, 3-PPP must overcome a low-energy barrier to adopt such a conformation. It is assumed that the energy cost involved in accessing the required conformer is offset by favorable interactions with

(8) Varying amounts of the precursor pyridines **10a,b** were formed during these reductions, usually in the 10–20% range, presumably via an elimination reaction of the *N*-alkyl group R_2 since the smallest amounts of the pyridine byproduct were observed when R_2 was a methyl or allyl group.
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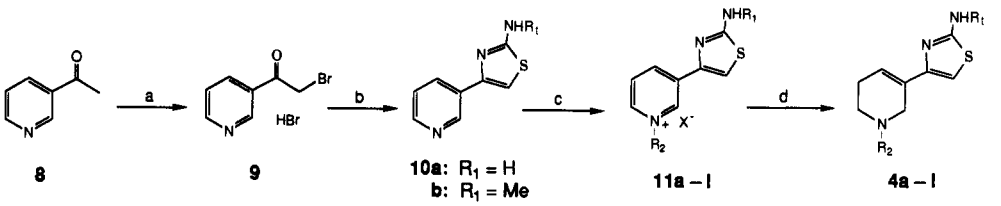
Table II. Binding Profile and Behavioral Activity of Target Compounds

no.	inhibn of [^{3}H]HPD[a,b] binding: IC_{50}, nM	inhibn of [^{3}H]NPA[b,c] binding: IC_{50}, nM	inhibn of locomotor activity, mouse:[d,e] ED_{50}, mg/kg ip	inhibn of locomotor activity, rat:[d,e] ED_{50}, mg/kg po	reversal of reserpine-induced depression, rat[f] ED_{50}, mg/kg sc
3	>1000[g]		10.0	18.9	
4a	1040		inactive[h]	inactive[i]	>30
4b	945	411	inactive[h]	inactive[i]	>30
4c	958	596	2.9	3.0[j]	>30
4d	2120	3985	7.3	5.4	>30
4e	1850	6396	4.1	15.6	>30
4f	>1000[k]	5328	>30		>30
4g	2170	5132	10.4	>30	>30
4h	2690	10000	8.7	26.1	>30
4i	440	257	2.8	*l*	8.7
4j	1080	911	18.1	33.6	5.8
4k	>1000[m]	>10000	10.0		
4l	>1000[m]		4.4	16.7	
16	>1000[n]		19.1		
18	>1000[o]		>30		
(±)-3-PPP	590	183		3.0[p]	>30
(+)-3-PPP	930	184		inactive[q]	~30
apomorphine	27	2.6		0.03[p]	0.1

[a] [^{3}H]Haloperidol. [b] IC_{50} values were determined from four to five concentrations by a nonlinear regression analysis. [c] [^{3}H]-*N*-Propylnorapomorphine. [d] ED_{50} values were generated from four to six doses; 5–12 animals were used per dose. [e] No ataxia was observed up to doses of 30 mg/kg. [f] ED_{50} values were generated from three or four doses; five animals were used per dose. [g] 15% inhibition at 10^{-6} M. [h] These compounds inhibited locomotor activity but without a clear dose–effect relationship. [i] No inhibition of locomotor activity was observed up to 3 mg/kg. Doses of 3 mg/kg and higher stimulated locomotor activity. [j] Maximal effect: 50% inhibition at 3 mg/kg. Higher doses produced stimulation (see Figure 1). ED_{50} = 0.3 mg/kg sc. [k] 36% inhibition at 10^{-6} M. [l] Maximal effect: 30% inhibition at 1 mg/kg. Inhibition of locomotor activity was more pronounced when **4i** was dosed sc, ED_{50} = 0.1 mg/kg. [m] 25% inhibition at 10^{-6} M. [n] 2% inhibition at 10^{-6} M. [o] 41% inhibition at 10^{-6} M. [p] Subcutaneous administration. [q] Maximal inhibition was 40% at 3 mg/kg sc. Higher doses produced stimulation.

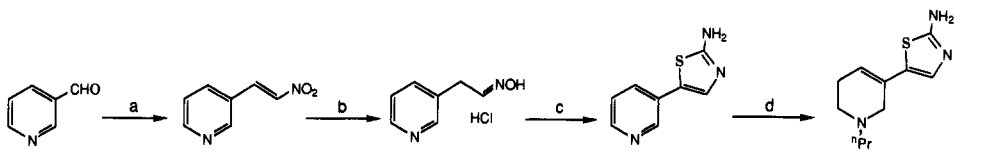
Scheme II[a]



8 **9** **10a**: R_1 = H; **b**: R_1 = Me **11a–l** **4a–l**

[a] (a) Br_2, HBr; (b) $R_1NHC(S)NH_2$, H_2O; (c) R_2X, EtOH; (d) $NaBH_4$, MeOH, H_2O.

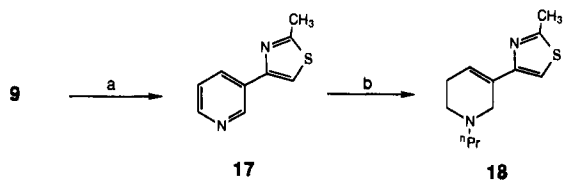
Scheme III[a]



12 **13** **14** **15** **16**

[a] (a) CH_3NO_2, CH_3NH_2·HCl, NaOH, EtOH; (b) H_2, 10% Pd/C, H_2O; (c) thiourea, I_2; (d) (i) ^{n}PrBr, CH_3CN; (ii) $NaBH_4$, MeOH, H_2O.

Scheme IV[a]

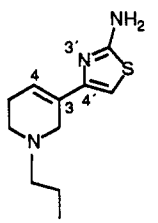


17 **18**

[a] (a) $CH_3C(S)NH_2$, H_2O; (b) (i) ^{n}PrBr, EtOH; (ii) $NaBH_4$, MeOH, H_2O.

the binding site. Since **3** does not present any significant rotational energy barrier, the coplanar conformation required for dopaminergic activity should be readily available.

Thus, our early results with **3** suggested that the 2-amino-4-thiazolyl moiety might not be a viable bioisosteric replacement for the phenol ring of 3-PPP. In an attempt to increase dopaminergic activity through structural modifications that favor the coplanar conformational populations postulated for 3-PPP, we undertook the synthesis of various analogues of **3**. One approach was the introduction of a double bond between positions 3 and 4 of the piperidine ring that can be expected to participate in the thiazole ring electron delocalization. Indeed, molecular mechanics studies applied to **4c** (PD 118440) demonstrated this conjugation factor: **4c** can undertake two deep minima corresponding to the symmetrical coplanar conformations **4c-1** and **4c-2**. Small rotations of



4c-1: $w(C_4–C_3–C_4'–N_3') = 0°$

4c-2: $w(C_4–C_3–C_4'–N_3') = 180°$

Table III. Effects of Selected Compounds on Brain DA Synthesis and DA Neuronal Firing in Rats

no.	% inhibn of DOPA accumulation in striatum[a] ± SEM	% inhibn of DA neuronal firing[b] ± SEM
3	55 ± 14	
4a	100 ± 2	100 ± 0
4b	92 ± 3	96 ± 4
4c	100 ± 6	100 ± 0
4d	0 ± 6	0 ± 0
4e	0 ± 9	
4i	100 ± 13	100 ± 0
4j	3 ± 12[c]	−33 ± 17

[a] Shown is the decrease of DOPA formation produced by 30 mg/kg ip of the test compound in the striatum of GBL-treated rats (n = 4 or 5). Endogenous levels of DA were not affected unless noted otherwise. [b] All compounds were administered at 2.5 mg/kg ip (n = 3). [c] A 70% reduction of endogenous DA levels was observed.

Table IV. Additional Tests Used To Evaluate 4c and 4i as DA Agonists

no.	reversal of 6-OHDA induced depression:[a] ED_{200}, mg/kg sc	stereotyped behavior in rats:[b] % animals (dose, mg/kg sc)	D_1 binding [^{3}H]SCH23390: IC_{50},[c] nM
4c	0.4	100 (3)	>50 000
4i	0.3	100 (3)	>50 000
apomorphine	0.006	100 (0.3)	384
(+)-3-PPP	0.5		>10 000

[a] ED_{50} values were estimated from three or four doses; six animals were used per dose. Locomotor activity was measured immediately after dosing for a period of 30 min. [b] Groups of six animals were tested at each dose level. The table shows the percentage of animals showing signs of stereotypy at the dose tested. [c] IC_{50} values were generated from four or five concentrations by a nonlinear regression analysis.

the rings lead to marked increases in energy; for example, rotation of the thiazole ring by just 20° from coplanar conformation **4c-2** requires 3.6 kcal/mol. As described below, the dopaminergic activity observed in these compounds would suggest that the 2-amino-4-thiazolyl moiety combined to an olefinic double bond provides a viable bioisosteric replacement for the phenol ring of 3-PPP.

Our expectation that the coplanarity of **4c** would translate into improved dopaminergic activity relative to **3** was borne out by the binding and behavioral data shown in Table II for **4c** and a series of *N*-alkyl analogues. The effects of selected compounds on brain DA synthesis and DA neuronal firing are described in Table III. The affinity of **4c** for the DA receptor was approximately the same as that of (+)-3-PPP when using [^{3}H]haloperidol as the radioligand but slightly weaker in the [^{3}H]NPA assay. Comparison of the IC_{50} values obtained for **4c** in these two assays (958 and 596 nM, respectively) suggests that **4c** is a DA D_2 agonist, with no significant affinity for the D_1 receptor, as evidenced by its inability to inhibit the binding of the selective D_1 antagonist [^{3}H]SCH23390[22] (0% inhibition at 10^{-5} M, Table IV). In addition, **4c** completely reversed the increase in DA synthesis induced by GBL in rat corpus striatum at 30 mg/kg ip, and it completely inhibited DA neuronal firing in rat brain at 2.5 mg/kg ip, an effect which was reversed by the DA antagonist haloperidol. These results indicate that **4c** has direct DA autoreceptor agonist activity. This was corroborated behaviorally by the inhibition of exploratory locomotor activity produced by **4c** in mice (ED_{50} = 2.9 mg/kg ip) and in rats (ED_{50} = 3.0 mg/kg po). However, as can be seen in Figure 1, **4c** displayed a biphasic locomotor-activity profile in rodents, with low doses of the compound inhibiting locomotor activity and higher doses increasing locomotion. This profile is typical of a DA agonist with both presynaptic and postsynaptic agonist activity.[14c]

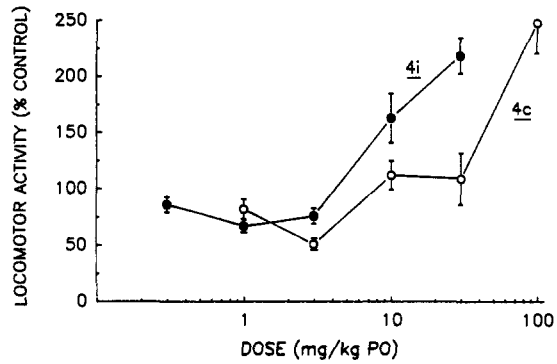


Figure 1. Effects of 4c and 4i on locomotor activity in rats.

The postsynaptic DA activity of **4c** was evaluated in more detail by measuring its ability to stimulate locomotor activity in reserpine-treated rats[17] and in 6-hydroxydopamine (6-OHDA) lesioned rats.[23] In the first of these tests, reserpine induces a depletion of stored neuronal DA that enables the test compound to be studied in the absence of endogenous DA in animals with somewhat supersensitive postsynaptic DA receptors. In the 6-OHDA test, destruction of the majority of afferent DA neurons leads to a more complete depletion of DA and a more marked supersensitivity of postsynaptic DA receptors. Compound **4c** was inactive in reversing reserpine-induced depression in rats, up to doses of 100 mg/kg sc (Table II). In the more sensitive 6-OHDA-lesioned rats, **4c** was very active, with an ED_{200} value of about 0.4 mg/kg sc (Table IV). Additionally, **4c** produced clear signs of stereotypy (sniffing and head swaying in all animals; gnawing in one out of six animals) in rats treated with 3 mg/kg sc of the compound, a dose 10 times the ED_{50} for locomotor inhibition.

Since **4c** is a selective D_2 agonist, these results agree with recent findings that selective D_2 agonists require a certain amount of D_1 activation (either from endogenous DA or coadministration of a D_1 agonist) in order to fully display their postsynaptic agonist effects.[24] Thus, **4c** may be unable to increase locomotor activity in DA-depleted animals due to the lack of D_1 activation while being able to produce marked stimulation in normal animals, in which D_1 receptors are activated by endogenous DA, and in 6-OHDA-treated animals, in which DA receptors are profoundly supersensitive. The stereotypy profile observed for **4c** is also consistent with a selective D_2 agonist, since only low-component signs were observed up to the dose tested, with few indications of the types of behavior (biting, gnawing) which would require both D_1 and D_2 receptor activation.[24c]

Table II shows the test results for a series of *N*-alkyl analogues of **4c**. Not surprisingly, the length of the alkyl substituent on the nitrogen atom was found to be critical to the dopaminergic activity of these compounds, in agreement with results obtained by other groups for a number of structurally diverse DA agonists.[1b,2b,25] Our

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results suggest that optimal DA agonist activity is obtained with a three-carbon substituent. The allyl analogue **4i** (PD 120697) is very similar to **4c**, as evidenced by its binding profile (Table II) and its reversal of the GBL-induced increase in brain DA synthesis and inhibition of DA neuronal firing (Table III). In the locomotor activity tests, **4i** also presented a profile comparable to that of **4c** (Figure 1), with low doses inhibiting locomotor activity, presumably via DA autoreceptor activation, and higher doses increasing locomotion, presumably by activation of postsynaptic DA receptors. Furthermore, **4i** was effective in producing stimulation in reserpine-treated rats (ED_{50} = 8.7 mg/kg sc) but only at a high multiple of the behaviorally active doses in normal animals. Examination of the full pharmacological profile of **4c** and **4i** suggests that both compounds are orally active DA agonists with some selectivity for DA autoreceptors, probably as a result of their selectivity for the D_2 subtype of receptors.

Compounds **4a** and **4b**, the *N*-methyl and *N*-ethyl analogues of **4c**, respectively, were also found to possess DA agonist properties, as indicated by their binding profile and their reversal of the GBL-induced increase in brain DA synthesis in rats. The behavioral assessment of these compounds in rodents was difficult. Both **4a** and **4b** inhibited locomotor activity in mice over a wide dose range, but there seemed to be no clear dose–effect relationship in this test. In rats both compounds produced marked excitation in the 3–30 mg/kg po range, but once again there was no dose–effect relationship.

In the 3-PPP series, DA agonist activity, although optimal with a *n*-propyl substituent, was retained with a variety of other groups, ranging from one- to five-carbon units.[1b,2b] In our series, replacement of the propyl group of **4c** with a butyl or larger group led to a complete loss of DA agonist activity. Interestingly, **4d** and **4e**, the butyl and pentyl analogues of **4c**, respectively, were quite effective at inhibiting locomotor activity in rodents, with no signs of stimulation at higher doses. Although these compounds did not inhibit brain DA synthesis in rats (Table III), they bound to the DA receptor with weak affinity (Table II). Their mechanism of action is unknown, but there are some indications (increase in rat brain striatal DA synthesis, blockade of apomorphine-induced climbing in mice at high doses) that they may have DA antagonist effects.

Compound **4j**, the phenethyl analogue of **4c**, produced stimulation in reserpine-treated rats with an ED_{50} of 5.7 mg/kg sc. However, this compound is not a DA agonist, as evidenced by its inability to reverse the GBL-induced increase in brain DA synthesis (Table III). Interestingly, a significant decrease in endogenous DA levels in rat striatum was observed during these experiments. The mechanism of action of **4j** has not been elucidated. In contrast, the phenethyl analogue of 3-PPP has been reported to be a DA autoreceptor agonist.[1,2,26]

The SAR of the 2-aminothiazole ring was explored further by preparing compound **16**, the 2-amino-5-thiazolyl isomer of **4c**. Compound **16** possessed low affinity for the DA receptor and it also was very weak in the locomotor activity tests (Table II). It seems that **16** is much weaker than **4c** as a DA agonist. We view the amino group as the bioisosteric replacement for the *m*-hydroxyl group of catechol-type DA agonists. McDermed et al.[27] have shown that this is the key hydroxyl group for DA D_2 agonist activity, while the *p*-hydroxyl group is not essential. The amino groups in **4c** and **16** are both meta to the point of attachment of the tetrahydropyridine ring. However, it is possible that the greater size of sulfur as compared to nitrogen places the amino group of **16** in a position, relative to the tetrahydropyridine ring, more similar to para than meta in a catechol ring, and this might serve to explain its weak activity.

The importance of the amino group for DA agonist activity in this series was explored with compound **18**, where the amino group of **4c** has been replaced by a methyl group. As seen in Table II, **18** had very weak affinity for DA receptors, comparable to that of **16**, and was inactive behaviorally in mice.

Compounds **4k** and **4l**, the N-methylated analogues of **4c** and **4d**, respectively, showed a decrease in their affinity for DA receptors and a lower toxicity threshold in mice. For these reasons, they were not studied further.

In conclusion, **4c** and **4i** seem to possess optimal features for DA agonist activity within this series of compounds. These features include a tetrahydropyridine ring, a three-carbon substituent on the nitrogen, and a 2-amino-4-thiazolyl ring conjugated to a double bond as the catechol bioisostere. These compounds exhibit some selectivity for DA autoreceptors at lower doses, but at higher doses they clearly stimulate postsynaptic DA receptors. This profile, together with their good oral efficacy, makes these compounds potential candidates for the treatment of conditions stemming from dopaminergic deficiency such as Parkinson's disease and hyperprolactinaemia-related conditions.[28]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were obtained on a Nicolet MX-1 FT spectrometer. The proton NMR spectra were recorded on an IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz) and were consistent with the proposed structures. The peaks are described in ppm downfield from TMS (internal standard). The mass spectra were obtained on a Finnigan 4500 mass spectrometer or a VG analytical 7070E/HF mass spectrometer and they are described by the relative intensity of the

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molecular peak (M) as well as the mass of the base peak. Where analyses are indicated by the symbols of the elements, the results were within 0.4% of the theoretical values. All organic starting materials were obtained from the Aldrich Chemical Co. (Milwaukee, WI) and were used without further purification.

Ethyl 1-Propyl-3-piperidinecarboxylate (6).[29] Ethyl nipecotate (185.5 g, 1.18 mol) and 1-bromopropane (160 g, 1.30 mol) were refluxed in absolute ethanol (1.25 L) with sodium bicarbonate (225 g, 2.5 mol) for 18 h. The mixture was filtered through a pad of Celite. The inorganic salts were washed with several portions of fresh ethanol. The combined filtrates were evaporated in vacuo and the residue was distilled to yield 193.6 g (83%) of **6** as a colorless liquid, bp 86–89 °C (1 mm). ^{1}H NMR ($CDCl_3$): 0.89 (3 H, t, J = 7.3 Hz), 1.25 (3 H, t, J = 7.1 Hz), 1.38–1.78 (5 H, m), 1.90–2.02 (2 H, m), 2.11 (1 H, t, J = 10.7 Hz), 2.26–2.34 (2 H, m), 2.50–2.61 (1 H, m), 2.73–2.82 (1 H, m), 2.96–3.03 (1 H, m), 4.13 (2 H, q, J = 7.1 Hz). IR (LF): 1735 cm^{-1}. MS: 199 (M, 6), 170 (100). Anal. ($C_{11}H_{21}NO_2$): C, H, N.

1-(1-Propyl-3-piperidinyl)ethanone (7). A solution of **6** (99.64 g, 0.50 mol) and anhydrous lithium hydroxide (13.18 g, 0.55 mol) was refluxed in absolute ethanol (1 L) under nitrogen for 24 h. The solvent was evaporated in vacuo and the solid residue was dried at 100 °C (0.2 mm) for 15 h. A solution of this salt in anhydrous THF (1 L) under nitrogen was cooled in an ice/salt bath and methyllithium (360 mL of 1.6 M MeLi·LiBr ether solution, 0.575 mol) was added dropwise over a 20-min period. the reaction mixture was gradually allowed to warm up to room temperature overnight. Acetone (25 mL) was added and the solvent was evaporated in vacuo. Distillation of the residue yielded 50.0 g (59%) of **7** as a colorless liquid, bp 65–70 °C (1 mm) (HCl salt, mp 108–111 °C). ^{1}H NMR ($CDCl_3$): 0.86 (3 H, t, J = 7.3 Hz), 1.26–1.72 (5 H, m), 1.83–2.11 (3 H, m), 2.13 (3 H, s), 2.23–2.31 (2 H, m), 2.53–2.63 (1 H, m), 2.74–2.80 (1 H, m), 2.91–2.99 (1 H, m). IR (LF): 1711 cm^{-1}. MS: 169 (M, 6), 140 (100). Anal. ($C_{10}H_{19}NO$): C, H, N.

4-(1-Propyl-3-piperidinyl)-2-thiazolamine (3). A mixture of **7** (2.5 g, 14.8 mmol), thiourea (2.28 g, 30 mmol), and iodine (3.81 g, 15 mmol) was heated on a steam bath for 24 h. The solid reaction mixture was triturated with boiling water (150 mL) and gravity-filtered. The filtrate was cooled in ice and made basic with ammonium hydroxide. The mixture was extracted with ethyl acetate (2 × 100 mL), and the combined organic extracts were washed with brine (2 × 100 mL) and dried over $MgSO_4$. Evaporation of the solvent left a dark residue, which was purified by flash chromatography (silica gel, acetone). Pure **3** was obtained as a reddish oil, which was dissolved in anhydrous ether and treated with HCl gas to yield 1.75 g (40%) of **3**·2HCl, mp 243–248 °C. ^{1}H NMR (DMSO-d_6): 0.93 (3 H, t, J = 7.3 Hz), 1.50–2.10 (6 H, m), 2.75–3.60 (7 H, m), 6.58 (1 H, s). MS: 225 (M, 27), 196 (100). Anal. ($C_{11}H_{19}N_3S$·2HCl): C, H, N.

General Procedure for the Preparation of 4-(1-Alkyl-1,2,5,6-tetrahydro-3-pyridinyl)-2-thiazolamines (4). Synthesis of 4-(1,2,5,6-Tetrahydro-1-propyl-3-pyridinyl)-2-thiazolamine (4c). A solution of 4-(3-pyridinyl)-2-thiazolamine[7] (**10a**, 14.16 g, 80 mmol) and 1-bromopropane (50.0 g, 0.40 mol) in absolute ethanol (500 mL) was refluxed for 24 h. Evaporation of the solvent yielded 30 g of crude **11c** as a yellow solid; a sample was recrystallized from ethanol/acetonitrile, mp 259–261 °C. A solution of **11c** (26.0 g, 68 mmol) in methanol (150 mL) and water (150 mL) was cooled to 0 °C and stirred vigorously. Sodium borohydride (25 g, 0.66 mol) was added over a 30-min period. The mixture was concentrated in vacuo to about $^1/_2$ of the original volume and carefully acidified by dropwise addition of concentrated hydrochloric acid. The resulting solution was basified with ammonium hydroxide and extracted with ethyl acetate (3 × 75 mL). The organic extract was dried (magnesium sulfate) and concentrated, leaving a yellow oil, which was purified by flash chromatography (silica gel; 2% NH_4OH, 98% ethyl acetate) to give 4.4 g (50%) of **4c**, mp 121–123 °C. ^{1}H NMR ($CDCl_3$): 0.90 (3 H, t, J = 7 Hz), 1.60 (2 H, m), 2.20–2.65 (6 H, m), 3.25 (2 H, m), 4.90 (2 H, br s, NH_2), 6.20 (1 H, s), 6.50 (1 H, m). Anal. ($C_{11}H_{17}N_3S$): C, H, N.

N-Methyl-4-(3-pyridinyl)-2-thiazolamine (10b). The procedure of Taurins and Blaga[7] for the preparation of **10a** was used to prepare the N-methyl analogue **10b** from **9** in 70% yield, mp 114–116 °C. ^{1}H NMR (DMSO-d_6): 2.86 (3 H, d, J = 4.8 Hz), 7.22 (1 H, s), 7.37 (1 H, dd, J = 8.0, 4.8 Hz), 7.65 (1 H, m, N*H*), 8.13 (1 H, dt, J = 8.0, 1.9 Hz), 8.44 (1 H, dd, J = 4.8, 1.7 Hz), 9.03 (1 H, d, J = 1.7 Hz). Anal. ($C_9H_9N_3S$): C, H, N.

Compounds **4k**,l were prepared from **10b** by the general procedure described above the for synthesis of **4c**.

5-(1,2,5,6-Tetrahydro-1-propyl-3-pyridinyl)-2-thiazolamine (16). An intimate mixture of 3-pyridineacetaldehyde oxime hydrochloride (**14**,[9] 4.60 g, 26.5 mmol) and thiourea (4.03 g, 53 mmol) was placed in a 50-mL flask and treated with iodine (6.72 g, 26.5 mmol) in small portions. The resulting paste was heated on a steam bath overnight and triturated with boiling water (100 mL). The mixture was gravity filtered, cooled in ice, and made basic with ammonium hydroxide. The product was extracted with dichloromethane (200 mL), dried over magnesium sulfate, and evaporated in vacuo. The oily residue was dissolved in ethanol and treated with an excess of hydrogen chloride in 2-propanol. The yellowish salt that formed was filtered and dried to obtain 1.9 g of **15**·HCl, mp 285–290 °C dec. A solution of **15** (6.5 g, 37 mmol; free base obtained by partition of the hydrochloride between dichloromethane and 5% ammonium hydroxide) in acetonitrile (500 mL) was refluxed overnight with 1-bromopropane (25.0 g, 200 mmol). Evaporation of the solvent in vacuo left a solid residue that was dissolved in water (50 mL) and methanol (50 mL) at 0 °C and treated with sodium borohydride (8.0 g, 200 mmol) in small portions. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. The pH of the mixture was adjusted to ca. 1 with hydrochloric acid and the methanol was removed in vacuo. The residue was made basic (ammonium hydroxide) and extracted with ethyl acetate. The organic extract was dried over magnesium sulfate and evaporated, and the residue was purified by flash chromatography to obtain **16** as a light oil, which crystallized when triturated with ether; 1.3 g (16%); mp 130–132 °C. ^{1}H NMR ($CDCl_3$): 0.94 (3 H, t, J = 7.3 Hz), 1.60 (2 H, m), 2.30 (2 H, m), 2.46 (2 H, m), 2.59 (2 H, m), 3.25 (2 H, br s), 5.04 (2 H, br s, N*H*$_2$), 5.79 (1 H, br s), 6.86 (1 H, s). MS: 223 (M, 25), 152 (100). Anal. ($C_{11}H_{17}N_3S$·0.2H_2O): C, H, N.

1,2,5,6-Tetrahydro-3-(2-methyl-4-thiazolyl)-1-propylpyridine (18). A homogeneous mixture of **9**[30] (28.0 g, 0.100 mol) and thioacetamide (15.0 g, 0.200 mol) was placed in a beaker and heated on a steam bath for about 15 min. Initially the mixture melted and later solidified. Glacial acetic acid (4 mL) was added to the solid mixture and the resulting paste was heated on the steam bath overnight. The reaction mixture was triturated with boiling water (200 mL) for several minutes and a few insoluble particles were gravity-filtered. The cooled filtrate was made basic with ammonium hydroxide and extracted with dichloromethane. Following purification by flash chromatography (2% NH_4OH in ethyl acetate), **17** was obtained (13.85 g, 78%) as a red oil, which solidified upon standing. A solution of **17** (3.0 g, 17 mmol) in absolute ethanol (100 mL) was treated with 1-bromopropane (6.15 g, 50 mmol) and refluxed for 24 h. The solvent was removed in vacuo, leaving 2.5 g of a crystalline residue, which was triturated with ether, filtered, and air-dried, mp 125–135 °C. This quaternary salt was dissolved in methanol (100 mL) and water (100 mL) and treated with sodium borohydride (3.4 g, 85 mmol) at 0 °C. After 1 h, the reaction was worked up in a manner similar to the example above. Flash chromatography (2% NH_4OH in EtOAc) of the crude product yielded **18** as a light oil, which was converted to its HCl salt in the usual way. **18**·HCl: 1.45 g (89%), mp 200–204 °C. ^{1}H NMR (DMSO-d_6): 0.95 (3 H, t, J = 7 Hz), 1.65–2.0 (2 H, m), 2.65 (3 H, s), 2.90–3.25 (3 H, m), 2.30–4.30 (8 H, m), 6.65 (1 H, br s), 7.55 (1 H, s). MS: 222 (M, 100). Anal. ($C_{12}H_{18}N_2S$·2HCl·H_2O): C, H, N, Cl.

Pharmacological Methods. [^{3}H]Haloperidol, [^{3}H]-*N*-Propylnorapomorphine, and [^{3}H]SCH23390 Receptor Binding Assays. The affinity of compounds for brain DA receptors was determined by standard receptor binding assays,[10,11,21]

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according to methods described previously.[31]

Effects on the Firing Rate of Substantia Nigra DA Neurons.[12] The action potential of zona compacta DA cells was recorded in chloral-anesthetized rats by using standard extracellular recording techniques. DA cells were identified by waveform and firing pattern, and recording sites were verified histologically. Drugs were administered intraperitoneally via an indwelling catheter. Base line firing rate was calculated by averaging the rate over the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal inhibition. Drug-induced inhibition of firing was reversed with the DA antagonist haloperidol to confirm a DA agonist mechanism.

Inhibition of spontaneous locomotor activity and motor coordination[14,15] were carried out according to methods described previously.[31]

Inhibition of GBL-Stimulated DA Synthesis.[13] Compounds were administered to male Long–Evans rats (Blue Spruce Farms, Altamont, NY) 1 h before sacrifice and GBL (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min and 25 min, respectively, before sacrifice. Brain striatal levels of DOPA were measured by HPLC with electrochemical detection.[32]

Effects on Spontaneous Locomotion in Reserpinized Rats.[17] Drugs were administered subcutaneously to normal rats treated with 5 mg/kg reserpine 24 h prior to testing. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.[15,31]

Stereotypy in Rats. Compounds were administered sc to naive rats and the animals were observed at 10, 20, and 30 min postdose for the presence of repetitive rearing, head-swaying, sniffing, licking, and gnawing of at least 5-s duration. Data were expressed as percentage of rats showing signs of stereotypy.

Effects on Spontaneous Locomotion in 6-OHDA-Lesioned Rats.[23] Drugs were administered subcutaneously to rats treated at least 1 month previously with central injections of 6-OHDA (200 μg icv) and systemic injections of pargyline (50 mg/kg ip) and desmethylimipramine (25 mg/kg ip) as described previously.[33] This treatment produced large selective depletion of brain DA (approximately 90%) as described previously[33] and as determined by brain DA determinations in representative animals. Locomotor activity was measured for 30 min beginning immediately after drug administration as described previously.[15,31] Data are reported as the ED_{200} value, the dose of compound needed to increase the locomotor activity of the animals to twice the level of control (unlesioned) animals.

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Registry No. **3**, 108351-93-5; **3**·2HCl, 118371-15-6; **4a**, 108351-94-6; **4a**·2HCl, 108351-95-7; **4b**, 108351-96-8; **4c**, 108351-90-2; **4d**, 108351-92-4; **4d**·2HCl, 108351-97-9; **4e**, 108351-98-0; **4e**·2HBr, 108351-99-1; **4f**, 108352-00-7; **4f**·2HCl, 108352-01-8; **4g**, 108352-02-9; **4g**·2HCl, 108352-03-0; **4h**, 108352-04-1; **4h**·2HCl, 108352-05-2; **4i**, 108351-91-3; **4j**, 108352-06-3; **4j**·2HCl, 108352-07-4; **4k**, 108352-11-0; **4l**, 122845-19-6; **4l**·2HCl, 122845-22-1; **5**, 5006-62-2; **6**, 100050-04-2; **7**, 118371-33-8; **7**·HCl, 122845-36-7; **9**, 6221-12-1; **10a**, 30235-27-9; **10b**, 56541-06-1; **11a**, 113259-07-7; **11b**, 122845-24-3; **11c**, 113259-08-8; **11d**, 122845-25-4; **11e**, 122845-26-5; **11f**, 122845-27-6; **11g**, 122845-28-7; **11h**, 122845-29-8; **11i**, 122845-30-1; **11j**, 122845-31-2; **11k**, 122845-32-3; **11l**, 122845-33-4; **14**·HCl, 112534-17-5; **15**·HCl, 122845-34-5; **16**, 122845-20-9; **17**, 122845-35-6; **18**, 122845-21-0; **18**·2HCl, 122845-23-2.

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Synthesis and Cardiotonic Activity of Novel Biimidazoles

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A series of substituted 2,2′-bi-1*H*-imidazoles and related analogues was synthesized and evaluated for inotropic activity. Structure–activity relationship studies based on a nonclassical bioisosteric approach indicated the necessity of a cyano group on one of the imidazole rings to obtain the desired pharmacological profile. 4(5)-Cyano-2,2′-bi-1*H*-imidazole (**15a**) was the most potent inotropic agent in the series. It produced a 25% increase in left ventricular dP/dt at 0.16 mg/kg iv ($ED_{25\%}$ = 0.16 mg/kg) and increased left ventricular contractile force 60% at 1 mg/kg iv in anesthetized dogs. Compound **15a** is a good inhibitor of type IV cyclic nucleotide phosphodiesterase isolated from dog heart having a potency similar to that of amrinone. Neither 5′-cyano-2,4′-bi-1*H*-imidazole (**44**) nor 4-cyano-2,4′-bi-1*H*-imidazole (**48**) demonstrated inotropic activity. In addition, the two possible 1,1′-dimethylcyano-2,2′-bi-1*H*-imidazoles (**24** and **25**) were inactive, indicating that an acidic NH as well as a cyano group are essential for inotropic activity.

For a number of years there has been a search for safe, orally active, inotropic agents for the treatment of congestive heart failure (CHF).[1,2] The disease is widespread and is on the rise due, in part, to the increasing longevity of the population. Until recently, the only inotropic agents available for the treatment of congestive heart failure were the sympathomimetic agents dobutamine and dopamine and the cardiac glycosides. Milrinone is now available for use, and other agents are currently undergoing clinical evaluation.[3-5]

We wish to report a new structural class of orally effective cardiotonic agents represented by 4(5)-cyano-2,2′-bi-1*H*-imidazole (**15a**). During our investigation of the pharmacology of a potential dopamine β-hydroxylase

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