pyridine-2,5-dicarboxylic acid, giving a mixture of the two compounds, which could be separated (as zwitterions) by fractional crystallizations (from water). Physicochemical constants and spectroscopic data were identical with those reported for *cis*- and *trans*-2,5-PDA.[50]

The rat cortical slice preparation for testing of excitatory amino acids described by Harrison and Simmonds[36] was used in a modified version.[35] Wedges (500 μM thick) of rat brain containing cerebral cortex and corpus callosum were placed with the cortex part between two layers of nappy liner and constantly perfused with a Mg^{2+}-free, oxygenated Krebs solution (at room temperature), while the corpus callosum was placed on the wick of an Ag/AgCl electrode electrically insulated from the cortex part. A reference electrode was placed in contact with the nappy liner and the potential difference between the electrodes was recorded directly on a Servogor 330 recorder. Standard compounds and test compounds were dissolved in the superfusion medium.

Acknowledgment. This work was supported by grants from the Danish Technical and the Danish Natural Sciences Research Councils and from the Lundbeck Foundation. The secretarial assistance of B. Hare and the technical assistance of J. Cohr and S. Stilling are gratefully acknowledged.

Registry No. *cis*-2,3-PDA, 82949-15-3; *trans*-2,3-PDA, 84229-42-5; *cis*-2,4-PDA, 84229-40-3; *trans*-2,4-PDA, 84229-43-6; *cis*-2,5-PDA, 84229-41-4; *trans*-2,5-PDA, 123099-49-0; *cis*-2,6-PDA, 59234-40-1; pyridine-2,5-dicarboxylic acid, 100-26-5.

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6-Benzoxazinylpyridazin-3-ones: Potent, Long-Acting Positive Inotrope and Peripheral Vasodilator Agents

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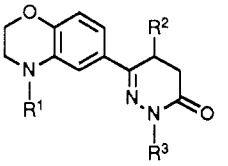
A series of 6-benzoxazinylpyridazin-3-ones was prepared and evaluated for inhibition of cardiac phosphodiesterase (PDE) fraction III in vitro and for positive inotropic activity in vivo. 6-[3,4-Dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (bemoradan) was found to be an extremely potent and selective inhibitor of canine PDE fraction III and a long-acting, potent, orally active inotropic vasodilator agent in various canine models. Additional benzoxazin-6-yl and -8-yl compounds were also prepared. Altering the pyridazinone substitution from the 6-position to the 7-position produced a 14-fold increase in the iv cardiotonic potency (ED_{50}) from 77 to 5.4 μg/kg while substitution at the 8-position reduced potency. Methyl substitution at various sites in the molecule was also examined. Positive inotropic activity was maintained for between 8 and 24 h after a single oral dose (100 μg/kg) of bemoradan in dogs, thus making it one of the most potent and long-acting orally effective inotropes yet described. Bemoradan is currently under development as a cardiotonic agent for use in the management of congestive heart failure.

The most widely used orally active inotropic agent currently available to manage congestive heart failure (CHF) is digoxin.[1] The low therapeutic ratio of digitalis, with its marginal efficacy and propensity to cause serious ventricular arrhythmias,[2] has prompted the search for new oral nonglycoside, noncatecholamine cardiotonic agents useful in the treatment of chronic CHF. A class of agents possessing both positive inotropic and systemic vasodilator activity (beneficial in reducing cardiac pre- and afterload[3]) with a much broader therapeutic ratio than digitalis has emerged recently. These agents, which may act via selective inhibition of cyclic AMP phosphodiesterase fraction III, include milrinone,[4] enoximone,[5] indolidan,[6] bemarinone (ORF 16600),[7] and others. In long-term clinical trials, milrinone has been shown to produce sustained symptomatic and hemodynamic improvement in CHF patients.[8] However, milrinone's short duration of action and inability to alter the high rate of mortality suggest that opportu-

Table I. Synthetic Routes and Physiochemical Data for 6-[4-Substituted-3,4-dihydro-1,4(2*H*)-benzoxazin-6-yl]-2-substituted-pyridazin-3-ones (4)



no.	R^1	R^2	R^3	mp, °C	formula[a]	method
4a	SO_2Me	H	H	244–245	$C_{13}H_{15}N_3O_4S$	A, F
b	SO_2Me	H	Me	162–165	$C_{14}H_{17}N_3O_4S$	A, F
c	SO_2Me	H	allyl	153–155	$C_{16}H_{19}N_3O_4S$	A, F, B
d	SO_2Me	H	pentyl	138–139	$C_{18}H_{25}N_3O_4S$	A, F, B
e	SO_2Me	H	phenyl	199–201	$C_{19}H_{19}N_3O_4S$	A, F
f	H	H	H	198–199	$C_{12}H_{13}N_3O_2$	A, F
g	acetyl	H	H	156–158	$C_{14}H_{15}N_3O_3$	A, F, C
h	H	Me	H	166–168	$C_{13}H_{15}N_3O_2$	A, D, F
i	acetyl	Me	H	185–188	$C_{15}H_{17}N_3O_3$	A, D, F, C
j	SO_2Me	Me	H	207–212	$C_{14}H_{17}N_3O_4S$	A, D, F

[a] Satisfactory elemental analyses (C, H, N) were obtained for all compounds.

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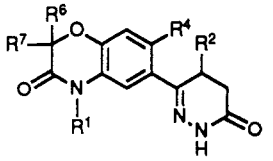
0022-2623/90/1833-0380$02.50/0

Table II. Synthetic Routes and Physiochemical Data for 6-[2,4,7-Substituted-3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-6-yl]pyridazin-3-ones (8)

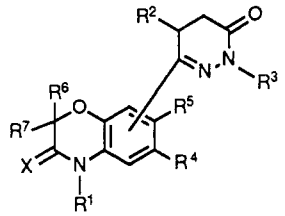


no.	R^1	R^2	R^4	R^6	R^7	mp, °C	formula[a]	method
8a	H	H	H	H	H	274–275	$C_{12}H_{11}N_3O_3$	E, A, F
b	H	Me	H	H	H	263–267	$C_{13}H_{13}N_3O_3$	E, a, D, F
c	Me	H	H	H	H	247–248	$C_{13}H_{13}N_3O_3$	E, A, G, F
d	H	Me	Me	H	H	143–144	$C_{14}H_{15}N_3O_3$	E, A, G, F
e	H	H	H	Me	H	273–275	$C_{13}H_{13}N_3O_3$	E, A, F
f	H	Me	H	Me	H	271–272	$C_{14}H_{15}N_3O_3$	E, A, D, F
g	Me	Me	H	Me	H	184–185	$C_{15}H_{17}N_3O_3$	E, A, D, G, F
h	iPr	Me	H	Me	H	204–205	$C_{17}H_{21}N_3O_3$	E, A, D, F
i	*c*-pentyl	Me	H	Me	H	220–223	$C_{19}H_{23}N_3O_3$	E, A, D, F
j	H	H	H	Me	Me	251–254	$C_{14}H_{15}N_3O_3$	E, A, F
k	Me	H	H	Me	Me	169–171	$C_{15}H_{17}N_3O_3$	E, A, G, F

[a] Satisfactory elemental analyses (C, H, N) were obtained for all compounds.

nities to find a superior cardiotonic still exist.

As a group, the 6-arylpyridazin-3-ones have been shown to possess both positive inotropic[9] and peripheral vasodilating[10] activities. We report here a class of 1,4-benzoxazinylpyridazinone derivatives (1) that possess enhanced cardiotonic potency and activity with a long duration of action as well as a wide margin of safety. In order to uncover the optimum geometry for activity, several regioisomers were synthesized for SAR studies. Further exploration of the geometric requirements of the active site of this enzyme was undertaken by the placement of methyl groups at various sites on the molecule.

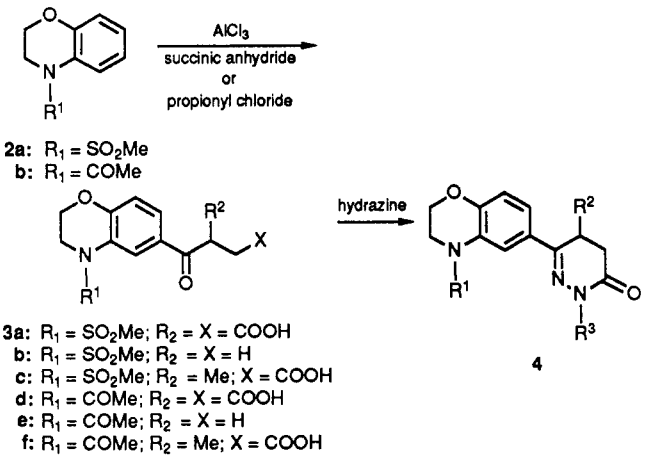


1

Chemistry

The compounds used in this study were prepared by different routes, depending on the site of pyridazinone ring substitution. The compounds in Table I were prepared by a Friedel–Crafts acylation of 3,4-dihydro-4-(methylsulfonyl)-1,4(2*H*)-benzoxazine (**2a**) with succinic anhydride and aluminum chloride using the modification of Thyes[11] (method A) (Scheme I). The resultant keto acid **3a** was treated with hydrazine to afford **4a**. Formation of the anion of **4a** with sodium hydride in DMF and alkylation with allyl bromide or pentyl bromide gave **4c** and **4d**, respectively (method B). Treatment of **3a** with methylhydrazine or phenylhydrazine gave **4b** and **4e**, respectively. Friedel–Crafts acylation of 4-acetyl-3,4-dihydro-1,4-(2*H*)-benzoxazine, as above, gave **3d**. Upon addition of hydrazine, the acetyl group was cleaved and **4f** was isolated. Reacetylation gave **4g** (method C).

Scheme I



The 5′-methyl pyridazinones **4h–j** were prepared by acylation of the appropriate benzoxazinone with propionyl chloride with subsequent elaboration of the ethyl ketone into the 3-methyl-4-oxobutyric acid side chain. This was accomplished by using the procedure of McEvoy and Allen,[12] which utilizes a Mannich reaction with formalin and dimethylamine hydrochloride in acetic anhydride, followed by quaternization of the resulting amine with iodomethane and displacement with cyanide ion. Hydrolysis with 6 N HCl gave the required oxocarboxylic acid (method D).

The method of Shridhar[13] was used to convert the appropriate aminophenol **5** to the desired benzoxazines **6** (method E) (Scheme II). 2-Chloropropionyl chloride and 2-bromoisobutyryl bromide were used instead of chloroacetyl chloride to give the monomethyl and geminal dimethyl analogues, respectively. These compounds were acylated with succinic anhydride to give oxobutyric acids **7a,c,d**. Cyclization to the pyridazinones with hydrazine (method F) gave **8a**, **8e**, and **8j** (Table II). Compounds **7a** and **7d** were N-methylated in DMF/NaH/MeI (method G) to give derivatives **7b** and **7e**, which were also cyclized to pyridazinones **8c** and **8k**. The process described above for converting an ethyl ketone to a 3-methyl-4-oxobutyric acid side chain was employed to prepare **7**, which provided

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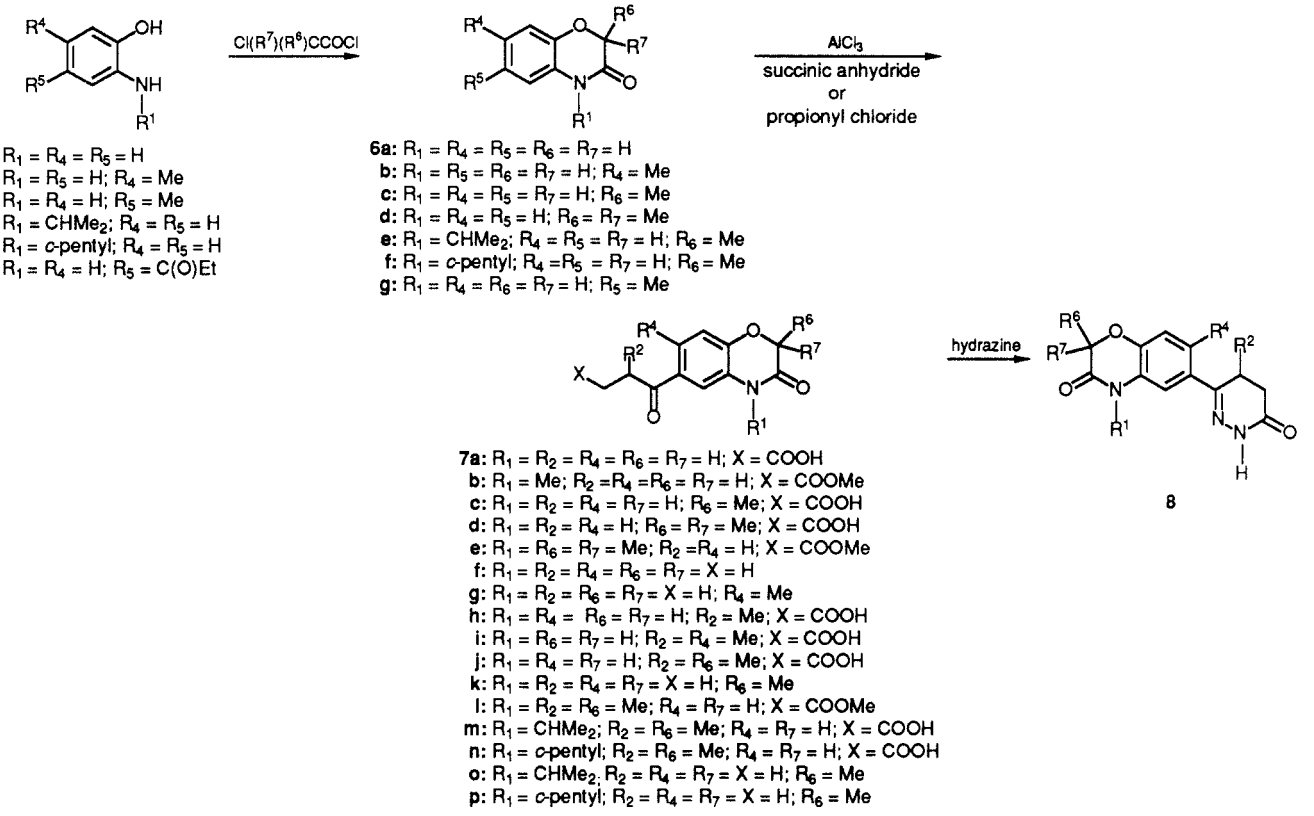
Scheme II



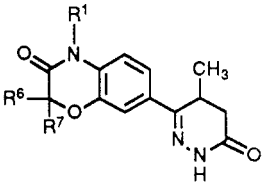
5a: $R_1 = R_4 = R_5 = H$
b: $R_1 = R_5 = H$; $R_4 = Me$
c: $R_1 = R_4 = H$; $R_5 = Me$
d: $R_1 = CHMe_2$; $R_4 = R_5 = H$
e: $R_1 = c$-pentyl; $R_4 = R_5 = H$
f: $R_1 = R_4 = H$; $R_5 = C(O)Et$

6a: $R_1 = R_4 = R_5 = R_6 = R_7 = H$
b: $R_1 = R_5 = R_6 = R_7 = H$; $R_4 = Me$
c: $R_1 = R_4 = R_5 = R_7 = H$; $R_6 = Me$
d: $R_1 = R_4 = R_5 = H$; $R_6 = R_7 = Me$
e: $R_1 = CHMe_2$; $R_4 = R_5 = R_7 = H$; $R_6 = Me$
f: $R_1 = c$-pentyl; $R_4 = R_5 = R_7 = H$; $R_6 = Me$
g: $R_1 = R_4 = R_6 = R_7 = H$; $R_5 = Me$

7a: $R_1 = R_2 = R_4 = R_6 = R_7 = H$; X = COOH
b: $R_1 = Me$; $R_2 = R_4 = R_6 = R_7 = H$; X = COOMe
c: $R_1 = R_2 = R_4 = R_7 = H$; $R_6 = Me$; X = COOH
d: $R_1 = R_2 = R_4 = H$; $R_6 = R_7 = Me$; X = COOH
e: $R_1 = R_6 = R_7 = Me$; $R_2 = R_4 = H$; X = COOMe
f: $R_1 = R_2 = R_4 = R_6 = R_7 = X = H$
g: $R_1 = R_2 = R_6 = R_7 = X = H$; $R_4 = Me$
h: $R_1 = R_4 = R_6 = R_7 = H$; $R_2 = Me$; X = COOH
i: $R_1 = R_6 = R_7 = H$; $R_2 = R_4 = Me$; X = COOH
j: $R_1 = R_4 = R_7 = H$; $R_2 = R_6 = Me$; X = COOH
k: $R_1 = R_2 = R_4 = R_7 = X = H$; $R_6 = Me$
l: $R_1 = R_2 = R_6 = Me$; $R_4 = R_7 = H$; X = COOMe
m: $R_1 = CHMe_2$; $R_2 = R_6 = Me$; $R_4 = R_7 = H$; X = COOH
n: $R_1 = c$-pentyl; $R_2 = R_6 = Me$; $R_4 = R_7 = H$; X = COOH
o: $R_1 = CHMe_2$; $R_2 = R_4 = R_7 = X = H$; $R_6 = Me$
p: $R_1 = c$-pentyl; $R_2 = R_4 = R_7 = X = H$; $R_6 = Me$

8

Table III. Synthetic Routes and Physicochemical Data for 6-[2,4-Substituted-3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-5-methylpyridazin-3-ones (**10**)

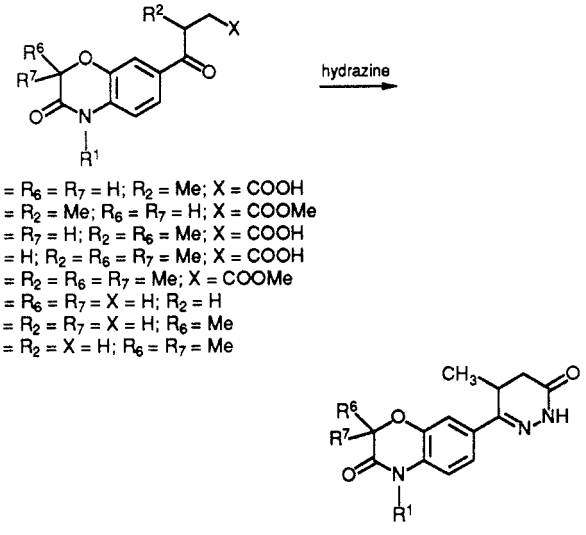


no.	R^1	R^6	R^7	mp, °C	formula[a]	methods
10a	H	H	H	306–307	$C_{13}H_{13}N_3O_3$	E, D, F
b	Me	H	H	188–190	$C_{14}H_{15}N_3O_3$	E, D, G, F
c	H	Me	H	269–270	$C_{14}H_{15}N_3O_3$	E, D, F
d	H	Me	Me	289–290	$C_{15}H_{17}N_3O_3$	E, D, F
e	Me	Me	Me	222–224	$C_{16}H_{19}N_3O_3$	E, D, G, F

[a] Satisfactory elemental analyses (C, H, N) were obtained for all compounds.

8b, **8d**, and **8f** upon addition of hydrazine. Methylation of **7g** followed by hydrazine treatment gave **8g**. Analgues **8h** and **8i**, with bulkier N-substitution, were made by treating compounds **5d** and **5e**[14] with 2-chloropropionyl chloride with subsequent acylation of the benzoxazines with propionyl chloride. Chain extension and addition of hydrazine gave the desired pyridazinones. The most potent members of this class are the analogues (**10**) having the pyridazinone ring at the 7-position (Table III). Since Friedel–Crafts chemistry on benzoxazines produces only 6-acyl isomers,[15] another method was required for the 7-substituted derivatives. Addition of a carboxylic acid to 1,3-benzoxazolin-2-one in polyphosphoric acid followed by hydrolysis of the cyclic urethane has been used to synthesize 1-(4-amino-3-hydroxyphenyl)-1-ethanone and 1-propanone.[16] We applied this technology with the improvement of using Eaton's reagent[17] to prepare the propanone **5f**, which was converted to **9f–h** by addition of the appropriate α-chloro acid chloride. Elaboration of the

Scheme III



9a: $R_1 = R_6 = R_7 = H$; $R_2 = Me$; X = COOH
b: $R_1 = R_2 = Me$; $R_6 = R_7 = H$; X = COOMe
c: $R_1 = R_7 = H$; $R_2 = R_6 = Me$; X = COOH
d: $R_1 = H$; $R_2 = R_6 = R_7 = Me$; X = COOH
e: $R_1 = R_2 = R_6 = R_7 = Me$; X = COOMe
f: $R_1 = R_6 = R_7 = X = H$; $R_2 = H$
g: $R_1 = R_2 = R_7 = X = H$; $R_6 = Me$
h: $R_1 = R_2 = X = H$; $R_6 = R_7 = Me$

10

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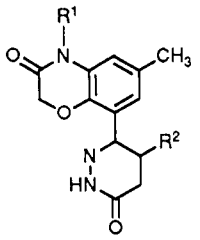
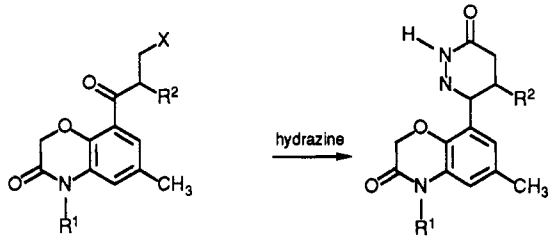
Table IV. Synthetic Routes and Physicochemical Data 6-[4-Substituted-3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-8-yl]-pyridazin-3-ones (**12**)



no.	R^1	R^2	mp, C	formula[a]	methods
12a	H	H	266–270	$C_{13}H_{13}N_3O_3$	A, F
b	Me	H	164–167	$C_{14}H_{15}N_3O_3$	A, G, F
c	H	Me	252–254	$C_{14}H_{15}N_3O_3$	A, D, F
d	Me	Me	212–214	$C_{15}H_{17}N_3O_3$	A, D, G, F

[a] Satisfactory elemental analyses (C, H, N) were obtained for all compounds.

Scheme IV



11a: $R_1 = R_2 = H$; X = COOH
b: R_1 = Me; R_2 = H; X = COOMe
c: $R_1 = R_2$ = X = H
d: R_1 = H; R_2 = Me; X = COOH
e: $R_1 = R_2$ Me; X = COOMe

12

oxopropyl side chain in the usual manner provided keto acids **9a,c,d**. The benzoxazine nitrogen of **9a** and **9d** was methylated as before to give keto esters **9b** and **9e**, respectively. Treatment of **9a–e** with hydrazine gave the desired pyridazinones **10** (Scheme III).

Friedel–Crafts acylation on 6-methylbenzoxazinone **6g** with succinic anhydride or propionic anhydride gave predominately 8-acylbenzoxazinones **11a** and **11c**, respectively, admixed with the 7-isomer. Separation of these isomers followed by addition of hydrazine to **11a** gave **12a**. Methylation of **11a** to **11b** followed by cyclization gave **12b**. Likewise, purification of the 8-propionyl isomer **11c** followed by the aforementioned chain extension gave **11d**. Cyclization to the pyridazinone gave **12c**, and methlation followed by cyclization gave **12d** (Table IV) (Scheme IV).

Discussion

Upon discovery of positive inotropic activity in a series of benzoxazin-6-ylpyridazinones, we first explored substitution at the pyridazine 2-nitrogen in compounds having a 4-(methylsulfonyl) moiety. We confirmed literature reports[6] that compounds without 2-substitution had the greatest activity. In a series of analogues, **4a** was more active than its methyl, allyl, amyl, or phenyl analogues (**4b–e**, Tables I and V). The effect of substitution on the benzoxazine nitrogen was then examined. Substitution at this position affected potency and peak activity in a variable manner, although acetyl substitution provided more activity than methylsulfonyl and potency the same as or better than hydrogen. In order to keep the amide linkage and explore other substitutions on the nitrogen atom, the lactam was synthesized, placing the amide bond within the ring and freeing the nitrogen atom for substitution. In a series of *N*-alkyl analogues, a significant, structurally related effect on contractile force was observed. In the series hydrogen, methyl, isopropyl, and cyclopentyl (**8f–i**), contractile force decreased from 157% to 4% as the size of the group increased. The fact that these same four compounds are equipotent canine fraction III phosphodiesterase inhibitors is significant and suggests that potent enzyme inhibition is not the only requirement for activity, as noted for other cardiotonic agents.[18]

Table V. Inotropic and Enzyme-Inhibiting Activity of 1,4(2*H*)-Benzoxazinylpyridazin-3-ones

no.	*N*[a]	dose, mg/kg	CF[b]	MAP[c]	HR[d]	ED_{50}, μg/kg[e]	PDE III IC_{50}, μM
4a	2	1.875	76	−14	24	1330	9.5
b	2	1.875	26	0	12	>1875	100
c	2	1.875	37	+4	10	>1875	
d	2	1.875	22	−6	−2	>1875	50
e	2	1.875	30	+9	6	>1875	200
f	2	1.875	105	−17	15	620	50
g	2	1.875	121	−14	20	370	100
h	3	0.470	149	−11	44	56	6
i	3	0.470	135	−31	35	56	30
j	2	0.470	99	−1	17	148	4
8a	2	1.875	95	−10	9	700	630
b	3	0.470	136	−14	26	77	2
c	3	0.470	74	−4	13	279	18
d	2	0.470	124	−4	20	137	20
e	2	1.875	138	−8	24	490	14
f	2	0.470	157	−10	18	70	5
g	2	0.470	117	−15	36	68	6
h	2	1.875	83	−16	8	470	5
i	2	1.875	36	−5	7	>1875	8
j	2	1.875	113	−6	14	650	23
k	2	1.875	125	−12	8	800	36
10a	3	0.075	127	−21	25	5.4	0.3
b	3	0.075	109	−20	17	12.8	0.3
c	3	0.075	154	−17	23	5.4	4
d	2	0.075	82	−28	16	16.2	4
e	2	0.075	85	−14	19	21.7	6
12a	1	1.875	32	−12	2	>1875	31
b	2	0.470	73	+1	9	258	26
c	3	1.875	51	−15	8	1800	28
d	4	1.875	98	−17	19	750	7.5
imazodan	4	0.188	77	−4	8	82.2	25.0
indolidan	5	0.075	110	−27	32	8.4	7.0
milrinone	11	0.100	105	−13	15	22	5.5

[a] *N* = number of dogs. [b] CF = myocardial contractile force. [c] MAP = mean arterial blood pressure. [d] HR = heart rate. [e] ED_{50} = iv dose of compound required to increase CF 50% above base line.

Substitution on the aromatic ring also tends to diminish potency. Compound **8d** (ED_{50} = 137 μg/kg) is half as potent as **8b** (ED_{50} = 77 μg/kg) in vivo. Inhibition of PDE fraction III shows the same trend (**8d**, IC_{50} = 20 μM; **8b**, IC_{50} = 2 μM). A single methyl group at the 2-position gave a small increase in activity and potency (**8a**, CF = 95%, ED_{50} = 700 μg/kg, vs **8e**, CF = 138%, ED_{50} = 490 μg/kg). Adding a second methyl group to give a geminal dimethyl substitution reduced inotropic activity (**8j**, CF = 113%) (Table V). In all cases, 5′-methyl substitution on the pyridazinone ring was superior to hydrogen. In the case of the benzoxazin-7-ylpyridazin-3-ones, the 5-methyl moiety was retained on the basis of the structure–activity relationships (SAR) described above for the benzoxazin-6-yl compounds.

Transposition of the pendant ring to the 7-position produced a dramatic increase in potency (**10a**, ED_{50} = 5.4 μg/kg, vs **8b**, ED_{50} = 77 μg/kg). The SAR derived from the 6-substituted compounds could also be applied to the 7-substituted series. Once again, a lone methyl substituent

(18) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. *J. Med. Chem.* **1985**, *28*, 537.

at C-2 caused a slight increase in activity (**10a**, CF = 127%, vs **10c**, CF = 154%) while geminal dimethyl substitution decreased activity (Table III). Phosphodiesterase inhibition of the compounds in this series was studied in some detail.[19] Bemoradan (**10a**) was found to be a selective PDE fraction III inhibitor.

With the pyridazinone ring substituent in the 8-position, less active compounds result. The SAR of the positional isomers suggests that an electron-donating group (oxygen or nitrogen) para to the pyridazinone ring is required for good activity. While the amide nitrogen is situated in the meta position relative to the pyridazinone ring in both the 6-pyridazinyl- and 8-pyridazinylbenzoxazines, the para oxygen atom in the series **8a–k** confers better activity and potency than the ortho oxygen in compounds **12a–d**. The para amide group in the 7-substituted series (**10a–e**), however, provided about 10 times the potency of the other regioisomers.

Two compounds (**10a,b**) were further examined for oral (po) activity in dogs (Table VI). The results show that bemoradan (**10a**) has excellent oral activity with nearly complete absorption through the gastrointestinal tract. Activity was maintained for 8–24 h, suggesting possible once a day therapy.

Conclusions

A series of pyridazinylbenzoxazines possessing potent cardiotonic properties has been discovered. While the mechanism of action of these compounds has not been thoroughly elucidated, they were found to be potent, selective inhibitors of cardiac phosphodiesterase (PDE) fraction III. Inhibition of this enzyme has been shown to produce elevated levels of cyclic AMP, causing an increase in myocardial contractility.[20] Good correlation between in vitro inhibition of canine heart PDE isozyme fraction III and in vivo positive inotropic activity in anesthetized dogs has been observed with a previous series of cardiotonic agents.[21]

The most active and potent compounds contain a methyl group at the 5-position of the pyridazinone ring which, in turn, is appended to the benzoxazinone ring at the 7-position. Substitution on either of the free nitrogen atoms reduces in vivo activity. 6-[3,4-Dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (bemoradan) (**10a**) has been chosen for further development as an orally active cardiotonic agent. With an iv ED_{50} of 5.4 μg/kg, excellent oral activity, and up to 24-h duration, bemoradan represents a potential once-daily therapy for CHF patients. Bemoradan (**10a**) possesses a single chiral center, and detailed data on the biochemistry and pharmacology of the racemic mixture and the resolution and biological properties of the optical isomers will be published elsewhere.

Experimental Section

Chemical Methods. Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were taken in chloroform-*d* with tetramethylsilane as the internal standard and recorded at 90 MHz on a Varian EM 390 instrument. Microanalyses were performed on a Perkin-Elmer Model 240c elemental analyzer, and infrared spectra were taken on a Perkin-Elmer 1430 ratio recording spectrometer as KBr pellets. Mass spectra were obtained at 70 eV by direct insertion with a Finnigan 1015c GC/MS instrument.

The following experimental methods represent general procedures for the synthesis of each of the compounds presented in the text. Methods used to prepare each compound are indicated in the tables. All numbered compounds had satisfactory elemental analyses and, where an assymetric center is present, represent pairs of enantiomers. Where two asymmetric centers are present, as in **8e–i** and **10c**, a mixture of all four diastereoisomers was obtained which was not separated.

Method A. 4-Oxo-4-[3,4-dihydro-2-methyl-3-oxo-1,4-(2*H*)-benzoxazin-6-yl]butyric Acid (7c). 3,4-Dihydro-2-methyl-3-oxo-1,4(2*H*)-benzoxazine (**6c**) (11.4 g, 0.07 mol) was ground to a fine powder with succinic anhydride (7.0 g, 0.07 mol) and the mixture added to aluminum chloride (93 g, 0.78 mol) and dimethylformamide (15.3 mL, 0.2 mol) according to the method of Thyes.[11] The mixture was stirred at 70 °C for 2.5 h and then poured into ice, giving a solid which was collected by filtration and washed with water. Drying under vacuum gave 16.5 g (90%) of **7c**, mp 198–200 °C.

Method B. 2,3,4,5-Tetrahydro-6-[3,4-dihydro-4-(methylsulfonyl)-1,4(2*H*)-benzoxazin-6-yl]-2-(2-propenyl)-pyridazin-3-one (4c). 2,3,4,5-Tetrahydro-6-[3,4-dihydro-4-(methylsulfonyl)-1,4(2*H*)-benzoxazin-6-yl]pyridazin-3-one was suspended in *N*,*N*-dimethylformamide (50 mL) under nitrogen and sodium hydride (0.39 g, 60% in oil dispersion, 9.7 mmol) added in portions. After 30 min, 3-bromopropene (1.4 mL, 9.7 mmol) was added dropwise and the reaction heated to 50 °C for 4 h. The reaction was poured into cold water (200 mL) and the preciptate collected by filtration and washed with water. The solid was purified by flash column chromatography (450 mL of silica gel, 1.5 L of 1:1 ethyl acetate/ethyl ether). Fractions containing the product were combined, dried in vacuo, and recrystallized from ethyl acetate to give analytically pure **4c** in 60% yield as off-white crystals, mp 153–155 °C.

Method C. 6-[4-Acetyl-3,4-dihydro-1,4(2*H*)-benzoxazin-6-yl]-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (4i). 6-[3,4-Dihydro-1,4(2*H*)-benzoxazin-6-yl]-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (**4h**) (2.24 g, 9.14 mmol) was dissolved in THF (20 mL) under nitrogen and chilled in an ice bath, and acetyl chloride (0.65 mL, 9.14 mmol) was added slowly. After 30 min the resultant suspension was filtered, and the filter cake was washed with diethyl ether and recrystallized from ethanol to give the product, mp 184.5–186 °C.

Method D. 4-Oxo-4-[3,4-dihydro-7-methyl-3-oxo-1,4-(2*H*)-benzoxazin-6-yl]-3-methylbutyric Acid (7i). 3,4-Dihydro-7-methyl-3-oxo-1,4(2*H*)-benzoxazine[13] (**6b**) was acylated with propionyl chloride by method A in 85% yield. The product from this process was converted to the title compound by the method of McEvoy and Allen.[12]

3,4-Dihydro-7-methyl-6-(1-oxopropyl)-3-oxo-1,4(2*H*)-benzoxazine (**7g**) (23.7 g, 0.1 mol) was added to a mixture of dimethylamine hydrochloride (13 g, 0.16 mol) and 37% aqueous formaldehyde solution (15 mL) in acetic anhydride (68 mL). After heating on a steam bath for 3 h, acetone (50 mL) was added and heating continued for 15 min. The solvents were removed by evaporation at reduced pressure and the residue dissolved in 1 N HCl and washed with ethyl acetate. The aqueous layer was basified with sodium hydroxide, and the resultant crystals were collected by filtration. This product was dissolved in acetone (500 mL) and iodomethane (10 mL, 0.16 mol) added. After heating at reflux overnight, the solid was collected by filtration and washed with acetone. The yield for these two steps was 80%. The product of this operation was dissolved in 50% aqueous methanol (400 mL), and potassium cyanide (18 g, 277 mmol) in water (200 mL) was added. After stirring overnight at 25 °C, the solid was collected and washed with water. The damp filter cake was suspended in 500 mL of 6 N HCl and heated at reflux for 1.5 h. Cooling gave a white precipitate, which was collected by filtration and washed with water to give 19.4 g (81% for two steps) of **7i**, mp 169.5–172 °C.

Method E. 4-Cyclopentyl-3,4-dihydro-2-methyl-3-oxo-1,4-(2*H*)-benzoxazine (6f). 2-(Cyclopentylamino)phenol[14] (**5e**) (8.0 g, 45 mmol) was dissolved in methyl isobutyl ketone (60 mL) and

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Table VI. Oral Actvity of Selected Pyridazinones in Conscious Dogs

no.	dose, mg/kg	N	dP/dt_{max}, %	after 8 h, %
10a (bemoradan)	0.01	4	43 ± 6	not determined[a]
	0.10	6	85 ± 9	31
	0.30	6	130 ± 8	65
10b	0.03	5	39 ± 10	not determined[b]
	0.10	6	83 ± 6	24
	0.30	6	128 ± 13	not determined[c]

[a] 2% after 4 h. [b] 39% after 6 h. [c] 74% after 6 h.

water (60 mL) containing sodium bicarbonate (12 g). 2-Chloropropionyl chloride (4.9 mL, 50 mmol) was added slowly and the mixture heated to reflux for 4 h and then allowed to stir overnight at 25 °C. The layers were separated, and the water layer was extracted with ethyl acetate. The organic layers were combined and evaporated to give an oil, which was used in the next step without further purification.

Method F. 6-[3,4-Dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-2,3,4,5-tetrahydro-5-methylpyridazin-3-one (10a). 4-Oxo-4-[3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-7-yl]-3-methylbutyric acid (**9a**) (31.0 g, 0.12 mol) was suspended in ethanol (300 mL), and anhydrous hydrazine (4.7 mL, 15 mol) was added. The mixture was heated at reflux overnight and cooled, and the white crystals were collected by filtration and washed with ethanol. The solid was dried at 1 mmHg and 100 °C, giving 28.5 g (93%), mp >300 °C.

Method G. Methyl 4-Oxo-4-[3,4-dihydro-4-methyl-3-oxo-1,4(2*H*)-benzoxazin-6-yl]butyrate (7b). 4-Oxo-4-[3,4-dihydro-3-oxo-1,4(2*H*)-benzoxazin-6-yl]butyric acid (1.0 g, 4.0 mmol) was dissolved in dimethylformamide (20 mL), and sodium hydride (0.32 g, 60% in oil suspension, 8.0 mmol) was added. After 30 min, iodomethane (1.15 g, 8.0 mmol) was added. The mixture was allowed to stir under nitrogen for 12 h and then poured into ice water (100 mL). The product was collected by filtration or by extraction into ethyl acetate and evaporation; mp 139–140 °C.

Isolated Canine Phosphodiesterase Activity. Enzyme Preparation. Canine heart (15.3 g) was homogenized for 1 min in 100 mL of cold distilled, deionized water. After sonication for 1 min at 4 °C, the crude material was centrifuged at 40000*g* for 20 min. The supernatant was filtered through Nylon mesh and applied to a DEAE-cellulose column (2.5 × 25 cm) equilibrated with 70 mM sodium acetate (pH 6.5) buffer containing 5 mM 2-mercaptoethanol and 30% ethylene glycol. After applying the red, clear supernatant, 2 bed volumes of equilibration buffer were used to wash the column. Fractions I, II, and III were eluted with 200, 350, and 800 mM sodium acetate buffer, respectively, at a flow rate of 60 mL/h. All buffers contained the 2-mercaptoethanol and 30% ethylene glycol. Each fraction (tube) was 10 mL (210 drops). The fraction III isozyme was pooled and dialyzed against 2 L of the equilibration buffer over a 6–7-h period at 4 °C. The material was divided into aliquots and stored at −20 °C until used.

Enzyme Assay. The cyclic AMP phosphodiesterase assay is essentially the one described by Thompson and Appleman.[22] The enzyme, buffer (0.05M Tris-HCl, pH 7.4, containing 5 mM $MgCl_2$), and inhibitor were placed into plastic tubes (final volume 0.40 mL). The cyclic AMP substrate (0.25 μM) contained approximately 200000 cpm of [^{3}H]cAMP as a tracer. The enzyme reaction was allowed to proceed for 20 min at room temperature before being terminated by placing the tube into a boiling water bath for 30 s. The tubes were removed and cooled. Snake venom (0.08 mL of a 1 mg/mL solution) is then added, which converts all of the 5′AMP (the product of the phosphodiesterase reaction) to uncharged adenosine molecules. After 25 min, resin (1 mL of a 1:3 AG1×8 slurry) was added, which binds and removes from solution all of the excess cyclic AMP substrate. After settling of the resin, an aliquot (0.20 mL) was removed from the supernatant and placed into a scintillation vial containing 5 mL of scintillation cocktail. Radioactivity was determined in the scintillation counter, and data were used to calculate enzyme activity. The IC_{50} value is the concentration (μM) required to inhibit 50% of the enzyme activity.

Cardiotonic Activity. Adult mongrel dogs were anesthetized with sodium pentobarbital (45 mg/kg, ip) and artificially respired. Mean arterial pressure (MAP) was recorded from a cannulated femoral artery, and drugs were infused into a cannulated femoral vein. The arterial pressure pulse was used to trigger a cardiotachometer for determination of heart rate (HR). A right thoracotomy was performed, and myocardial contractile force (CF) was measured with a Walton Brodie strain gauge sutured to the right ventricle. The ventricular muscle was stretched to produce a base-line tension of 100*g*. A standard dose of dopamine (10–15 μg/kg/min for 3 min) was administered to determine myocardial responsiveness to inotropic stimulation.

Test compounds were solubilized in a small volume of DMF diluted to a final concentration of 10% in physiological saline. Vehicles were tested in appropriate volumes and found to exert less than a 5% effect on contractile force. Compounds were administered by infusion pump (one drug per animal) at rates of 0.58–2.2 mL/min in three to four stepwise increasing doses. Each dose was infused over 5 min immediately after the effect of the previous dose peaked. MAP, HR, and CF responses were continuously monitored on a Beckman or Gould recorder and expressed as a percent change from predrug control values vs the cumulative dose of drug administered. Quantitation of the inotropic potency was obtained by calculation of the contractile force (CF) ED_{50}. This was defined as the dose of compound that produced a 50% increase above base line in myocardial contractile force. The values were obtained from the dose–response relationships either graphically or by regression analysis.

Conscious Instrumented Canine Preparation. Mongrel dogs, quarantined and selected for a calm disposition, were anesthetized through a cephalic vein with 6–10 mL of a 5% solution of thiamylal sodium in saline. Under sterile surgical technique, heparin-filled Tygon catheters were inserted into a femoral artery and vein, tunneled subcutaneously, and exteriorized at the neck above the shoulder blades. A left thoracotomy was performed, and a calibrated Konigsberg pressure transducer was placed in the left ventricle through a stab wound in the apex of the heart. This transducer was used to derive left ventricular dP/dt_{max}, an index of contractility. Blood pressure was recorded from the arterial line, and heart rate was determined with a cardiotachometer. At least 1 week was allowed for recovery. Animals were trained to lie quietly on a padded table in an isolation room. Base-line values for mean arterial pressure (MAP), heart rate (HR), and dP/dt_{max} were obtained. For oral evaluation, compounds were suspended in 0.1% methylcellulose in a volume of 10 mL and administered by gavage through a gastric tube. Changes in hemodynamic indices were monitored over time and reported as the percent change from base line.

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Registry No. **2a**, 114603-40-6; **2b**, 70801-52-4; **3a**, 114603-43-9; **3d**, 114603-44-0; **4a**, 114603-23-5; **4b**, 114603-24-6; **4c**, 114603-26-8; **4d**, 114603-25-7; **4e**, 123169-77-7; **4f**, 114603-27-9; **4g**, 114603-08-6; (±)-**4h**, 123169-78-8; (±)-**4i**, 123169-79-9; (±)-**4j**, 123169-80-2; **5e**, 123170-12-7; **6a**, 5466-88-6; **6b**, 39522-25-3; (±)-**6c**, 123170-00-3; **6d**, 10514-70-2; (±)-**6f**, 123170-11-6; **6g**, 123169-98-2; **7a**, 26518-86-5; **7b**, 114603-45-1; **7c**, 123169-99-3; **7d**, 117278-87-2; **7e**, 117259-71-9; **7g**, 114603-58-6; (±)-**7i**, 123170-10-5; **8a**, 114603-14-4; (±)-**8b**, 123169-81-3; **8c**, 114603-28-0; (±)-**8d**, 123169-82-4; (±)-**8e**, 123169-83-5; (±)-(*R**,*S**)-**8f**, 123169-84-6; (±)-(*R**,*R**)-**8f**, 123169-93-7; (±)-(*R**,*S**)-**8g**, 123169-85-7; (±)-(*R**,*R**)-**8g**, 123169-94-8; (±)-(*R**,*S**)-**8h**, 123169-86-8; (±)-(*R**,*R**)-**8h**, 123169-95-9; (±)-(*R**,*S**)-**8i**, 123169-87-9; (±)-(*R**,*R**)-**8i**, 123169-96-0; **8j**, 114603-02-0; **8k**, 117259-82-2; (±)-**9a**, 123170-01-4; (±)-**9b**, 123170-02-5; (±)-(*R**,*S**)-**9c**, 123170-03-6; (±)-(*R**,*R**)-**9c**, 123170-13-8; (±)-**9d**, 123170-04-7; (±)-**9e**, 123170-05-8; **9f**,

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114603-35-9; (±)-**9g**, 123170-06-9; **9h**, 123170-07-0; (±)-**10a**, 123169-88-0; (±)-**10b**, 123169-89-1; (±)-(*R**,*R**)-**10c**, 123169-90-4; (±)-(*R**,*S**)-**10c**, 123169-97-1; (±)-**10d**, 123169-91-5; (±)-**10e**, 123188-08-9; **11a**, 117259-73-1; **11b**, 114603-49-5; **11c**, 123170-08-1; (±)-**11d**, 123170-09-2; **12a**, 114602-97-0; **12b**, 114602-98-1; (±)-**12c**, 123169-92-6; (±)-**12d**, 123188-09-0; PDE, 9025-82-5; succinic anhydride, 108-30-5; 4-acetyl-3,4-dihydro-1,4(2*H*)-benzoxazine, 70801-52-4; propionic anhydride, 123-62-6.

Synthesis and Serotonin Binding Site Studies of Some Conformationally Restricted Indolylethylamine Analogues Based on 2-Amino-3-(3′-indolyl)bicyclo[2.2.2]octane

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The bicycloannulation reaction between cyclohexenone and indolyl enamines yields *trans*-3-(cyclic amino)-2-(3′-indolyl)bicyclo[2.2.2]octan-5-ones, and these adducts are conformationally restricted analogues of indolylethylamine (tryptamine) which exhibit structure-dependent affinity for the serotonin $5HT_2$ and $5HT_{1a}$ receptors. The stereochemistry of the isomeric endo and exo adducts obtained is assigned from the ^1H NMR spectra of the specifically deuterated alkenes prepared from the ketones by the Bamford–Stevens reaction. Molecular mechanics calculations indicate that the conformational flexibility of the amino and indolyl groups is restricted through van der Waals interactions with the bridges of the bicyclic unit. These compounds inhibit the binding of [^3H]ketanserin to $5HT_2$ sites in mouse cerebrocortical membranes, and the binding of [^3H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^3H]-8-OH-DPAT) to $5HT_{1a}$ sites in mouse hippocampal membranes. The endo compounds are the most potent, and molecular mechanics calculations indicate that these isomers have a less bulky bicyclo bridge proximate to the amine group and more conformational freedom about the C_α–C_β–N^+–H dihedral angle (τ^3). In the $5HT_2$ assay, *endo-trans*-3-(*N*-piperidinyl)-2-(3′-indolyl)bicyclo[2.2.2]octan-5-one (**10a**) is the most potent, and endo-*trans*-3-(*N*-pyrrolidinyl)-2-(3′-indolyl)bicyclo[2.2.2]oct-5-ene (**12a**) is the most potent in the $5HT_{1a}$ assay. A phenyl-substituted adduct shows the least affinity in these two assays. These data provide insight into the structural differences between the $5HT_{1a}$ and $5HT_2$ receptor sites.

Conformationally restricted synthetic analogues of bioactive arylethylamines can be used as effective tools for probing the structure of the binding sites for these physiologically important substances. Much effort is currently directed to the development of compounds that bind, with high specificity, to serotonin binding site subtypes in order better to evaluate structural and functional features of these numerous receptors.[1,2] The serotonin receptors are still very poorly understood, and more specific information on the requirements for binding at particular serotonin binding site subtypes should facilitate the design of more specific agonists and antagonists. Active analogues are also candidates for new selective drugs.

We are investigating the structure–activity relationships that govern the affinity of conformationally restricted analogues for serotonin binding sites, and we report here the synthesis and characterization of the indolylethylamine (tryptamine) analogues **9**, **10**, **12**, and **13** and the phenylethylamine analogue **11**, and studies on their activity at inhibiting the binding of tritiated ketanserin to $5HT_2$ sites in mouse cerebrocortical membranes and of tritiated 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) to $5HT_{1a}$ sites in mouse hippocampal membranes.[3]

We have developed a facile preparation of indolylethylamine analogues in which the indole and amine moieties are attached in a vicinal trans fashion to an ethano bridge of the bicyclo[2.2.2]octane skeleton.[4] These adducts bear a carbonyl group on one of the two remaining ethano bridges, giving rise to geometric isomers: endo when the carbonyl is syn to the amine moiety and exo when the carbonyl is syn to the indole group.[5] This structure provides a framework from which additional analogues can be made by changing the amine substituent (different sized cyclic amines), the indole substituent (substituted indole, phenyl, substituted phenyl), and the

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(4) Schlecht, M. F.; Giandinoto, S. *Heterocycles* **1987**, *25*, 485. The spectral data for compounds **4b** and **4c** in this earlier paper (**9a** and **9b** in the present work) should be reversed.

(5) For this series we define endo and exo on the basis of which substituent (indole or amine) is syn to the carbonyl. We assign a higher priority to the amine group since the carbon of the bicyclic skeleton is bonded to nitrogen for this substituent, versus a bond to carbon for the indole substituent. Thus the isomers **9a**, **10a**, and **11** are endo isomers, with the carbonyl syn to the higher priority substituent, and **9b** and **10b** are exo isomers. Analogous assignments are used for the corresponding alkenes.

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