on alumina, eluting with $CHCl_3$. The product was either crystallized from EtOAc or converted into its hydrochloride salt.

***endo*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl) 1-Indolinecarboxylate (2d).** A solution of tropine (1.13 g, 8 mmol) and KO-*t*-Bu (0.94 g, 8.4 mmol) in dry diglyme (50 mL) was stirred at room temperature for 1 h and then evaporated. The residue was treated with a solution of carbamate **5** (2.4 g, 8.5 mmol) in dry diglyme (50 mL) and heated under reflux for 36 h. The solvent was evaporated and the residue was partititoned between 5 N HCl (10 mL) and Et_2O (30 mL). The aqueous phase was separated and basified with K_2CO_3 and the product was extracted into CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated and the residue was purified by column chromatography on alumina, eluting with CH_2Cl_2. Crystallization from Et_2O afforded **2d** (0.7 g).

General Procedure for Preparation of 1-Indolecarboxamides 3b,i,j,k. A solution of the monohydrochloride salt of the appropriate 1-indolinecarboxamide **2b,i,j,k** (1.6 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.41 g, 1.8 mmol) in dry $CHCl_3$ (100 mL) was heated under reflux for 6 h. The cooled reaction mixture was washed with saturated K_2CO_3 (20 mL), dried, and concentrated. The residue was filtered through a short alumina column, eluting with $CHCl_3$ to give the appropriate indole-1-carboxamide, which was converted into its hydrochloride salt.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3,3-dimethyl-1-indenecarboxamide Hydrochloride (9).** A stirred solution of 3,3-dimethylindene-1-carbonyl chloride (1.1 g, 5.3 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was treated with a solution of *endo*-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (0.8 g, 5.7 mmol) in dry CH_2Cl_2 (50 mL). After 2 h the reaction mixture was diluted with ether (300 mL) to give **9** (1.6 g): ^1H NMR (DMSO-d_6) δ 8.20 (br s 1 H), 7.80–7.70 (m, 1 H), 7.48–7.38 (m, 1 H), 7.30–7.15 (m, 2 H), 7.03 (s, 1 H), 2.64 (s, 3 H), 1.32 (s, 6 H).

Pharmacology. The compounds were evaluated for antagonism of the BJ reflex evoked by 5-HT in the anesthetised rat by the method of Fozard.[4,8] Male rats (260–290 g) were anesthetized with urethane (1.25 g/kg ip) and blood pressure and heart rate were recorded. A submaximal dose of 5-HT (6 μg/kg iv) was given repeatedly, and the changes in heart rate were quantified. Compounds were given intravenously prior to administration of 5-HT, and the dose required to reduce the 5-HT-evoked response to 50% of the control response (ID_{50}) was determined.

Acknowledgment. We thank C. S. Fake and G. J. Sanger for their help and support.

(8) Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 77.

5-Hydroxytryptamine (5-HT_3) Receptor Antagonists. 3. Ortho-Substituted Phenylureas

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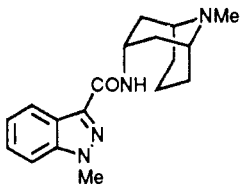
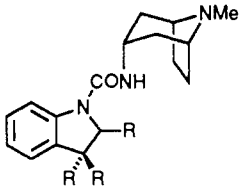
Beecham Pharmaceuticals Research Division, The Pinnacles, Harlow, Essex, England. *Received October 12, 1989*

A novel series of potent 5-HT_3 receptor antagonists, ortho-substituted phenylureas **6a–z**, is described in which the 5-membered ring of the previously reported indazoles and indolines has been replaced by an intramolecular hydrogen bond. High potency was found both for carbamate **6a** and urea **6b**. Granatane **6c** was less potent than the equivalent tropane. Phenylurea **11c** lacking the ortho substituent was inactive. Whereas further substitution could not be tolerated in the aromatic ring, activity was retained with a range of *O*-alkyl groups, compounds **6k–t**. In addition, good activity was found for ortho ester **6u** and sulfonamide **6x**. The ortho-substituted phenylureas can therefore be regarded as bioisosteres of the 6,5-heterocycles indole, indazole, and indoline.

In part 1 of this series of papers indazole **1** (BRL 43694) was shown to be a potent and selective 5-hydroxytrypt-



1 BRL 43694

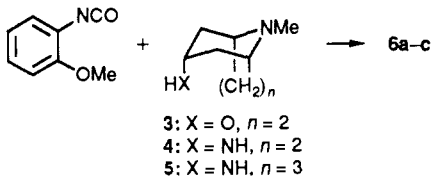


2

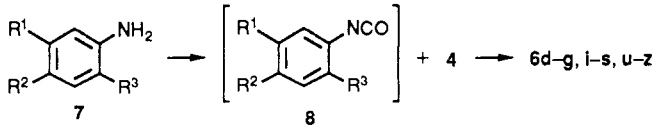
amine 5-HT_3 receptor antagonist.[1] It was also shown to be a highly effective inhibitor of cytotoxic drug and X-irradiation induced emesis in ferrets and is currently being developed as an antiemetic for use in conjunction with anticancer therapy in man. In part 2 we showed that high potency was retained with indolines of general formula **2**.[1] It was concluded that, provided an "in plane" orientation of the carbonyl linkage was not disfavored, aromaticity in the fused 5-membered ring was not necessary. It was therefore considered possible that the 5-membered ring could be replaced by a "pseudo" ring in the form of a hydrogen-bonded system. Although a 5-membered cyclic hydrogen bonded system is weak,[2] the stabilization afforded under suitable conditions may be sufficient to favor an "in plane" orientation of a strategically placed carbonyl linkage.

The present paper describes the synthesis and 5-HT_3 receptor antagonist activity of a series of ortho-substituted phenylureas, **6a–z**, which are capable of forming an intramolecular hydrogen bond.

Scheme I. Synthesis of Ureas **6a–c**



Scheme II. Synthesis of Ureas **6d–g,i–s,u–z**

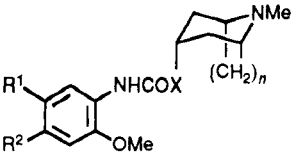


(1) *J. Med. Chem.* Preceding papers in this issue.

(2) Blaney, F. E.; Clark, M. S. G.; Gardner, D. V.; Hadley, M. S.; Middleton, D.; White, T. J. *J. Med. Chem.* **1983**, *26*, 1747.

0022-2623/90/1833-1932$02.50/0

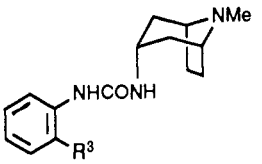
Table I. Structure and Activities of Ureas **6a–j**



no.	R^1	R^2	X	n	formula	% yield	anal.	mp, °C	inhibn of BJ reflex: ID_{50}, μg/kg iv (± SEM)	inhibn of BJ reflex: no. of rats
6a	H	H	O	2	$C_{16}H_{22}N_2O_3 \cdot HCl \cdot 0.25H_2O$	60	C, H, N	240–242	2.4 ± 0.5	3
6b	H	H	NH	2	$C_{16}H_{23}N_3O_2$	34	C, H, N	210–211	2.5 ± 0.7	7
6c	H	H	NH	3	$C_{17}H_{25}N_3O_2$	63	C, H, N	203–204	7.5 ± 4.1	6
6d	F	H	NH	2	$C_{16}H_{22}FN_3O_2 \cdot 0.25H_2O$	13	C, H, N	189–194	7.0 ± 1.7	4
6e	Me	H	NH	2	$C_{17}H_{25}N_3O_2$	44	C, H, N	190–191	>10	3
6f	NO_2	H	NH	2	$C_{16}H_{22}N_4O_4$	67	C, H, N	237–250	>10	3
6g	MeO	H	NH	2	$C_{17}H_{25}N_3O_3$	53	C, H, N	192	>10	3
6h	HO	H	NH	2	$C_{16}H_{23}N_3O_3 \cdot HCl \cdot H_2O$	88	C, H, N[a]	174–178	>10	3
6i	H	F	NH	2	$C_{16}H_{22}NFN_3O_2$	48	C, H, N[b]	191–194	>10	3
6j	H	MeO	NH	2	$C_{17}H_{25}N_3O_3$	40	C, H, N	170–171	>10	3
11c	H	H	NH	3	$C_{17}H_{23}N_3O$	65	C, H, N	191–193	>100	3
12	ICS 205-930								1.4 ± 0.4	5

[a] N, 11.20; required 11.70. [b] N, 13.2; required 13.7. [c] Desmethoxy.

Table II. Structure and Activities of Ureas **6k–z**

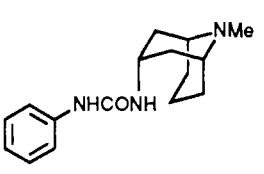


no.	R^3	formula	% yield	anal.	mp, °C	inhibn of BJ reflex: ID_{50}, μg/kg iv (± SEM)	inhibn of BJ reflex: no. of rats
6k	OEt	$C_{18}H_{27}N_3O_2 \cdot 0.25H_2O$	71	C, H, N	170–175	3.1 ± 0.8	3
6l	OPr-*n*	$C_{19}H_{29}N_3O_2 \cdot 0.1H_2O$	75	C, H, N	163–165	9.8 ± 1.5	4
6m	OPr-*i*	$C_{19}H_{29}N_3O_2$	57	C, H, N	163–164	4.2 ± 1.3	3
6n	O-allyl	$C_{19}H_{27}N_3O_2 \cdot 0.25H_2O$	46	C, H, N	156–157	2.6 ± 0.6	3
6o	OBu-*n*	$C_{20}H_{29}N_3O_2$	45	C, H, N[a]	139–141	8.3 ± 3.0	4
6p	OBu-*s*	$C_{20}H_{29}N_3O_2$	66	C, H, N[b]	136–137	2.7 ± 0.6	3
6q	OBu-*t*	$C_{20}H_{29}N_3O_2$	50	C, H, N[c]	150–151	>10	5
6r	OPh	$C_{21}H_{25}N_3O_2$	67	C, H, N	198–199	5.4 ± 1.4	3
6s	OCH_2Ph	$C_{22}H_{27}N_3O_2 \cdot 0.25H_2O$	57	C, H, N	174–176	5.2 ± 0.5	3
6t	OH	$C_{15}H_{21}N_3O_2 \cdot HCl$	53	C, H, N	267–269	11.6 ± 5.6	4
6u	CO_2Me	$C_{17}H_{23}N_3O_3 \cdot 0.25H_2O$	35	C, H, N	125–127	2.1 ± 0.3	4
6v	CO_2Et	$C_{18}H_{25}N_3O_3 \cdot 0.25H_2O$	62	C, H, N	145–147	5.2 ± 1.1	3
6w	$CONMe_2$	$C_{18}H_{26}N_4O_2 \cdot H_2O$	54	C, H, N	196–197	>10	3
6x	SO_2NMe_2	$C_{17}H_{26}N_4O_3S \cdot 0.25H_2O$	60	C, H, N	162–163	2.2 ± 0.7	4
6y	CH_2OMe	$C_{17}H_{25}N_3O_2$	48	C, H, N	148–149	13.4 ± 4.2	5
6z	SMe	$C_{16}H_{22}N_3OS \cdot HCl \cdot 0.25H_2O$	53	C, H, N	284–285	12.7 ± 3.7	5

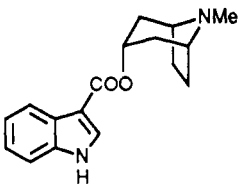
[a] H, 9.3; required 8.8. [b] N, 13.2; required 12.7. [c] H, 9.3; required 8.8.

Chemistry

The (*o*-methoxyphenyl)ureas **6a–c** were prepared by the addition of *O*-methoxyphenyl isocyanate to the appropriate amino alcohol **3** or diamine **4**[3] or **5**[4] (Scheme I). Ureas **6d–z**, with the exception of **6h** and **6t**, were prepared from the appropriately substituted aniline by in situ conversion to the isocyanate by phosgene followed by addition to diamine **4** (Scheme II). Ureas **6h** and **6t** were prepared by catalytic hydrogenolysis of the *O*-benzyl group in **10** and **6s**, respectively. Urea **10** itself was prepared from 5-(benzyloxy)-2-methoxybenzoic acid (**9**)[5] via Curtius rearrangement of the azide derivative to the isocyanate (Scheme III). Urea **11** was prepared by addition of phenylisocyanate to **5**.



11



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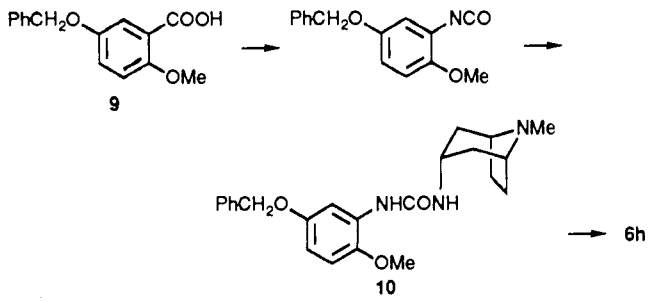
Results

The compounds were evaluated for their potency as 5-HT_3 receptor antagonists in vivo by their ability to inhibit the Benzold–Jarisch reflex evoked by 5-HT in rats (Tables I and II).[6] This effect is mediated by activation

(3) Archer, S.; Lewis, T. R.; Unser, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 4194.
(4) Donatsch, P.; Engel, G.; Bruno, H.; Richardson, B. P.; Stadler, P. GB 2,125,398A, 1984.
(5) Schmidt, U.; Lieberknecht, A.; Bokens, H.; Griesser, H. *J. Org. Chem.* **1983**, *48*, 2680.
(6) Fozard, J. R. *Neuropharmacol.* **1984**, *23*, 1473.

Scheme III. Synthesis of Urea 6h



of 5-HT_3 receptors located in the wall of the right ventricle.[7] Potency was expressed as an ID_{50}, which was the dose required to inhibit by 50% the control response to 5-HT. Because of the high potency found both within this series and with others,[1] an ID_{50} of >10 μg/kg by intravenous administration (iv) was generally regarded as insufficiently potent for further consideration.

Carbamate **6a** and urea **6b** were both found to be potent $5HT_3$ receptor antagonists and only marginally less potent than indole ester **12** (ICS 205-930[8]) (Table I). Granatane analogue **6c** was less potent than tropane **6b**. Thus it would appear that, of the four series of 5-HT_3 receptor antagonists, 3-indoles, 3-indazoles, 1-indolines,[1] and the ortho-substituted ureas, it is only in the 3-indazole series that the granatane analogues are particularly potent. The requirement of an ortho substituent was confirmed by the lack of potency of unsubstituted urea **11**.

For the indazole and indoline series,[1] substitution in the benzo ring resulted in a marked reduction in potency. Similarly, for this series, introduction of substituents as in compounds **6d–j**, even with 5-hydroxy analogue **6h**, which incorporates hydroxy substitution in the equivalent position to that in 5-HT itself, resulted in a marked reduction in potency. It would therefore appear that the steric effects are the overiding factors with respect to loss of potency. The lack of potency of **6h** would also suggest that the aryl 6-membered ring of the antagonists does not necessarily bind to the same part of the 5-HT_3 receptor as the benzo-fused ring of 5-HT itself. If, therefore, it is assumed that the tertiary nitrogen of the antagonists binds to the same part of the receptor as the primary nitrogen of 5-HT, from an investigation of molecular models it would appear that the carboxyl oxygen atom of the amides and ureas is capable of mimicking the 5-hydroxy oxygen atom of 5-HT. Antagonist activity may therefore be a consequence of the presence of the 6-membered aromatic ring.[9]

Replacement of the *o*-methoxy group by larger alkoxy substituents as in compounds **6k–p** (Table II) maintained reasonable potency until the relatively bulky *tert*-butyl substituent (**6q**) was reached. However it was disappointing that no increase in potency was observed considering the beneficial effect of bulk in the equivalent 3-position of indolines **2**.[1] This result can be rationalized in terms of the bulk of the alkyl group interfering with the orientation of the oxygen lone pair required for the hydrogen bond. This misalignment could counteract the beneficial effect of an increase in lipophilicity.

We have previously shown that a 6,6-bicyclic system related to **2** was inactive.[1] It was therefore surprising that the pseudo 6-membered ring hydrogen-bonded analogues **6u** and **6x** retained activity. Simple homologation, however, to ethyl ester **6v** resulted in a reduction in potency, seen also with amide **6w**. Weak activity was also retained with both benzyl ether **6y** and thioether **6z**.

In conclusion, therefore, it is possible to replace the 5-membered ring of the 6,5-system of the 5-HT_3 receptor antagonists by either a 5- or 6-membered hydrogen-bonded system and still retain most of the antagonist potency. The *o*-methoxyphenylureas can therefore be regarded as bioisosteres of indoles,[8] indazoles, and indolines.[1]

Experimental Section

Chemistry. Melting points are uncorrected. Elemental analyses (Tables I and II) are within 0.4% of the theoretical values unless specified. All evaporations of solvent were carried out by rotary evaporation under reduced pressure and organic extractions were dried over K_2CO_3 unless specified. For column chromatography, the alumina used was neutral Brockman Grade I and the compounds were preabsorbed for loading. Light petroleum refers to the fractions boiling between 60 and 80 °C. Yields quoted are nonoptimized and generally refer to the results of a single experiment. *endo*-8-Methyl-8-azabicyclo[3.2.1]octan-3-amine[3] (**4**) and *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine[4] (**5**) were prepared by the literature procedures.

***endo*-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl *N*-(2-Methoxyphenyl)carbamate Hydrochloride (6a).** A solution of **3** (1.4 g, 10 mmol) and 2-methoxyphenyl isocyanate (1.5 g, 10 mmol) in dry xylene (50 mL) was heated under reflux for 4 h. The reaction was cooled and concentrated, and the residue was purified by column chromatography on alumina, eluting with CH_2Cl_2 containing increasing quantities of $CHCl_3$. The purified product was converted to its hydrochloride salt, **6a** (2.0 g), recrystallized from EtOH/Et_2O.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-*N'*-(2-methoxyphenyl)urea (6b).** To a stirred solution of **4** (1.5 g, 11 mmol) in dry Et_2O (50 mL) at 0 °C was added a solution of 2-methoxyphenyl isocyanate (1.5 g, 10 mmol) in dry Et_2O (5 mL). The reaction mixture was stirred at room temperature overnight and product **6b** was collected and dried (1.0 g).

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-*N'*-(2-methoxyphenyl)urea (6c).** By following the procedure outlined for **6b**, amine **5** (1.6 g, 10 mmol) was converted to **6c** (2.5 g).

General Procedure for the Synthesis of Ureas 6d–g,i–s,u–z. A solution of phosgene (7 mL, 12.5% in toluene) was added to a stirred solution of the appropriate aniline (8 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C and stirring was continued for 10 min. Triethylamine (2.5 mL) was then added, and after a further 10 min, a solution of **4** (1.1 g, 8 mmol) in CH_2Cl_2 (10 mL) was also added. The reaction was stirred at room temperature for 4 h, washed with saturated $NaHCO_3$ solution (2 × 50 mL), dried, and concentrated. The residue was purified by column chromatography on alumina as described for **6a** followed by either recrystallization from EtOAc/light petroleum or by conversion into its hydrochloride salt.

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-*N'*-(5-hydroxy-2-methoxyphenyl)urea Hydrochloride (6h).** A solution of 5-(benzyloxy)-2-methoxybenzoic acid[4] (1.1 g, 4.2 mmol) in $SOCl_2$ (5 mL) was heated on a steam bath for 1 h. The $SOCl_2$ was removed by rotary evaporation and the residue was dissolved in dry acetone (125 mL). NaN_3 (0.8 g, 12 mmol) was added and the reaction was heated under an atmosphere of dry N_2 at 50 °C for 1.5 h. Light petroleum (100 mL) was added to the cooled reaction and the mixture was filtered through a Kieselguhr pad. The filtrate was evaporated to dryness and the residue was heated in toluene (50 mL) on a steam bath for 30 min. Amine **4** (0.56 g, 4 mmol) was added and the solution was stirred at room temperature for 18 h. The solvent was removed and the residue was purified by column chromatography on alumina, eluting with CH_2Cl_2, to give urea **10**, which was converted to its hydrochloride salt (0.86 g, 50%). A solution of the hydrochloride salt (0.86 g, 2 mmol) was dissolved in EtOH (100 mL) and hydrogenated at atmospheric pressure and room temperature over 10% Pd/C until hydrogen uptake had ceased. The catalyst was removed by filtration and the filtrate was concentrated. Trituration of the

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(8) Richardson, B. P.; Engel, G.; Donatsch, P.; Stadler, P. A. *Nature* **1985**, *316*, 126.
(9) King, F. D.; Sanger, G. J. *Drugs Future* **1989**, *14*, 875.

residue with Et_2O gave **6h** (0.6 g).

***endo*-*N*-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-*N'*-(2-hydroxyphenyl)urea Hydrochloride (6t).** By following the procedure described for the conversion of **10** to **6h**, **6s** (1.9 g, 5 mmol) was converted via its hydrochloride salt to **6t** (0.83 g).

***endo*-*N*-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)-*N'*-phenylurea (11).** By following the procedure outlined for **6b**, phenyl isocyanate (2.4 g, 20 mmol) was converted to title compound 11 (3.6 g).

Pharmacology. The compounds were evaluated for antagonism of the Bezold–Jarisch (BJ) reflex evoked by 5-HT in the anesthetized rat by the method of Fozard.[6,10] Male rats (260–290 g) were anesthetized with urethane (1.25 g/kg ip) and blood pressure and heart rate were recorded. A submaximal dose of 5-HT (6 μg/kg iv) was given repeatedly, and the changes in heart rate were quantified. Compounds were given intravenously prior to administration of 5-HT and the dose required to reduce the 5-HT evoked response to 50% of the control response (ID_{50}) was determined.

Acknowledgment. We thank C. S. Fake and G. J. Sanger for their support.

(10) Sanger, G. J. *Br. J. Pharmacol.* **1987**, *91*, 77.

Conformational Restriction of Angiotensin II: Cyclic Analogues Having High Potency

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Cyclic analogues of angiotensin II (AII) were synthesized by connecting the side chains of residues 3 and 5 via a disulfide bridge. Appropriate conformational constraints afforded an analogue, [$Hcy^{3,5}$]AII, having high contractile activity (pD_2 = 8.48 vs 8.81 for AII) and excellent binding affinity (IC_{50} = 2.1 nM vs 2.2 nM for AII). This type of cyclization was also used to prepare a highly potent AII antagonist, [Sar^1,$Hcy^{3,5}$,Ile^8]AII (pA_2 = 9.09 vs 9.17 for [Sar^1,Ile^8]AII; IC_{50} = 0.9 nM vs 1.9 nM for [Sar^1,Ile^8]AII). Model building suggests that this ring structure is consistent with a receptor-bound conformation having any of a variety of three-residue turns, including a γ-turn. In contrast, the receptor-bound conformation of AII does not appear to accommodate a β-turn or an α-helix which includes residues 3–5.

Since its discovery 50 years ago, the linear octapeptide angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe; AII; 1) has been the subject of numerous studies.[2] These investigations have shown that this hormone, being a potent pressor agent, has a vital role in regulation of blood pressure. In order to help establish the relationship between biological activity and conformation, several spectroscopic examinations of 1 and closely related analogues have been reported. These have included nuclear magnetic resonance (NMR) spectroscopy in a variety of solvents[3-8] as well as in the presence of lipid vesicles,[9] circular dichroism,[10-13] and infrared spectroscopy.[14-16] In addition, theoretical approaches[17-19] as well as pH[20-22] and other physicochemical studies[23-27] have also provided insights into the conformation of 1. This work has led to the proposal of several structural models for AII, including conformations which contain an α-helix,[27] a β-turn,[10,14,24] and a γ-turn.[4,24] Other, more complicated structures have also been suggested.[3,18,28] These widely differing conformational analyses serve to emphasize the lack of consensus on the solution conformation of 1. Indeed, Glickson and Marshall et al.[5,29,30] have cogently argued that several of

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