Communications to the Editor

N^6-Bicycloalkyladenosines with Unusually High Potency and Selectivity for the Adenosine A_1 Receptor

Sir:

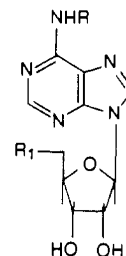
Adenosine elicits a wide variety of physiological responses[1] via interactions with two major subtypes of extracellular adenosine receptors, designated as A_1 and A_2. A_1 and A_2 receptors differ in their structure–activity relationships[2] and have opposite effects on adenylate cyclase.[3] With the advent of the A_2 binding assay,[4,5] it has been possible to measure the A_1/A_2 affinity ratios of different adenosine agonists and antagonists, leading to the identification of compounds with selectivity for one or the other receptor subtype. The N^6-cycloalkyladenosines are among the most A_1-selective agonists reported to date,[6] and N^6-cyclopentyladenosine (CPA, 1), the most A_1-selective compound of the series, is used in the A_2 binding assay to eliminate the A_1 component of [^{3}H]NECA binding.[5] N^6-Cyclohexyladenosine (CHA), although somewhat less potent and selective, is widely used as a radioligand to label A_1 receptors.[5,7] The present study describes several novel N^6-bicycloalkyladenosines that are the most potent and A_1-selective agonists reported to date. On the basis of the stereochemistry of these molecules, we have derived a detailed map of the N^6 domain of the A_1 receptor.

It was evident from earlier structure–activity studies that aralkyl derivatives such as N^6-[(*R*)-1-methyl-2-phenylethyl]adenosine (*R*-PIA), although potent at the A_1 receptor, do retain significant affinity for the A_2 receptor[5,8] and thus would not appear to be optimal chemical leads for the development of highly A_1 selective agonists. However, the N^6-cycloalkyl derivatives are equally potent at the A_1 receptor, but generally have less binding affinity at the A_2 receptor.[6] Thus, this series of compounds attracted our attention as a promising starting point for the identification of more potent and selective agonists for the A_1 receptor.

Initially we synthesized the epimeric N^6-(2-*endo*- and -*exo*-norbornyl)adenosines (2 and 3, respectively) from commercially available materials.[9] Interestingly, both compounds showed high potency and selectivity for the A_1 receptor (Table I). The N^6-(2-*endo*-norbornyl)-adenosine (2) was slightly more potent (K_i = 0.42 nM) and significantly more selective (A_2/A_1 K_i ratio 1790) than CPA. Our A_1 binding results differ slightly from those of Daly and colleagues,[10] who found 2 to be equipotent with 1. However, compound 2 has also been shown to be the most potent of an extensive series of N^6-modified adenosine analogues for inhibition of neurotransmitter release from the rat vas deferens,[11] thus confirming the possibility that 2 might be a lead toward more potent and selective A_1 agonists. The exo isomer was less potent and less A_1 selective by a factor of 2, in agreement with published results.[10,11]

This observation, along with the known stereoselectivity of the N^6 domain of the A_1 receptor,[8] prompted us to further evaluate the influence of stereochemistry on binding affinity in this series. In particular, compound 2 is actually a mixture of two isomers having enantiomeric side chains at N^6 (since the ribose moiety is D in both, the two compounds are diastereomers). For initial evaluation, we chose to separate these diastereomers by analytical HPLC. A problem in this separation was posed by the fact that this mixture of diastereomers behaves physicochemically as if it were a mixture of enantiomers. This is partly due to the fact that the chiral centers at N^6 are too far from the chiral centers in the ribose moiety for any significant interaction to occur. Thus, usual techniques such as fractional crystallization or chromatographic separation

Table I. Affinities in A_1 and A_2 Adenosine Receptor Binding of N^6-Bicycloalkyladenosines



no.	R	R_1	K_i,[a] nM A_1	K_i,[a] nM A_2	ratio A_2/A_1
1	cyclopentyl	OH	0.59	462	780
2	2-*endo*-norbornyl	OH	0.42	750	1790
3	2-*exo*-norbornyl	OH	0.91	970	1070
4	1*R*,2*S*,4*S* isomer[b] of 2	OH	0.30	1390	4700
5	1*S*,2*R*,4*R* isomer of 2	OH	1.65	610	370
6	cyclopentyl	Cl	0.72	1870	2600
7	2-*endo*-norbornyl	Cl	0.42	2100	4900
8	1*R*,2*S*,4*S* isomer of 7	Cl	0.24	3900	16000
9	1*S*,2*R*,4*R* isomer of 7	Cl	1.86	3000	1600

[a] A_1 binding was carried out with [^{3}H]CHA in rat brain membranes as described,[5] and A_2 binding was carried out with [^{3}H]-NECA in the presence of 50 nM CPA in rat striatal membranes.[5] Concentration–inhibition curves were carried out in triplicate with six or more concentrations of test agent, and IC_{50} values were calculated using nonlinear least-squares curve fitting.[5] IC_{50} values were converted to K_i values by multiplying by 0.5671 (A_1) or 0.6745 (A_2) as described.[5] All values are means of three or more independent experiments. Standard errors of K_i values averaged 6.8% for A_1 binding and 10.5% for A_2 binding. [b] The absolute stereochemistry of examples 4 and 5 was determined from synthesis of the corresponding chiral amines.[25]

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(2) Hamprecht, B.; van Calker, D. *Trends Pharmacol. Sci.* 1985, *6*, 153.
(3) Londos, C.; Cooper, D. M. F.; Wolff, J. *Proc. Natl. Acad. Sci. U.S.A.* 1980, *77*, 2551.
(4) Yeung, S. M. H.; Green, R. D. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1984, *325*, 218.
(5) Bruns, R. F.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* 1986, *29*, 331.
(6) Moos, W. H.; Szotek, D. S.; Bruns, R. F. *J. Med. Chem.* 1985, *28*, 1383.
(7) Bruns, R. F.; Daly, J. W.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* 1980, *77*, 5547.
(8) Kusachi, S.; Thompson, R. D.; Bugni, W. J.; Yamada, N.; Olsson, R. A. *J. Med. Chem.* 1985, *28*, 1636.
(9) Fleysher, M. H. *J. Med. Chem.* 1972, *15*, 187.
(10) Daly, J. W.; Padgett, W.; Thompson, R. D.; Kusachi, S.; Bugni, W. J.; Olsson, R. A. *Biochem. Pharmacol.* 1986, *35*, 2467.
(11) Paton, D. M.; Olsson, R. A.; Thompson, R. T. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1986, *333*, 313.

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on silica gel were not effective for separating these diastereomers. We therefore separated the isomers of 2 using reverse-phase HPLC on a β-cyclodextrin column.[12] Cyclodextrin columns have been used to separate drug enantiomers, an application that is based on the ability of a chiral, hydrophobic cavity in the oligosaccharide ring of the cyclodextrin to bind small molecules in a stereospecific manner.[13] Isolation of small quantities of pure diastereomers 4 and 5 using this method and evaluation in the receptor binding assays once again confirmed the stereospecificity of both receptors. Interestingly, although the diastereomer 4 was more potent than 5 at the A_1 receptor (K_i = 0.30 nM compared to 1.65 nM), it was actually less potent than 5 at the A_2 receptor (K_i = 1390 nM versus 610 nM), and was therefore more A_1-selective than the parent mixture 2 (4700-fold, compared to 370-fold for 5 and 1790-fold for the mixture). The structure–activity relationships of the N^6-norbornyladenosines can be explained in terms of the geometry of the norbornyl group and the known SAR of the N^6 domain of the adenosine receptor. In particular, Paton and colleagues[11] have commented that the norbornyl group has two surfaces, one being essentially a cyclopentyl ring backed by a two-carbon bridge and the other being a cyclohexyl ring backed by a one-carbon bridge (Figure 1). The greater potency of the 2-*endo*-norbornyl isomers (2) relative to the 2-*exo*-norbornyl isomers (3) probably occurs because 2 binds to the receptor with its cyclopentyl surface facing the receptor, whereas 3 is forced to bind with the less favorable cyclohexyl ring facing the receptor.[11,14,15]

The higher A_1 affinity of 4 relative to 5 also undoubtedly has its basis in the shape of the norbornyl group. Cyclopentane exists mainly in an "envelope" conformation, in which four of the carbons form the corners of a flat, almost square envelope, and the fifth carbon represents the apex of a triangular flap, which projects at an angle of about 120° from the body of the envelope (Figure 1). Although any of the carbons can take the out-of-plane position in cyclopentane, in norbornane the bridging carbon is locked in this position. The greater affinity of 4 compared to that of 1 is most likely due to the former being locked in the optimal conformation, with the bridging methylene presumably projecting into a small hydrophobic depression on the receptor surface (Figure 1). Since 5 has poorer affinity than 4 or 1, it follows that the methylene bridge of 5 must project to a less favorable site on the A_1 receptor.

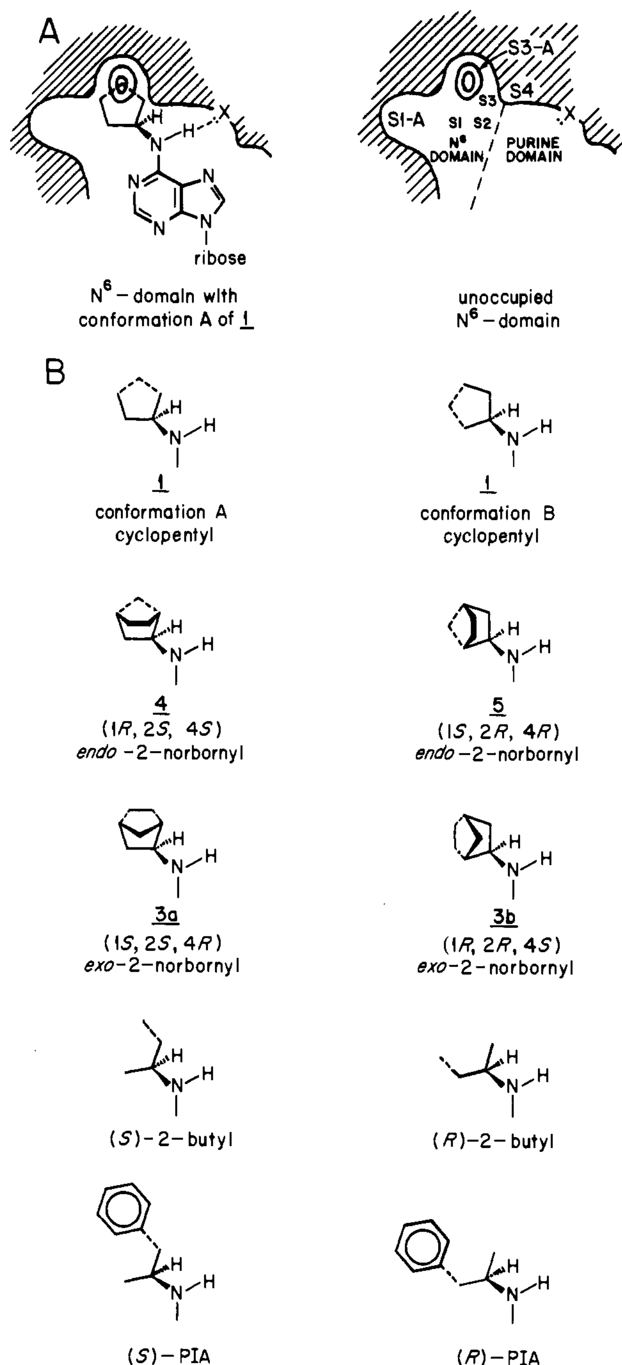

Figure 1. Stereochemistry of the N^6 domain of the A_1 receptor. (A) Model of the N^6 domain. The S1···S4 nomenclature is taken from Kusachi et al.[8] For simplicity, the N^6 domain is drawn as though coplanar with the purine-binding domain; examination of a Dreiding model of 4 suggests that the N^6 domain may actually be rotated toward the observer by roughly 70° along an axis (dashed line) that marks the boundary between the N^6 and purine domains. (B) Chiral N^6 side chains. Compounds that have the *S* configuration at the proximal carbon are shown in the left column, and *R* isomers in the right column. Compounds **3a** and **3b** are the individual diastereomers of 3.

By comparing the stereochemistry of 2 with that of previously reported compounds,[8,10,11] it is possible to build a fairly detailed model of the N^6 domain of the A_1 receptor (Figure 1). The rotation of the 6-amino group is fixed because of electronic factors and hydrogen bonding of the N^6 hydrogen to the receptor.[16] Since the S4 region of the

(12) A 20–200-μg quantity of 2 was injected on a 250 × 4.6 mm Cyclobond I column (ASTEC Inc., Whippany, NJ) and eluted at 1 mL/min with methanol/water 45:55 with 0.5% formic acid adjusted to pH 4.0 with aqueous ammonia. Detection was at 295 nm. Compound 4 eluted before 5. In order to prepare sufficient quantities of the isomers for receptor binding studies, several 200-μg samples of 2 were subjected to two cycles of chromatographic purification, resulting in about 1.5 mg of each isomer.

(13) Armstrong, D. W.; Ward, T. J.; Armstrong, R. D.; Beesley, T. E. *Science* **1986**, *232*, 1132.

(14) For steric reasons, when the carbon attached to N^6 is substituted with two alkyl groups and a hydrogen, the hydrogen must face the receptor (see ref 8, 10, and 11). This implies that the cyclopentyl ring faces the receptor in 2, while the cyclohexyl ring must face the receptor in 3. The cyclohexyl ring of 3 is also in boat conformation, while that of N^6-cyclohexyladenosine is almost exclusively in chair conformation.

(15) It should be noted that the SAR analyses in ref 11 and in the present study are based on the assumption that only one face of the cycloalkyl group contacts the receptor surface, so that the groups on the other face do not influence affinity except indirectly via conformational effects. This assumption is supported by the high degree of bulk tolerance at N^6. In addition, if both faces contacted the receptor, one might expect much more drastic differences in affinity between compound 1 (second face unsubstituted) and compounds 2 and 3 (one- or two-carbon bridge projecting out from the second face).

receptor (nomenclature of Kusachi et al.[8]) cannot accommodate any group larger than hydrogen, the rotation of the proximal carbon is also fixed when the latter is substituted with two alkyl groups. Thus, the configuration of the 6-amino group and proximal carbon is probably the same for all of the N^6 derivatives in Figure 1. Examination of Figure 1 indicates that the C1 bridgehead of **4** occupies S3, the location occupied by the methyl group of *R*-PIA. The small depression that is occupied by the out-of-plane carbon of **1** and **4** is thus located in the distal part of S3 (S3-A). This observation explains the interesting finding of Daly et al.[10] that the *S* isomer of N^6-(2-butyl)adenosine is slightly more active than the *R* isomer in A_1 binding: the distal carbon of the *S* isomer occupies the hydrophobic depression in S3-A, while the corresponding carbon of the *R* isomer occupies the S1-A region, which is presumably less favorable for hydrophobic binding. The poor hydrophobic binding of the S1-A region is illustrated by the observation that *R*-PIA is less than twice as potent as its desphenyl analogue N^6-(2-propyl)adenosine.[8]

An examination of Figure 1 shows that the major difference between **4** and the 1*S*,2*S*,4*R* isomer of **3** is the presence in the latter of a two-methylene unit projecting into the hydrophobic depression distal to S3, compared to a one-methylene unit in **4**. The poorer activity of **3** compared to that of **2** probably implies that the S3 depression is only able to easily accommodate a single methylene unit.

The above analysis applies only to the A_1 receptor. Since **5** is more potent than **4** in A_2 binding, and since *R*-PIA is about 5 times as potent as its desphenyl derivative at the dog A_2 receptor,[8] it is likely that the S3-A region of the A_2 receptor is smaller or less hydrophobic than that of the A_1, while the S1-A region is probably more hydrophobic than at the A_1 receptor.

N^6-Cyclopentyladenosine (**1**) is about 600-fold more potent than N^6-methyladenosine (A_1 K_i = 360 nM).[5] The four additional methylene groups of **1** therefore contribute an average of 0.95 kcal/mol in binding energy. This value is rather high for a van der Waals interaction,[17] suggesting that **1** may have a nearly optimal fit to a hydrophobic surface. The affinity difference between **4** and **5** is equivalent to 1.0 kcal/mol, implying a tight fit between the hydrophobic depression at S3-A and the apex of the cyclopentane envelope of **4**, which cannot be achieved with **5**.

The high affinity of **4** led us to explore its use as a potential improved radioligand for adenosine A_1 binding. The need for such a ligand is apparent from the fact that many peripheral tissues that are known to possess A_1 responses cannot be easily studied with available ligands due to their very low A_1 receptor densities.[18] Compound **4** (which we have abbreviated (*S*)-ENBA) was labeled with tritium by catalytic exchange to 29.3 Ci/mmol. [^{3}H]-(*S*)-ENBA bound to rat brain membranes with about 4-fold higher affinity (K_d = 0.33 nM) than the widely used ligand [^{3}H]CHA (Figure 2). Although the saturation results indicated only a single site, biphasic dissociation kinetics were observed, with 60% of binding representing a rapidly dissociating component ($t_{1/2}$ 12.4 min) and the remaining 40% representing a slowly dissociating component ($t_{1/2}$ 216 min). Kinetic constants were k_{on} = 1.18 $\times$ 10^{-4} pM^{-1} min^{-1}, fast k_{off} = 5.59 $\times$ 10^{-2} min^{-1}, slow k_{off} = 3.21 $\times$ 10^{-3} min^{-1}, fast K_d = 473 pM, slow K_d = 27.1 pM. Binding of [^{3}H](*S*)-ENBA was inhibited potently (K_i = 0.57 nM) and monophasically by the A_1-selective antagonist[19] 8-cyclopentyl-1,3-dipropylxanthine. These results indicate that [^{3}H](*S*)-ENBA may have advantages compared to [^{3}H]CHA as a ligand for labeling of low-density A_1 receptor populations.

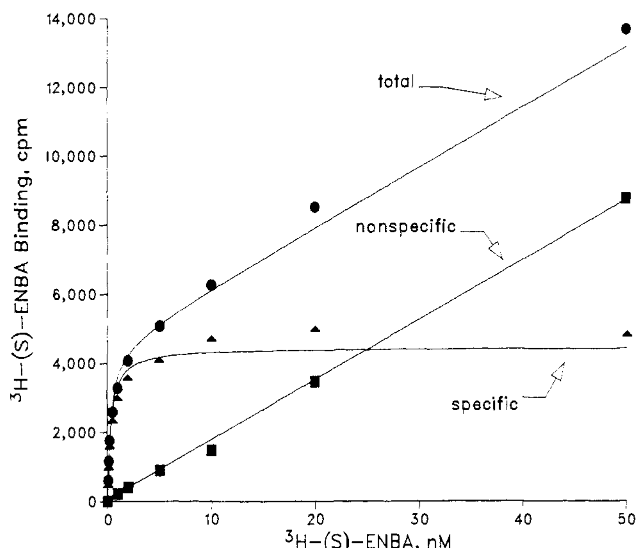

Figure 2. Saturation of specific [^{3}H](*S*)-ENBA binding to A_1 receptors in rat brain membranes. Binding was carried out with 5 mg original tissue wet weight of rat brain membranes in 2 mL for 1 h at 25 °C in 50 mM Tris·HCl buffer, pH 7.7, with 0.1 unit/mL adenosine deaminase (Sigma). Nonspecific binding was determined in the presence of 100 μM *R*-PIA. Binding parameters calculated from least-squares curve fitting[5] were K_d, 0.332 nM; B_{max}, 16 pmol/g wet weight; nonspecific binding, 1.74% of added radioactivity.

Encouraged by the results described above, we followed up on our earlier observations[20,21] that 5′-chloro-5′-deoxy modification of N^6-substituted adenosines can increase A_1 selectivity by selectively deteriorating A_2 potency. For instance, 5′-chloro-5′-deoxy-CPA (**6**) has the same A_1 affinity as **1** but about 3-fold better A_1 selectivity. Unlike the enhancement of A_2 affinity by 5′-ethylcarboxamide substitution, which holds for adenosine but not for N^6-modified adenosines,[22,23] the deterioration of A_2 affinity by 5′-chloro substitution appears to hold regardless of the N^6-substituent.[20,21] This led us to prepare the corresponding 5′-chloro derivative of N^6-(2-*endo*-norbornyl)adenosine (**7**).[20] As expected, this compound also showed the same affinity as **2** (0.42 nM) at the A_1 receptor, whereas its A_2 affinity was significantly lower (2100 nM versus 750 nM). Compound **7** is therefore one of the most A_1 selective compounds to be reported in the literature, and it should prove to be useful as a pharmacological tool. We have

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(18) Jacobson, K. A. In *The Adenosine Receptors*; Cooper, D. M. F., Londos, C., Eds.; A. R. Liss: New York, 1988; p 1.
(19) Bruns, R. F.; Fergus, J. H.; Badger, E. W.; Bristol, J. A.; Santay, L. A.; Hartman, J. D.; Hays, S. J.; Huang, C. C. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1987**, *335*, 59.
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(23) Bridges, A. J.; Bruns, R. F.; Ortwine, D. F.; Priebe, S. R.; Szotek, D. S.; Trivedi, B. K. *J. Med. Chem.* **1988**, *31*, 1282.

already used compound **7** to mask out the A_1 component of [^{3}H]NECA binding in tissues such as dog or human brain where CPA does not appear to be sufficiently selective for this purpose.[24]

Separation by cyclodextrin HPLC of the individual diastereomers of **7** afforded compounds **8** and **9** (compound **9** eluted before **8**). Compound **8** is the most potent (K_i = 0.24 nM) and selective (16000-fold) agonist for the A_1 receptor to be reported to date. As anticipated, the other diastereomer (**9**) is less active and less selective for the A_1 receptor.

In summary, in this study we have identified novel N^6-[2.2.1]bicycloalkyladenosines with unusually high potency and selectivity for the adenosine A_1 receptor. Compounds **4**, **7**, and **8** should serve as important tools for further characterization of subpopulations of adenosine receptor subtypes in various tissues.

Acknowledgment. We thank James Fergus for [^{3}H]-CHA and [^{3}H](*S*)-ENBA binding data, Gina Lu for [^{3}H]NECA binding data, and Jon Hartman and Che Huang for purification of [^{3}H](*S*)-ENBA.

(24) Bruns, R. F.; Lu, G. H., unpublished observations.
(25) Hamilton, H. W.; Johnson, S., personal communication.
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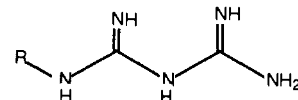
Perfluoro-*N*-[4-(1*H*-tetrazol-5-ylmethyl)phenyl]alkanamides. A New Class of Oral Antidiabetic Agents[§]

Sir:

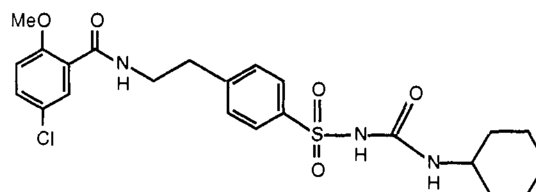
The withdrawal of the biguanides from the U.S. market in 1977 has left only one class of oral hypoglycemic agent, the sulfonylureas, for the treatment of non-insulin-dependent diabetes mellitus (NIDDM) in this country.[1] Despite an improvement of 250-fold in potency over the last 33 years (e.g. glibenclamide), the sulfonylureas are still afflicted with the serious and sometimes fatal problem of drug-induced hypoglycemia,[2] apparently the result of hyperinsulinemia.

In 1982 Takeda revealed a potential alternative to the insulin-releasing sulfonylureas. Ciglitazone[3] represents a series of lipophilic benzylthiazolidinediones that lower plasma glucose in NIDDM but not insulin-dependent (IDDM) or nondiabetic animal models. Unlike insulin secretagogues such as glibenclamide, ciglitazone attenuates hyperinsulinemia and does not promote hypoglycemic action beyond normalization.[4] In addition, ciglitazone improves oral glucose tolerance (OGT) and effects positive changes in lipid metabolism. Recently, Takeda,[5] Sankyo,[6] Wyeth,[7] and Pfizer[8] have disclosed variants of the lipophilic portion of the thiazolidinediones.

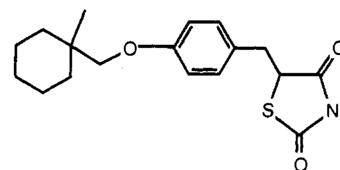


biguanides: R = Me; metformin

R = $Ph(CH_2)_2$; phenformin

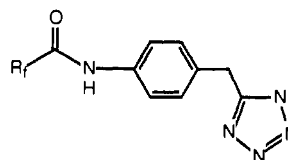


glibenclamide



ciglitazone

We report here the first example of a non-thiazolidinedione-containing oral antidiabetic series, perfluoro anilides **1**, that possess a pharmacologic profile similar to that of ciglitazone in two genetic animal models of NIDDM: obese (ob/ob) and diabetic (db/db) mice.[9]



1 (R_f = C_1-C_{10} perfluoroalkyl)

The perfluorinated anilides **1** (**a–j**, Table I) were readily prepared in a two-step procedure (Scheme I). 4-Aminobenzyl cyanide (Aldrich) and the corresponding commercially available perfluoro acid or derivative were coupled to give the 4-cyanomethyl perfluoro anilides. Treatment of the nitriles with sodium azide and ammonium chloride in hot DMF gave tetrazoles **1**.

Initially we found that perfluorobutyramide **1c** (Table I), like ciglitazone, normalized plasma glucose and insulin

§ This work was presented in part before the Division of Medicinal Chemistry, 196th National Meeting of the American Chemical Society, Los Angeles, CA, September 1988.

(1) The National Diabetes Data Group estimates that 90–95% of the ~5.8 million diagnosed diabetics in the USA are NIDDM; *Diabetes in America, 1985*, National Institutes of Health: Bethesda, MD.
(2) Ferner, R. E.; Neil, H. A. W. *Br. Med. J. 296*, 949.
(3) (a) Ciglitazone synthesis and SAR: Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3580. (b) Pharmacology: Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H.; Suzuoki, Z. *Diabetes* **1983**, *32*, 804. Chang, A. Y.; Wyse, B. M.; Gilchrist, B. J.; Peterson, T.; Diani, A. R. *Ibid.* 830, and 839. (c) Clinical results: Baba, S.; Doi, K.; Matsuura, M.; Kawora, A.; Tanaka, T.; Ooe, M. *Diabetes* **1982**, *31* (Suppl. 2), 77A.
(4) We use "normalization" in diabetic animal models to mean the level of glucose found in lean nondiabetic littermates.
(5) Meguro, K.; Fujita, T. U.S. Patent 4687777, 1987, and EP-117-353-A, EP-208-420-A, 1985 (DERWENT 87-009064/O2).
(6) Yoshioka, T.; Kitazawa, G.; Kurumada, T.; Mitsuo, Y.; Hasegawa, K.; Fujita, T. AU-8654-122-A, 1985, and JP 035325, 1985 (DERWENT 86-278945/43).
(7) Kees, K.; Cheeseman, R. U.S. Patent 4728739, 1988.
(8) Eggler, J.; Holland, G.; Johnson, M.; Volkmann, R. U.S. Patent 4738972, 1988.
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(10) (a) Control (glucose (mg/dL); insulin (μunit/mL)), 194 ± 9, 139 ± 6; ciglitazone, 114 ± 9, 50 ± 5; **1c**, 117 ± 7, 48 ± 7. (b) At 300 mg/kg per day × 4 days; control, 178 ± 18, 206 ± 16; ciglitazone, 92 ± 8, 116 ± 18; **1c**, 90 ± 4, 61 ± 5.

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