2,6,8-Trisubstituted 1-Deazapurines as Adenosine Receptor Antagonists

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In this study we developed a refined pharmacophore model for antagonists of the human adenosine A_1 receptor, based on features of known pyrimidine and purine derivatives. The adoption of these updated criteria assisted us in synthesizing a series of 1-deazapurines with consistently high affinity as inverse agonists for the adenosine A_1 receptor. These 1-deazapurines (otherwise known as 3*H*-imidazo[4,5-*b*]pyridines) were substituted at their 2- and 6-positions, yielding a series with five of the derivatives displaying K_i values in the subnanomolar range. The most potent of these, compound **10** (LUF 5978), displayed an affinity of 0.55 nM at the human adenosine A_1 receptor with >300-fold and 45-fold selectivity toward A_{2A} and A_3 receptors, respectively. Compound **14** (LUF 5981, K_i = 0.90 nM) appeared to have the best overall selectivity with respect to adenosine A_{2A} (>200-fold) and A_3 (700-fold) receptors.

Introduction

The adenosine A_1 receptor is the most extensively researched of the family of adenosine receptors, which also include the A_{2A}, A_{2B}, and A_3 receptors. Many different classes of ligands have been designed, synthesized, and tested at the A_1 receptor as antagonists, and these encompass all kinds of different mono-, bi-, tri-, and even quadricyclic mostly nitrogen-containing aromatic compounds.[1]

In a previous publication[2] we showed how the purine skeleton could be substituted in accordance with the pharmacophore shown in Figure 1, resulting in a series of ligands with particularly good affinity for the adenosine A_1 receptor. The purine derivatives that were devised in that particular publication came about as a direct result of their structural similarity to a series of 4-amido-2,6-diphenylpyrimidines.[3] However, the 4-amido-2,6-diphenylpyrimidines were eclipsed by the analogous 2-amido-4,6-diphenylpyrimidines in terms of displaying similar levels of affinity and better selectivity for the adenosine A_1 receptor. By extrapolation of the 2-amido-4,6-diphenylpyrimidines in the same manner as the 4-amido-2,6-diphenylpyrimidines, 5,7-diphenyl-3,3a-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidines are fashioned (Figure 1b). The specifications of the model still demand only the fulfilment of three hydrogen-bonding regions; thus it is reasonable to assume that the extra nitrogen atom in the triazolopyrimidine ring will not play an important role in the affinity of the compound for the A_1 receptor, in terms of hydrogen bonding. Moreover, this nitrogen disturbs the planarity of the central core; therefore, its replacement with a carbon is more compliant with the model. The removal of this nitrogen also somewhat reduces the polar surface area of the molecule, known to be important for bioavailability, from approximately 46 to 41 Å^2. This principle of bioisosteric replacement has found wide application in the search for novel scaffolds for adenosine A_1 receptor antagonists (see ref 1 and references therein).

Trivially, the resulting 3*H*-imidazo[4,5-*b*]pyridine (Figure 1c) is also known as 1-deazapurine (and 4-azabenzimidazole). Figure 2 shows the numbering about the ring for the systematic nomenclature (a) and the numbering system adopted from the purines (b). In this paper, the trivial name and numbering system are used for the purpose of easy comparison to purines. The new stipulations of the model disclosed in the previous publication require the L2 lipophilic group (here labeled as R^3) to be a branched alkyl group, with a chain length of 2−3 carbons. In this paper, further refinements to the pharmacophore outlined are investigated and confirmed.

Results and Discussion

Chemistry. Synthesis of the 1-deazapurines was less than straightforward, with little or no precedent for creating compounds with two aromatic substituents in the 2- and 6- positions of the ring. Several strategies were investigated.

The first option focuses on incorporating groups on the pyridine part of the 1-deazapurine system as the initial phase of the synthesis. The second route requires the introduction of the 8-substituent in an intact functional deazapurine ring. Both methods should ideally provide intermediates that allow late-stage variation of the three positions of interest, C2, C6 and C8.

First, the route exploiting the commercially available and intact 1-deazapurine was undertaken (Scheme 1). There is precedent to form 2,6-disubstituted 1-deazapurines where the substituents are often amines,[4] sulfides,[5] halogens,[6,7] or mixtures of these. Cristalli et al.[8] have reported on the synthesis of 1-deaza analogues of 2-chloroadenosine from the commercially available unsubstituted intact 1-deazapurine species. This procedure starts with the manipulation of the reactivity about the pyridine ring allowing chloro substitution of C2 and C6, leading to the possibility of further functional group interconversions. Attempts were then made to functionalize the 8-position of the 1-deazapurine ring. The relatively acidic N9 proton was found to disrupt the intended reactions and thus protection of this group was necessary (studies have also shown that N3 and N7 substitutions occur as minor isomers in these reactions). This was performed with a benzyl moiety. Unfortunately, the stability of this benzyl group presented difficulties in isolating the target compounds; standard catalytic hydrogenation with H_2 was

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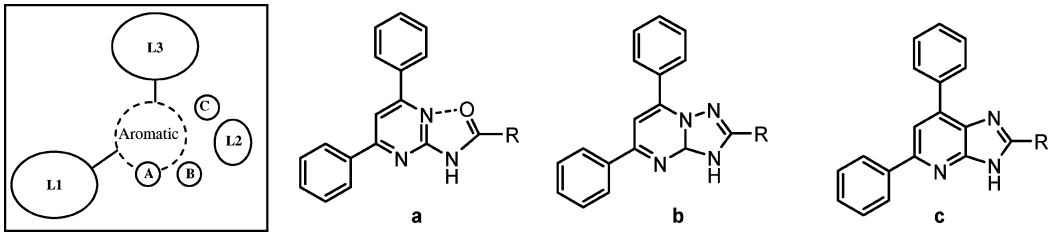


Figure 1. (Left) Refined model: A and B represent H-bond accepting and donating regions, repectively. An H-bond acceptor is denoted by C. Three lipophilic domains are represented by L1, L2, and L3. (a) Fixation of the hydrogen-bond acceptor at the top of the 2-amido-4,6-diphenylpyrimidine molecule; (b) change of the heteroatom to accomplish this fixation, resulting in a 5,7-diphenyl-3,3a-dihydro-[1,2,4]triazolo-[1,5-*a*]pyrimidine; (c) 2,6-diphenyl-1-deazapurine.

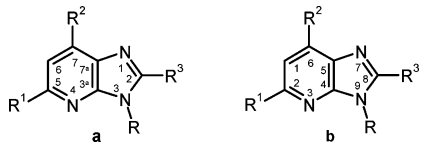
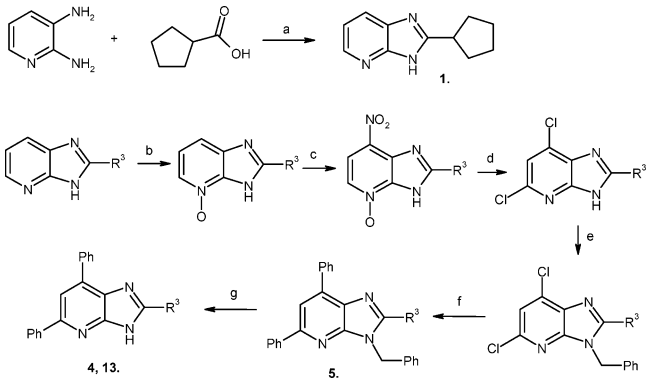


Figure 2. (a) Systematic (IUPAC) name: 3*H*-imidazo[4,5-*b*]pyridine with the corresponding numbering system; (b) 1-deazapurine and the purine numbering system.

Scheme 1[a]



[a] Reagents: (a) Polyphosphoric acid; (b) H_2O_2, 70 °C, 19 h; (c) HNO_3, 90 °C, 3 h; (d) $POCl_3$, DMF, reflux, 2 h; (e) benzyl chloride, DMF; (f) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene, microwave 150 °C, 30 min; (g) $Pd(OH)_2$/C, ammonium formate, EtOH, microwave 150 °C, 20 min.

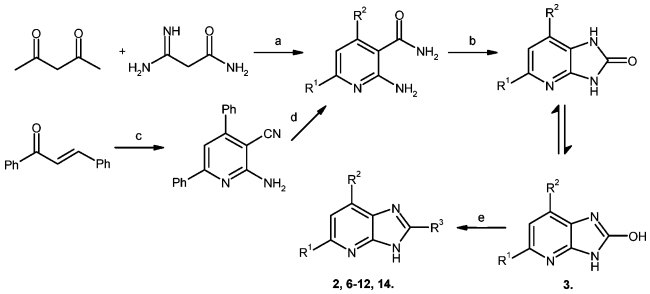
sluggish, as was microwave-assisted catalytic transfer hydrogenation, despite reaching pressures of more than 20 bar at 150 °C.

Three compounds were synthesized following this method detailed in Scheme 1, the unsubstituted forms (**4** and **5**, R^3 = H), where the deazapurine was already commercially available, and 8-cyclopentyl-2,6-diphenyldeazapurine (**13**). The intermediate 2,6-dichloro-1-deazapurine was benzyl−protected; subsequent aryl coupling gave **5** and deprotection yielded compound **4**. The third derivative was made by reacting 2,3-diaminopyridine with cyclopentylcarboxylic acid in the presence of PPA. The product, 8-cyclopentyl-1-deazapurine, was then subjected to the first three steps described by Cristalli et al.[8] The inclusion of a C8 substituent dramatically changed the reactivity of the species and each of the subsequent steps was significantly worse than the unsubstituted equivalent, in terms of yields and ease of handling.

Structure−activity relationships revealed from the series detailed in previous publications[2,3] suggest that the most favorable target compounds at C8 are directly linked alkyl groups. However, Suzuki reaction on 8-iodo-1-deazapurines failed, and the reaction of alkyl iodides as the electrophile of choice to quench 8-lithiated deazapurines gave very low yields.

Attention was thus turned to another alternative procedure that seemed to offer a more encouraging pathway. In the process

Scheme 2[a]

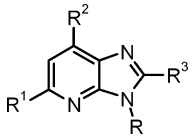


[a] Reagents: (a) KOH, MeOH, RT; (b) KOH, $PhI(OAc)_2$, MeOH, RT; (c) NH_4OAc, EtOH, Δ; (d) KOH, EtOH, Δ; (e) $MgCl_2$, R^3CO_2H, $R^3COOCOR^3$, microwave.

development of angiotensin II antagonists at Merck, a new approach to the key intermediate MK-996, benzylated imidazolutidine, was investigated.[9,10] Malonamamidine was condensed with a β-diketone to provide a nicotinamide (Scheme 2). The Hoffman rearrangement of this nicotinamide resulted in the isocyanate, which then reacted intramolecularly with the 2-amino group to give the urea. This compound was ingeniously found to react with a mixture of a carboxylic acid and anhydride in the presence of $MgCl_2$ to give 8-alkyl-2,6-dimethyl-1-deazapurines. Compound **2** (R^1 = R^2 = Me, R^3 = Et) was prepared in this way. Our fear for utilizing this reaction pathway, similarly to many previous attempts to make 2,6-diaryl-1-deazapurine analogues, was that the desired diaryl substituents would have a major (negative) influence on the reactivity of first the diketone, followed by each of the subsequent steps. As mentioned in a publication by Batt and Houghton,[11] the condensation of dibenzoylmethane with nitroacetamide to produce 2-amino-3-nitro-4,6-diphenylpyridine failed due to the unreactive nature of the diketone. In this case the ring closure of dibenzoylmethane with malonamamidine was extremely low-yielding (6%). We thus sought the construction of the nicotinamide in a different manner. A two-step approach employing a chalcone and malononitrile in the presence of ammonium acetate formed a cyanopyridine, which upon hydrolysis gave the target nicotinamide (Scheme 2). This route also allows regioselective substitution about the pyridine ring if so desired, a feature not possible in the original route with the diketone. The Hoffman rearrangement proceeded without any significant problems and a substantial amount of the 2,6-diphenyl-8-hydroxy-1-deazapurine (**3**) could be made.

Substitution of the 8-OH was performed as described by Senanayake et al.[9] by use of a mixture of an acid and the corresponding anhydride in the presence of $MgCl_2$. The one main difference introduced was the use of the microwave for this procedure. Aromatic substituents at the 2- and 6-positions of the 1-deazapurine ring significantly lower its reactivity, and the employment of conventional heating methods resulted in very low yields and considerable quantities of byproducts, which

Table 1. Affinities of the 2,6,8-Trisubstituted 1-Deazapurines **1**−**14** in Radioligand Binding Assays of Human Adenosine Receptors



					K_i (nM) or % disp[a]		
	R^1	R^2	R^3	R	hA_1[b]	hA_{2A}[c]	hA_3[d]
1	H	H	cPent	H	6%	3%	0%
2	Me	Me	Et	H	101 ± 26	8%	49%
3	Ph	Ph	OH	H	8.6 ± 3	192 ± 97	262 ± 25
4	Ph	Ph	H	H	1.2 ± 0.3	39 ± 9.0	180 ± 70
5	Ph	Ph	H	Bn	38%	2%	15%
6	Ph	Ph	Me	H	14 ± 5	375 ± 28	61 ± 14
7	Ph	Ph	Et	H	2.4 ± 0.4	177 ± 13	8.5 ± 6
8	Ph	Ph	Pr	H	2.5 ± 0.2	114 ± 34	69 ± 22
9 (LUF 5980)	Ph	Ph	iPr	H	0.61 ± 0.04	230 ± 40	7.3 ± 2
10 (LUF 5978)	Ph	Ph	2-MePr	H	0.55 ± 0.3	189 ± 23	25 ± 16
11 (LUF 5983)	Ph	Ph	1-EtPr	H	0.87 ± 0.1	247 ± 61	171 ± 49
12	Ph	Ph	tBu	H	5.5 ± 2	1055 ± 129	115 ± 15
13 (LUF 5816)	Ph	Ph	cPent	H	0.62 ± 0.3	49%	6.9 ± 1
14 (LUF 5981)	Ph	Ph	cHex	H	0.90 ± 0.2	194 ± 57	637 ± 71

[a] K_i ± SEM ($n = 3$) or % displacement ($n = 2$) of specific binding at 1 μM concentrations. [b] Displacement of specific [^{3}H]DPCPX binding in CHO cell membranes expressing human adenosine A_1 receptors or % displacement. [c] Displacement of specific [^{3}H]ZM 241385 binding in HEK 293 cell membranes expressing human adenosine A_{2A} receptors or % displacement. [d] Displacement of specific [^{125}I]AB-MECA binding in HEK 293 cell membranes expressing human adenosine A_3 receptors or % displacement.

made the final product difficult to isolate. By use of the microwave, rapid heating of the sealed vessel quickly created very high temperatures and elevated pressures. This method improved the synthesis dramatically, leading to much better yields, few byproducts as observed by thin-layer chromatography (TLC), and thus easier isolation of the final target products **6**−**12** and **14**.

The carboxylic acid anhydrides used were all commercially available, except for the cyclohexyl variant. This was synthesized according to a method described by Kazemi et al.[12] employing tosyl choride and potassium carbonate with minimal use of solvents. To remove the excess acid/anhydride reagents, the crude material was distilled azeotropically with water. Removal of the last traces of water was subsequently performed by azeotropic distillation with dry toluene.

Structure−Activity Relationships. The compounds **1**−**14** were tested in radioligand binding assays, and the results of these assays are presented in Table 1. It is clear that substitution at C2 (R^1) and C6 (R^2) of the 1-deazapurines is vital for affinity at the adenosine receptors. Compound **1**, lacking substituents at these positions, displays no affinity for the A_1, A_{2A}, or A_3 adenosine receptors. The π-electrons of the phenyl groups at these two positions provide seemingly essential interactions with the receptor pocket, although alkyl groups may afford some contact points for interaction, that is, **2** [$K_i(hA_1) = 101$ nM]. Further substitution at the phenyl rings was not conducted due to the negative outcome obtained in the pyrimidine and the purine series.[2,3]

Of the 2,6-diphenyl compounds, the derivative with the unsubstituted C8 position (**4**) was an encouraging start with an affinity of 1 nM at the A_1 receptor. The N9-substituted compound (**5**) again showed that the free proton is necessary as a hydrogen-bond donor from the ligand to the receptor. The C8-substituent was shown to have a drastic influence on the affinity (and selectivity) for the A_1 receptor. The intermediate compound of the final route (Scheme 2), **3**, shows that although an alkyl group is more tolerated at this position, the hydrogen-bonding potential of the hydroxyl group does not disturb too greatly the binding affinity of the deazapurines. Ethyl [**7**, $K_i(hA_1) = 2.4$ nM] and propyl [**8**, $K_i(hA_1) = 2.5$ nM] substitution confirmed the requisites of the model, in that as groups with a chain length of either 2 or 3 carbons, they were more effective than the methyl variant [**6**, $K_i(hA_1) = 14$ nM]. Fortifying the claims of the refined model, the predicted secondary-branched substituents possessed by far the greatest affinity for the adenosine A_1 receptor (**9**−**11**, **13**, and **14**) with subnanomolar K_i values. The single tertiary-branched variety, the *t*-butyl derivative (**12**, $K_i = 5.5$ nM), displayed a 9-fold loss of potency at the A_1 receptor compared to the isopropyl derivative (**9**).

The selectivity of the 1-deazapurines for the A_1 over the A_{2A} receptor was better than that of the analogous purine compounds. Derivatives **4**, **9**, **13**, and **14** had selectivity ratios of 33, 377, >1600, and 215, respectively, compared to 13, 180, 190, and 161 from the analogous purines.[2] The binding affinity of the deazapurines at the adenosine A_3 receptor was also shown to be worse than those measured at the A_1 receptor. Namely, compounds **11** and **14** with selectivity ratios of 199 and 718, respectively, were significant examples. From analysis of the A_3 affinity values of the whole series, it seems that there is an obvious optimal two-carbon chain length. Of the simple unbranched alkyl groups (**6**−**8**), the ethyl moiety was easily the most potent at this receptor. Similarly, in the branched alkyl series (**9**−**11**) the iPr with an affinity of 7 nM was the best compound compared to the 2-methylpropyl (**10**, $K_i = 25$ nM) and 1-ethylpropyl (**11**, $K_i = 173$ nM). Of the two cycloalkyl variants made, the cyclopentyl (**13**) was also more influential at the A_3 receptor, with an affinity of 6.9 nM, than the cyclohexyl group (**14**) with its three-carbon chain length ($K_i = 646$ nM). Finally, we also tested the most potent compounds (**9**−**11**, **13**, and **14**) in a radioligand binding assay for the human adenosine A_{2B} receptor with [^{3}H]MRS1754[a] as the radioligand. The compounds were only modestly active in this assay with affinities between 300 and 3000 nM (data not shown).

The recent discoveries involving non-adenosine agonists[13,14] required our attention to also focus on performing functional assays at the adenosine A_1 receptor with these compounds. The five most potent compounds, **9**, **10**, **11**, **13** and **14** ($K_i = 0.61$, 0.55, 0.87, 0.62, and 0.90 nM, respectively) were selected and tested in cAMP assays to assess their ability to modulate adenosine A_1 receptor activity. As the A_1 receptor is coupled to an inhibitory G protein, forskolin was used to induce the production of cAMP. In Figure 3 the effects of a number of reference ligands (CPA, DPCPX, and N0840) and the above-mentioned compounds were assessed on this forskolin-stimulated cAMP production. Whereas the agonist CPA inhibited the production of cAMP at both 100 nM and 1 μM, DPCPX (1 μM) and N-0840 (100 μM) further stimulated the forskolin effect. N-0840, which has been reported in [^{35}S]GTPγS binding experiments to be a neutral antagonist, apparently behaved as an inverse agonist like DPCPX in this whole cell cAMP assay. This may be the logical consequence of the different read-out at two levels of the receptor signaling complex, G protein binding and adenylate cyclase activation, respectively. Compounds **10**, **11**, **13**, and **14**, at concentrations of at least 100K_i, were all shown to increase the amount of cAMP present to levels

[a] Abbreviations: DPCPX, 1,3-dipropyl-8-cyclopentylxanthine; N-0840, N^6-cyclopentyl-9-methyladenine; CPA, N^6-cyclopentyladenosine; ZM241385, 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-*a*][1,3,5]triazin-5-ylamino]ethyl)phenol; AB-MECA, N^6-(4-aminobenzyl)adenosine 5′-methyluronamide; MRS1754, *N*-(4-cyanophenyl)-2-[4-(2,6-dioxo-1,3-dipropyl-2,3,4,5,6,7-hexahydro-1*H*-purin-8-yl)-phenoxy]acetamide.

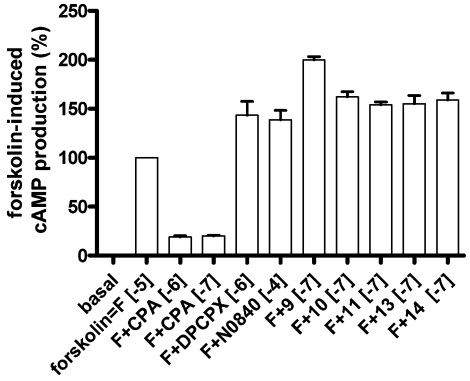


Figure 3. Functional assays performed with compounds **9**, **10**, **11**, **13**, and **14** (final concentration 100 nM) on the human adenosine A_1 receptor. The effects of the compounds in the sole presence of forskolin (10 μM) are represented. 100% cAMP (i.e., in the presence of 10 μM forskolin) amounts to approximately 15 pmol/well. 0% cAMP (control values in the absence of forskolin) corresponds to approximately 1.3 pmol/well. Data are the mean ± SEM of three experiments.

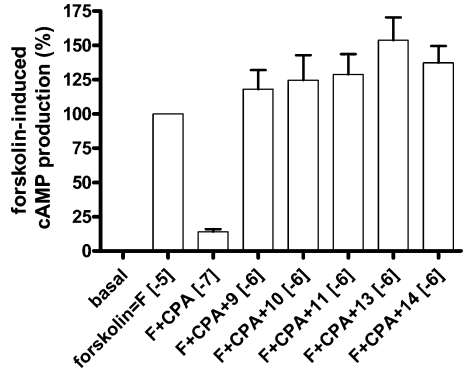


Figure 4. Functional assays performed with compounds **9**, **10**, **11**, **13**, and **14** (final concentration 1 μM) on the human adenosine A_1 receptor. The effects of the compounds in the simultaneous presence of forskolin (10 μM) and CPA (100 nM) are represented. 100% cAMP (i.e., in the presence of 10 μM forskolin) amounts to approximately 15 pmol/well. 0% cAMP (control values in the absence of forskolin) corresponds to approximately 1.3 pmol per well. Data are the mean ± SEM of three experiments.

comparable to DPCPX, whereas compound **9** appeared to induce an even greater effect. In the combined presence of forskolin (10 μM) and CPA (100 nM) the five compounds, all tested at 1 μM, antagonized the action of CPA (Figure 4). Compound **14** was studied in more detail by recording a concentration−effect curve, again in the presence of 10 μM forskolin and 100 nM CPA (Figure 5 for a typical experiment), yielding an IC_{50} value of 1.7 ± 0.3 μM ($n = 3$) for this deazapurine derivative. Note that the maximum effect of compound **14** was 2.5 times that of forskolin. It can therefore be stated that the 1-deazapurines described in this paper are of an inverse agonistic nature.

Conclusions

This series of 1-deazapurines confirms that the subtle refinements to the model in the previous paper on similar purine derivatives[2] are substantial enough to produce compounds with very good affinity for the adenosine A_1 receptor. In particular, compound **10** with a K_i value of 0.55 nM at the A_1 receptor is noteworthy in terms of affinity. However, compound **14** with a K_i value of 0.90 nM and selectivity ratios over the A_{2A} and A_3 receptors of 216 and 718, respectively, is overall the most interesting 1-deazapurine derivative presented in this paper. From the data obtained in the functional cAMP assay, we conclude that most tested compounds are best characterized as being inverse agonists.

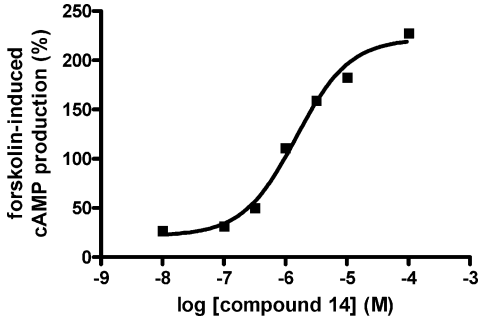


Figure 5. Concentration−effect relationship for compound **14** in the presence of forskolin (10 μM) and CPA (100 nM) on the human adenosine A_1 receptor. 100% cAMP (i.e., in the presence of 10 μM forskolin) amounts to approximately 15 pmol/well. 0% cAMP (control values in the absence of forskolin) corresponds to approximately 1.3 pmol/well. A typical experiment with data points performed in duplicate is shown.

Experimental Section

Materials and Methods. All reagents used were obtained from commercial sources and all solvents were of an analytical grade. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^{1}H NMR, 200 MHz; ^{13}C NMR, 50.29 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in δ (ppm) and the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Microwave reactions were performed on an Emrys Optimizer (Biotage AB). The wattage was automatically adjusted so as to maintain the desired temperature. Melting points were determined on a Büchi melting point apparatus and are uncorrected. The value stated for each compound is the initial temperature at which the compound begins to melt. Elemental analyses were performed by the Leiden Institute of Chemistry and are within 0.4% of the theoretical values unless otherwise stated. Reactions were routinely monitored by TLC on Merck silica gel F_{254} plates.

1-Deazapurine *N*-Oxide.[15] To a solution of 4-azabenzimidazole (1-deazapurine) (1.3 g, 10.9 mmol) in acetic acid (6.5 mL) was added H_2O_2 (35% in H_2O) (1.2 mL), and the mixture was stirred at 70 °C for 3 h. A further aliquot of H_2O_2 was then added (0.9 mL) and the reaction was heated at 60 °C for 16 h. The reaction mixture was allowed to cool to room temperature (RT), upon which a precipitate formed. This was filtered to give a crystalline product (96%). ^{1}H NMR δ (MeOD) 8.45 (s, 1H, C8-*H*), 8.34 (d, 1H, J = 7.3 Hz, C6-*H*), 7.87 (d, 1H, J = 7.3 Hz, *C*2-*H*), 7.34−7.29 (m, 1H, C1-*H*).

6-Nitro-1-deazapurine *N*-Oxide.[15] 1-Deazapurine *N*-oxide (1.4 g, 10.4 mmol) was dissolved in trifluoroacetic acid (TFA) (9.7 mL, 125 mmol, 12 equiv) at 0 °C, and to this was added fuming HNO_3 (6.6 mL, 157 mmol, 15 equiv). The reaction mixture was then heated at 90 °C for 3 h and left to cool to RT. Only slight precipitation occurred; thus the mixture was neutralized carefully with concentrated NH_4OH, revealing further product. This was filtered and the yellow solids were dried in vacuo at 40 °C (67%). ^{1}H NMR δ (DMSO) 8.27 (s, 1H, C8-*H*), 8.10 (d, 1H, J = 7.3 Hz, C2-*H*), 7.89 (d, 1H, J = 6.58 Hz, C1-*H*).

2,6-Dichloro-1-deazapurine.[8] 6-Nitro-1-deazapurine *N*-oxide (1.2 g, 6.66 mmol) was added portionwise to an ice-cooled solution of $POCl_3$ (20 mL) in *N*,*N*-dimethylformamide (DMF) (10 mL). The reaction mixture was then refluxed for 2 h, allowed to cool, and then added slowly to crushed ice. After careful neutralization with 2 M NaOH solution, the product was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with H_2O (3 × 100 mL), dried over $MgSO_4$, and concentrated to give an off-white solid (80%). ^{1}H NMR δ (MeOD): 8.45 (s, 1H, C8-*H*), 7.46 (s, 1H, C1-*H*).

2,6-Dichloro-9-benzyl-1-deazapurine. 2,6-Dichloro-1-deazapurine (0.34 g, 1.80 mmol) was dissolved in DMF (15 mL). K_2CO_3 (0.77 g, 5.60 mmol, 3.1 equiv) was added and the mixture was stirred for 30 min. Benzyl chloride (0.29 mL, 2.53 mmol, 1.4 equiv) was then added and the reaction mixture was stirred for 16 h at RT. The solids were filtered off and the filtrate was separated between EtOAc (100 mL) and H_2O (100 mL). The aqueous layer was then further extracted with EtOAc (2 × 50 mL), the combined organic layers were washed with H_2O (3 × 150 mL) and dried over $MgSO_4$, and the solvents were evaporated in vacuo to give a yellow oil. This crude product was chromatographed on SiO_2 and eluted with a mixture of petroleum ether (bp 40−60 °C) and EtOAc (gradient elution 5:1 to 2:1) to give the title compound (42%). ^{1}H NMR δ ($CDCl_3$) 8.02 (s, 1H, C8-*H*), 7.35−7.30 (m, 6H, Ar), 5.42 (s, 2H, CH_2).

2,6-Diphenyl-9-benzyl-1-deazapurine (5). 2,6-Dichloro-9-benzyl-1-deazapurine (150 mg, 0.54 mmol), phenylboronic acid (197 mg, 1.62 mmol, 3 equiv), $Pd(PPh_3)_4$ (32 mg, 0.03 mmol, 0.05 equiv), K_2CO_3 (112 mg, 0.81 mmol, 1.5 equiv), and toluene (5 mL) were heated in a sealed vessel in the microwave for 30 min at 150 °C. The reaction mixture was then filtered and the filtrate was preabsorbed onto SiO_2 and chromatographed, eluted with petroleum ether (bp 40−60 °C) and EtOAc (gradient elution 5:1 to 2:1). A white solid was obtained (91%), which was further recrystallized from acetonitrile: mp 143 °C; ^{1}H NMR δ ($CDCl_3$) 8.17−8.13 (m, 4H, Ph), 8.04 (s, 1H, C8-*H*), 7.89 (s, 1H, C1-*H*), 7.56−7.29 (m, 11H, Ph), 5.50 (s, 2H, CH_2); ^{13}C NMR δ ($CDCl_3$) 152.8, 148.0, 143.8, 140.3, 139.7, 136.2, 136.0, 132.0, 129.1, 128.8, 128.6, 128.1, 127.9, 127.1, 114.1, 47.0; MS (ES^+) 362.0 Da; Anal. ($C_{25}H_{19}N_3 \cdot 0.2CH_3CN$) C, H, N.

2,6-Diphenyl-1-deazapurine (4). 2,6-Diphenyl-9-benzyl-1-deazapurine (100 mg, 0.233 mmol), $Pd(OH)_2$/C (20% Pd, Pearlman's catalyst) (20 mg), ammonium formate (147 mg, 2.3 mmol, 10 equiv), and EtOH (3 mL) were heated in a sealed vessel in the microwave at 140 °C for 5 min (pressure reached 11 bar). Upon cooling, the septum was pierced carefully to release the remaining pressure trapped in the vessel. TLC showed only a slight trace of a new product. Further ammonium formate was added (300 mg), and the vessel was resealed and heated at 150 °C for 15 min (pressure reached 22 bar). The reaction mixture was preabsorbed onto SiO_2 and chromatographed, eluted with CH_2Cl_2 and MeOH (gradient elution 98:2 to 90:10). A white solid was obtained (41%): mp 259−261 °C; ^{1}H NMR δ (DMSO) 8.52 (s, 1H, C8-*H*), 8.28−8.02 (m, 5H, Ph + C1-*H*), 7.65−7.41 (m, 6H, Ph); ^{13}C NMR δ (DMSO) 163.0, 156.6, 156.3, 151.6, 139.4, 135.8, 29.0, 128.7, 126.9; MS (ES^+) 272.1 Da; Anal. ($C_{18}H_{13}N_3 \cdot 0.2$DMF) C, H, N.

8-Cyclopentyl-1-deazapurine (1). Polyphosphoric acid (∼5 mL) was added to 2,3-diaminopyridine (0.43 g, 3.94 mmol), followed by cyclopentylcarboxylic acid (0.52 mL, 4.73 mmol, 1.2 equiv). This was then stirred at 100 °C for 5 h, cooled in an ice−water bath to 0 °C, and neutralized carefully with concentrated NH_4OH. The product was extracted with EtOAc (3 × 50 mL), and the organic phases were dried over $MgSO_4$ and then concentrated. Chromatography on SiO_2, eluting with CH_2Cl_2 and MeOH (gradient elution 98:2 to 90:10), gave an off-white solid. Recrystallization from MeOH provided the title product (10%): mp 161 °C; ^{1}H NMR δ ($CDCl_3$) 8.18 (d, 1H, 4.4 Hz, C6-*H*), 7.90 (d, 1H, J = 7.32 Hz, C2-*H*), 7.11−7.06 (m, 1H, C1-*H*), 3.36 (pent, 1H, J = 8.0 Hz, C*H*), 2.17−1.63 (m, 8H, 4CH_2); ^{13}C NMR δ (DMSO) 161.0, 149.2, 141.3, 135.0, 125.9, 117.3, 39.9, 31.8, 25.5; MS (ES^+) 188.2 Da; Anal. ($C_{11}H_{13}N_3 \cdot 0.1H_2O$) C, H, N.

8-Cyclopentyl-1-deazapurine *N*-Oxide. To a solution of 8-cyclopentyl-1-deazapurine (1.0 g, 5.51 mmol) in acetic acid (5 mL) was added H_2O_2 (35% in H_2O) (0.9 mL), and the mixture stirred at 70 °C for 3 h. A further aliquot of H_2O_2 was then added (0.7 mL), and the reaction mixture was heated at 60 °C for 16 h and then allowed to cool to RT. The reaction mixture was concentrated to approximately 1 mL, a few drops of H_2O were then added, and the oil was left to stand at room temperature, upon which precipitation occurred. The solid was collected and dried in vacuo to give a quantitative amount of the crude product. ^{1}H NMR δ (DMSO) 8.12−8.09 (d, 1H, J = 6.6 Hz, C6-*H*), 7.45−7.44 (m, 1H, C2-*H*), 7.17−7.11 (m, 1H, C1-*H*), 1.94−1.71 (m, 9H, 4CH_2 + C*H*).

9-Benzyl-8-cyclopentyl-2,6-dichloro-1-deazapurine. 8-Cyclopentyl-1-deazapurine *N*-oxide (1.1 g, 5.51 mmol) was dissolved in TFA at 0 °C. To this was added fuming HNO_3 (3.5 mL), and the mixture was heated at 90 °C for 3 h. This was allowed to cool to room temperature. Upon neutralization with concentrated NH_4OH, no precipitation occurred (unlike for the unsubstituted analogue described earlier). The solution was then concentrated to half its volume, whereby some solids appeared. This was probably inorganic matter (no UV chromophore); thus the mixture was filtered and the filtrate was collected and further concentrated. The resulting solids were taken on to the next step without further purification. These solids were dissolved in DMF (10 mL) at 0 °C, and careful addition of $POCl_3$ (25 mL) was followed by 30 min of reflux. The reaction mixture was then poured carefully onto ice (∼300 mL) and brought to pH 6−7 with 2 M NaOH. Organic material was extracted with EtOAc (3 × 150 mL) and dried ($MgSO_4$), and solvents were evaporated in vacuo. The TLC at this point showed no clear product spot; thus the crude material was again taken on to the next step without further purification. Dissolution in DMF (10 mL) was followed by the addition of K_2CO_3 (3.4 g, 0.025 mol) and benzyl chloride (1.27 mL, 11 mmol). After being stirred at RT for 48 h, the solids were filtered off. The filtrate was taken up in EtOAc (200 mL) and H_2O (200 mL) and separated. Further extraction of the aqueous layer with EtOAc (2 × 100 mL) followed. The combined organic phases were washed with H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), and concentrated to a brown oil. Chromatography on SiO_2, eluting with petroleum ether and EtOAc (gradient elution 5:1 to 3:1), resulted in a yellow oil that solidified upon standing: 140 mg, 7.4% overall yield; ^{1}H NMR δ ($CDCl_3$) 7.37−7.2 (m, 6H, Ar), 5.80 (s, 2H, CH_2), 3.00−2.80 and 2.30−1.90 (m, 9H, cyclopentyl).

9-Benzyl-8-cyclopentyl-2,6-diphenyl-1-deazapurine. 9-Benzyl-8-cyclopentyl-2,6-dichloro-1-deazapurine (140 mg, 0.39 mmol), $PhB(OH)_2$ (171 mg, 1.40 mmol, 3.5 equiv), $Pd(PPh_3)_4$ (27 mg, 0.02 mmol, 0.05 equiv), K_2CO_3 (97 mg, 0.7 mmol, 1.8 equiv), and toluene (5 mL) were heated in a sealed tube in the microwave at 150 °C for 20 min. The reaction mixture was then filtered, concentrated, and chromatographed on SiO_2, eluted with petroleum ether and EtOAc mixtures (gradient elution 10:1 to 5:1): yield 70%; ^{1}H NMR δ ($CDCl_3$) 8.25−8.21 (m, 2H, Ph), 8.07−8.02 (m, 2H, Ph), 7.86 (s, 1H, C1-*H*), 7.59−7.40 (m, 11H, Ph), 5.89 (s, 2H, CH_2), 2.86−2.78, 2.47−2.04, 1.97−1.89 (m, 9H, cyclopentyl).

8-Cyclopentyl-2,6-diphenyl-1-deazapurine (13). 9-Benzyl-8-cyclopentyl-2,6-diphenyl-1-deazapurine (40 mg, 0.093 mmol), ammonium formate (120 mg, 0.47 mmol, 10 equiv), $Pd(OH)_2$/C (20% Pd, Pearlman's catalyst) (20 mg), and EtOH (3 mL) were heated in a sealed vessel in the microwave at 140 °C for 5 min. The pressure reached 18 bar and upon cooling remained at 11 bar; this was released by piercing the septum carefully. Chromatography on SiO_2, eluting with petroleum ether and EtOAc mixtures (gradient elution 10:1 to 5:1), resulted in a white solid: yield 32%; mp 236 °C; ^{1}H NMR δ ($CDCl_3$) 8.03−7.96 (m, 3H, Ph + N*H*), 7.89 (s, 1H, C1-*H*), 7.71−7.64 (m, 2H, Ph), 7.57−7.40 (m, 6H, Ph), 3.41−3.35 (m, 1H, C*H*), 2.21−2.19 (m, 2H, CH_2), 1.99−1.95 (m, 2H, CH_2), 1.94−1.89 (m, 2H, CH_2), 1.77−1.76 (m, 2H, CH_2); ^{13}C NMR δ (MeOD + $CDCl_3$) 157.1, 144.7, 142.6, 141.1, 133.6, 133.4, 133.2, 132.2, 131.9, 131.7, 131.3, 119.6, 44.9, 37.1, 30.3; MS (ES^+): 340.3 Da; Anal. ($C_{23}H_{21}N_3 \cdot 1.2H_2O$) C, H, N.

2-Amino-4,6-dimethylnicotinamide.[10] Malonamamidine hydrochloride (1.38 g, 10 mmol, 1 equiv) was added as a solid to a solution of potassium hydroxide (0.67 g, 12 mmol, 1.2 equiv) in methanol (35 mL). 2,4-Pentanedione (1.03 mL, 10 mmol) was then added to the solution, which was stirred at RT for 24 h. Solvents were then evaporated and the crude material was chromatographed on SiO_2, eluted with CH_2Cl_2 and MeOH mixtures (gradient elution 95:5 to 80:20): yield 34%; white solid; ^{1}H NMR δ (MeOD) 6.43 (s, 1H, py-*H*), 2.28 (s, 6H, 2CH_3).

2,6-Dimethyl-8-hydroxy-1-deazapurine.[10] 2-Amino-4,6-dimethylnicotinamide (0.56 g, 3.4 mmol) was dissolved in MeOH (12 mL). To this was added KOH (0.68 g, 12 mmol, 3.5 equiv) and MeOH (10 mL). The mixture was stirred for 30 min before being cooled to −5 °C. Iodobenzene diacetate was then added (1.09 g, 3.4 mmol, 1 equiv) and the mixture allowed to warm to RT overnight. The crude solid was collected by filtration and purified by chromatography on SiO_2, eluted with CH_2Cl_2 and MeOH mixtures (gradient elution 95:5 to 80:20): yield 48%; ^{1}H NMR δ (DMSO) 6.64 (s, 1H, py-*H*), 2.34 (s, 3H, CH_3), 2.23 (s, 3H, CH_3).

2,6-Dimethyl-8-ethyl-1-deazapurine (2).[10] 2,6-Dimethyl-8-hydroxy-1-deazapurine (0.27 g, 1.6 mmol) was added to a mixture of propionic acid (2.3 mL, 31 mmol, 19 equiv) and propionic anhydride (2.3 mL, 18 mmol, 11 equiv). $MgCl_2$ (0.16 mg, 1.6 mmol, 1 equiv) was added and the mixture was heated at 120 °C for 16 h. The reaction mixture was allowed to cool to approximately 60 °C, and MeOH (3 mL) was added. After being stirred for 10 min, the mixture was evaporated to near-dryness, followed by azeotropic distillation with H_2O to remove the excess acid/anhydride. Further codistillation with toluene removed the last traces of water. The remaining solid was purified by chromatography on SiO_2, eluted with CH_2Cl_2 and MeOH mixtures (gradient elution 99:1 to 95:5): yield 56%; mp 142−146 °C (lit. 143 °C[8] and 147−148 °C[24]); ^{1}H NMR δ (MeOD) 6.94 (s, 1H, C8-*H*), 2.92 (q, 2H, J = 7.3 Hz, CH_2), 1.40 (t, 3H, CH_3); ^{13}C NMR δ (MeOD) 158.9, 153.1, 148.8, 145.2, 136.0, 119.7, 23.4, 23.3, 16.3, 12.7; MS (ES^+) 176.2 Da; Anal. ($C_{18}H_{13}N_3$·0.7MeOH) C, H, N.

2-Amino-4,6-diphenylnicotinonitrile.[16] Chalcone (benzylideneacetophenone) (20.8 g, 100 mmol), malononitrile (6.6 g, 100 mmol, 1 equiv), and ammonium acetate (61.6 g, 800 mmol, 8 equiv) were dissolved in EtOH (15 mL) and refluxed for 5 h, whereupon no starting material was evident by TLC. The reaction mixture was allowed to cool to RT and the solvents were evaporated to leave a yellow solid. This was taken up in approximately 10 mL of hot EtOH and filtered. The remaining off-white solids were then washed with petroleum ether. This was recrystallized from hot ethanol to give white crystals: yield 40%; mp 170−174 °C; ^{1}H NMR δ (DMSO) 8.17−8.14 (m, 2H, Ph), 7.73−7.50 (m, 8H, Ph), 7.30 (s, 1H, py-*H*), 7.05 (br s, 2H, NH_2); ^{13}C NMR δ (DMSO) 160.8, 158.6, 154.9, 137.5, 137.0, 130.1, 129.5, 128.6, 128.3, 127.2, 117.0, 109.2. MS (ES^+) 272.0 Da; Anal. ($C_{18}H_{13}N_3$·0.16Hex) C, H, N.

2-Amino-4,6-diphenylnicotinamide.[17] 2-Aminodiphenylnicotinonitrile (10.8 g, 39.7 mmol) was refluxed in 20% aqueous KOH (30 mL) and EtOH (150 mL) for 22 h. Water (100 mL) was then added and the reaction mixture was allowed to stand, upon which crystallization occurred. This yellow solid was collected and dried in vacuo at 40 °C: quantitative yield; ^{1}H NMR δ (DMSO) 8.03−8.00 (m, 2H, Ph), 7.62−7.58 (m, 2H, Ph), 7.47−7.31 (m, 6H, Ph), 6.98 (s, 1H, py-*H*).

2,6-Diphenyl-8-hydroxy-1-deazapurine (3).[18] 2-Amino-4,6-diphenyl-nicotinamide (12.75 g, 44 mmol) was dissolved in a solution of KOH (6.43 g, 110 mmol, 2.5 equiv) in MeOH (300 mL) and stirred for 30 min at RT. The reaction mixture was then cooled to −5 °C, iodobenzenediacetate (14.2 g, 44 mmol, 1 equiv) was added, and the mixture was allowed to warm to room temperature and left to stand for 40 h. The reaction mixture was then further dissolved/diluted with methanol (175 mL) and H_2O (100 mL) and the solution was neutralized with 1 M HCl and then stirred with cyclohexane to remove traces of the iodobenzenediacetate. The hexane layer was then separated and the remaining MeOH/H_2O layer was concentrated to leave a yellow solid. Recrystallization from EtOH gave a white solid: yield 27%; mp 240−244 °C; ^{1}H NMR δ (DMSO) 8.02−7.98 (m, 2H, Ph), 7.71−7.67 (m, 2H, Ph), 7.60−7.36 (m, 7H, C1-*H* + Ph); ^{13}C NMR δ (DMSO) 155.2, 147.9, 145.8, 139.1, 135.2, 129.0, 128.6, 128.3, 128.0, 126.2, 120.3; MS (ES^+) 287.6 Da; Anal. ($C_{18}H_{13}N_3O$·0.4EtOH) C, H, N.

General Procedure for Preparation of 8-Alkyl-2,6-diphenyl-1-deazapurines (6−12, 14). 2,6-Diphenyl-8-hydroxy-1-deazapurine (200 mg, 0.7 mmol), an alkylcarboxylic acid (16.2 mmol, 23 equiv), the corresponding alkylcarboxylic anhydride (9.0 mmol, 13 equiv), and $MgCl_2$ (66 mg, 0.7 mmol, 1 equiv) were heated in a sealed vessel in the microwave at 180 °C for 10 h. The reaction mixture was then concentrated and codistilled with water to remove the excess acid/anhydride. Codistillation with toluene removed the last traces of water. The crude material was then purified by column chromatography on SiO_2, eluting with CH_2Cl_2 and MeOH (99:1), and then recrystallized from a $CHCl_3$/EtOH mixture. All further data for these compounds are in the Supporting Information.

Biology: Materials and Methods. [^{3}H]DPCPX and [^{125}I]AB-MECA were purchased from Amersham Biosciences (Netherlands). [^{3}H]ZM 241385 was obtained from Tocris Cookson, Ltd. (U.K.). CHO cells expressing the human adenosine A_1 receptor were provided by Dr. A. Townsend-Nicholson, University College London. HEK 293 cells stably expressing the human adenosine A_{2A} and A_3 receptor were gifts from Dr. J. Wang (Biogen, U.S.A.) and Dr. K.-N. Klotz (University of Würzburg, Germany), respectively.

All compounds made were tested in radioligand binding assays to determine their affinities at the human adenosine A_1, A_{2A}, and A_3 receptors as described previously.[3] The human A_1 receptors were expressed in CHO cells, and [^{3}H]DPCPX was used as the radioligand. The A_{2A} and A_3 receptors were expressed in HEK 293 cells, and [^{3}H]ZM 241385 and [^{125}I]AB-MECA were used as the respective radioligands.

A number of compounds specified in the text were tested in functional assays for their ability to influence the levels of cAMP in the test system under various experimental conditions: (i) in the presence of forskolin (10 μM) and (ii) in the presence of both forskolin (10 μM) and CPA (100 nM).

CHO cells expressing the human adenosine A_1 receptor were grown overnight as a monolayer in 24-well tissue culture plates (400 μL/well; 2×10^5 cells/well). cAMP generation was performed in Dulbecco's modified Eagle's medium (DMEM)/*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethansulfonic acid (HEPES) buffer (0.60 g of HEPES/50 mL of DMEM, pH 7.4). Each well was washed twice with HEPES/DMEM buffer (250 μL), and the following were added: adenosine deaminase (0.8 IU/mL), rolipram (50 μM), and cilostamide (50 μM). This was then incubated for 30 min at 37 °C, followed by introduction of the compound of interest. After a further 10 min of incubation, forskolin was added (10 μM). After a subsequent 15 min, incubation was stopped by aspirating the assay medium and by adding 200 μL of ice-cold 0.1 M HCl. The amount of cAMP was determined by competition with [^{3}H]cAMP for protein kinase A (PKA). Briefly, the sample, approximately 1.8 nM [^{3}H]cAMP, and 100 μL of PKA solution were incubated on ice for 2.5 h. The incubations were stopped by rapid dilution with 2 mL of ice-cold Tris-HCl buffer (pH 7.4), and bound radioactive material was then recovered by filtration through Whatman GF/C filters. Filters were additionally rinsed with 1 mL of Tris-HCl buffer and then the radioactivity was counted in Packard Emulsifier Safe scintillation fluid (3.5 mL). All data reflect at least three independent experiments performed in duplicate.

Data Analysis. K_i values were calculated by use of a nonlinear regression curve-fitting program (GraphPad Prism 4, GraphPad Software Inc., San Diego, CA). K_D values of the radioligands were 1.6 nM, 1.0 nM, and 5.0 nM for [^{3}H]DPCPX, [^{3}H]ZM 241385, and [^{125}I]AB-MECA, respectively. The data from the functional assays were also analyzed with GraphPad Prism, and the figure was generated by evaluating the data to relate to the known ligand CPA (set at 0%) and forskolin (set at 100%).

Supporting Information Available: Table of the elemental analysis results (**1**−**14**) and summary of routine experimental and spectroscopic data (**6**−**12**, **14**). This material is available free of charge via the Internet at http://pubs.acs.org.

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