A New Synthesis of Sulfonamides by Aminolysis of *p*-Nitrophenylsulfonates Yielding Potent and Selective Adenosine A_{2B} Receptor Antagonists

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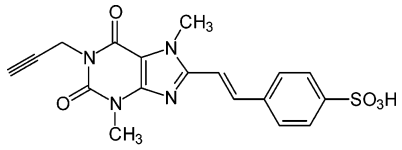
Received March 13, 2006

1-Propyl- and 1,3-dimethyl-8-*p*-sulfophenylxanthine (PSB-1115 and SPT) were used as starting compounds for the development of adenosine A_{2B} receptor antagonists with a sulfonamide structure. Since standard reactions for sulfonamide formation failed or resulted in very low yields, we developed a new method for the preparation of sulfonamides. *p*-Nitrophenoxide was used as a suitable leaving group with well balanced stability−reactivity properties. A large variety of amines, including aniline, benzylamine, phenethylamine, propylamine, butylamine, 2-hydroxyethylamine, aminoacetic acid, and *N*-benzylpiperazine reacted with *p*-nitrophenoxysulfonylphenylxanthine derivatives yielding the desired sulfonamides in satisfying to very good yields. The obtained sulfonamides were much more potent at A_{2B} receptors than the parent sulfonates. The most active compound of the present series was 8-[4-(4-benzylpiperazide-1-sulfonyl)phenyl]-1-propylxanthine (**11**, PSB-601) exhibiting a K_i value of 3.6 nM for the human A_{2B} receptor combined with high selectivity versus the other human adenosine receptor subtypes (575-fold versus A_1, 134-fold versus A_{2A}, and >278-fold versus A_3).

Introduction

Sulfonamide derivatives belong to the most important structural classes of drug molecules. Antibacterial agents with a sulfonamide structure, e.g. sulfadiazine, and diuretics, such as hydrochlorothiazide, have been therapeutically used for many decades.[1] Examples for recently approved drugs with a sulfonamide structure are the antihypertensive agent bosentan,[2] the antiviral HIV protease inhibitor amprenavir,[3] and the phosphodiesterase-5 inhibitor sildenafil.[4] In addition, numerous sulfonamide derivatives have been in preclinical development. The sulfonamide partial structure appears to belong to the so-called "privileged structures" in medicinal chemistry,[5] and it exhibits favorable pharmacokinetic properties including metabolic stability.

Xanthine derivatives were the first and still are one of the most important classes of adenosine receptor antagonists.[6] Adenosine receptors (AR) are subdivided into four different subtypes, A_1, A_{2A}, A_{2B}, and A_3. Xanthine derivatives with high potency at either A_1 or A_2 receptors were developed by introducing certain lipophilic substituents into the 8-position of the xanthine nucleus (e.g., cycloalkyl for A_1, phenyl for A_1 and A_2) and by variation of the substituents at the purine ring nitrogen atoms. The resulting compounds, for example, 1,3-dipropyl-8-phenylxanthine, generally exhibit rather low water solubility. To increase their hydrophilicity, compounds bearing a sulfonate group, such as 3,7-dimethyl-1-propargyl-8-(*p*-sulfostyryl)xanthine (**1**, SS-DMPX), 8-*p*-sulfophenyltheophylline (**2**, SPT), 1,3-dipropyl-8-*p*-sulfophenylxanthine (**3**, DPSPX), and 1-propyl-8-*p*-sulfophenylxanthine (**4**) were introduced (Figure 1).[7−9] Xanthin-8-ylbenzenesulfonates have become useful pharmacological tools, although the sulfonate group generally led to a decrease in adenosine receptor affinity. 1,3-Dialkylxanthin-8-yl-benzenesulfonamides were first introduced by Hamilton et al.[8] Because of their amphoteric nature, they are soluble across a wide pH range and can be perorally absorbed in contrast to the highly polar sulfophenylxanthine derivatives.



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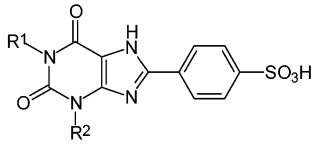

2 SPT $R^1 = R^2$ = methyl
3 DPSPX $R^1 = R^2$ = propyl
4 PSB-1115 R^1 = propyl, R^2 = H

Figure 1. Structures of sulfostyryl- and sulfophenylxanthine derivatives.

We have recently discovered that 3-unsubstituted 1-alkyl-8-phenylxanthine derivatives, such as 1-propyl-8-*p*-sulfophenylxanthine (**4**), are potent and selective A_{2B} adenosine receptor antagonists.[10] A_{2B}-selective antagonists are of considerable interest as novel drugs: they have been found to exhibit analgesic, antiinflammatory, antiallergic, antiasthmatic, and antidiabetic activity in vitro and in vivo.[10−19] They seem to have great potential, for example, for the treatment of asthma and related pulmonary diseases[17,19] and as novel antidiabetic drugs.[15,16] Furthermore, A_{2B} antagonists that are able to cross the blood−brain barrier might attenuate neurodegenerative processes in the brain and thus may be useful novel therapeutics, for example, for Alzheimer's disease.[18,20] Due to their clinical relevance there have been a number of efforts to develop A_{2B}-selective adenosine receptor antagonists,[13] derived from xanthines, ad-

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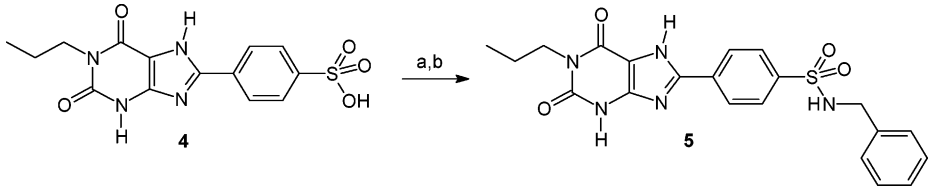
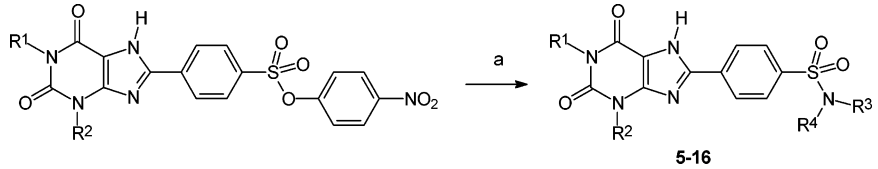
10.1021/jm060277v CCC: $33.50
Published on Web 06/13/2006

Scheme 1. Synthesis of 8-[4-(Benzylamidosulfonyl)phenyl]-1-propylxanthine (**5**)[a]



[a] Reagents and conditions: (a) chlorosulfonic acid, r.t. overnight; (b) benzylamine, anhydrous pyridine/DMF, r.t., 3 days; reflux, 3 h.

Scheme 2. Synthesis of Xanthin-8-yl-benzenesulfonamide Derivatives[a]



[a] Reagents and conditions: (a) primary or secondary amine; method A = DMSO, 150 °C, 3 h; method B = DMSO, 150 °C, 5 h; method C = DMSO, r.t., 72 h, argon; method D = DMF, r.t., 48 h; reflux, 1 h. For R^1, R^2, R^3, and R^4, see Table 1.

enine, or other heterocyclic lead structures that had been identified by screening approaches. Major problems with many of the published and currently available A_{2B} antagonists are (i) moderate or no selectivity versus other AR subtypes,[16,21−25] (ii) high lipophilicity and low water solubility,[26−29] (iii) insufficient peroral bioavailability and lack of brain penetration (e.g., **4**),[10] and (iv) metabolic instability (e.g., anilides such as compound **17** (see Figure 2)[26] (Kalla R., Zablocki J. et al., poster presentation at Purines 2004, Chapel Hill, NC).

To increase the A_{2B} affinity and selectivity of our lead structure 1-propyl-8-*p*-sulfophenylxanthine (**4**)[10,11] and to obtain perorally bioavailable drugs, we planned to synthesize a series of sulfonamide derivatives of **4** and the related 8-*p*-sulfophenyltheophylline (**2**) with broad variation of the substitution pattern at the sulfonamide nitrogen. Since initially examined standard procedures for the preparation of the target sulfonamide derivatives failed or gave only poor yields, we developed a new strategy employing *p*-nitrophenoxide as a leaving group in nucleophilic substitution. Thereby we obtained some novel sulfonamides with high affinity and selectivity for adenosine A_{2B} receptors.

Synthesis

Initially, we investigated various standard methods for the synthesis of the target sulfonamide derivatives. The most frequently used method for the preparation of sulfonamides is the conversion of a sulfonic acid to the corresponding chlorosulfonyl derivatives with thionyl chloride, chlorosulfonic acid, phosphorus oxychloride, or phosphorus pentachloride, followed by reaction of the chlorosulfonyl derivative with the appropriate amine.[30] This method usually gives good yields of sulfonamides at ambient temperature or under reflux conditions. However, when this method was applied to our lead compound 1-propyl-8-*p*-sulfophenylxanthine (**4**), the desired sulfonamides could not be isolated in most cases, with the exception of 8-[4-(benzylamidosulfonyl)phenyl]-1-propylxanthine (**5**). 1-Propyl-8-*p*-sulfophenylxanthine was converted to its sulfonyl chloride derivative by reaction with chlorosulfonic acid, which was subsequently treated with benzylamine (Scheme 1). A moderate yield of 14% of compound **5** was obtained, after tedious purification by column chromatography. Attempts to increase the reactivity of the sulfophenylxanthine derivative either by introduction of a fluorosulfonic moiety at the para-position of 8-phenyl-1-propylxanthine by reaction with fluorosulfonic acid[31] or by conversion of the chlorosulfophenyl xanthine to the fluorosulfophenyl derivative using potassium fluoride[32] failed.

Another approach was to prepare the *p*-sulfonamidobenzoic acid derivatives as precursor molecules.[33,34] However, coupling of 5,6-diamino-3-propyluracil with *p*-sulfonamidobenzoic acid derivatives in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) failed under various conditions.

Since the first approach starting from the *p*-sulfophenylxanthine derivative had been somewhat more successful so far (Scheme 1), we decided to follow the same strategy but to investigate whether nitrophenoxides would be more suitable leaving groups than halogenides. Nitrophenoxysulfonylbenzenexanthine derivatives can easily be prepared in high yields;[21] they are crystalline compounds, highly lipophilic, and well soluble in a number of generally used organic solvents; in addition, they are quite stable and easy to handle.[21] In initial experiments, 1,3-dimethyl-8-[4-[[*m*-nitrophenoxy]sulfonyl]phenyl]xanthine[21] was treated with benzylamine under various reaction conditions. However, no substitution reaction was observed, even though different bases, for example, sodium hydride and (dimethylamino)pyridine, were tried as catalysts. Thus the *m*-nitrophenoxide was not a suitable leaving group for the aminolysis. Since *p*-nitrophenylsulfonate esters are less stable than *m*-nitrophenylsulfonate ester toward nucleophilic attack, for example, by hydroxide ions,[21] we expected *p*-nitrophenoxide to be a more suitable leaving group. Initial experiments were performed with 1,3-dimethyl-8-[4-[[*p*-nitrophenoxy]sulfonyl]phenyl]xanthine,[21] which was treated with the appropriate amine in dimethyl sulfoxide (DMSO) at r.t. for 30 min followed by heating at 150 °C for 3 h (method A), yielding the desired sulfonamides in good yields (Scheme 2). Since the 3-unsubstituted xanthine derivatives were less reactive, harder reaction conditions had to be applied to achieve aminolysis. The desired sulfonamide derivatives of the lead structure **4** could be obtained by prolongation of the heating time to 5 h at 150 °C in DMSO (method B), by stirring at r.t. for 72 h in DMSO under an atmosphere of argon (method C), or by stirring for 48 h in dimethylformamide (DMF) followed by refluxing for 1 h (method D). The sulfonamide derivatives could be successfully obtained and purified by column chromatography. In Table 1 the yields of the synthesized xanthin-8-yl-benzenesulfonamide derivatives are collected. Nitrophenoxide has turned out to be a suitable leaving group for a very efficient synthesis of

Table 1. Methods and Yields of Synthesized Xanthin-8-yl-benzenesulfonamide Derivatives

compd	R^1	R^2	R^3	R^4	method[a]	yield (%)[c]
5	Pr	H	Bn	H	D	51
					b	14
6	Pr	H	$-CH_2CH_2Ph$	H	B	88
7	Pr	H	$-CH_2CH_2OH$	H	B	28
					C	53
					b	0
8	Pr	H	$-CH_2COOH$	H	B	34
9	Pr	H	Pr	Pr	B	33
					b	0
10	Pr	H	Ph	H	B	40
11	Pr	H	$-CH_2-CH_2-N(Bn)CH_2-CH_2-$		D	57
12	Me	Me	^{i}Pr	H	A	61
13	Me	Me	$-CH_2CH_2Ph$	H	A	42
14	Me	Me	Bu	H	A	44
15	Me	Me	$-CH_2CH_2OH$	H	A	51
16	Me	Me	$-CH_2COOH$	H	A	28

[a] For methods, see Results and Discussion and Experimental Section. [b] Preparation via the chlorosulfonate (standard method, see Scheme 1).[8,30] [c] Yields after purification by column chromatography.

sulfonamides. Yields of chromatographically purified products were in most cases higher than 30%, in one case even 88% was achieved (**6**). Not only primary amines could easily be reacted but also secondary amines could be employed, as well as amino alcohols, amino acids, aniline, and piperazine derivatives (Table 1).

It has been reported that nucleophilic substitution reactions of such phenyl benzenesulfonates may proceed via competing pathways: (a) attack at the electron-deficient sulfur atom or (b) attack at the electron-deficient carbon atom of the phenyl ester.[35,36] In our investigations, we have observed nucleophilic attack of amines only at the sulfur atom of *p*-nitrophenyl xanthinebenzenesulfonic acid esters yielding the desired sulfonamides. The competing reaction, which would result in the formation of *p*-nitrophenylamines was not observed under the applied reaction conditions. According to investigations by Choi et al.[35] with model compounds, the described nucleophilic substitution reaction is likely to proceed via an S_{N2} mechanism in which the attack of the nucleophile and thus the formation of intermediate **17** is the rate-limiting step (Scheme 3). Recently, Caddick et al. introduced pentafluorophenoxide as a leaving group for sulfonamide synthesis, but in the reported reaction, strong bases (DBU, NaH) were required even with nucleophilic amines present pointing to a different reaction mechanism via a sulfene intermediate.[37,38]

The optimized, balanced chemical reactivity of the *p*-nitrophenylsulfonates (*p*-nosylates) is important for the success of this reaction. The chemical reactivity is determined by the nature of the sulfur center and the characteristics as a leaving group (nucleofugality) of the group displaced. The reactivity of *m*-nosylates is too low; however, compounds with a higher reactivity than the *p*-nosylates may lead to greater hydrolytic instability and would produce lower reaction selectivity.[35] The new method for the preparation of sulfonamides, which may be generally applicable and useful, has the following advantages: (i) good yields, (ii) relatively short reaction times, (iii) easy handling and purification, (iv) avoidance of the use of pyridine, and (v) broad applicability to a wide range of amines with different degrees of nucleophilicity. *p*-Nitrophenylsulfonates may be a useful replacement for the more reactive, unstable sulfonyl chlorides, which are sometimes difficult to prepare and to handle. They could be employed in combinatorial solid-phase synthesis approaches to produce chemical libraries of sulfonamides.

Biological Activity

The xanthine sulfonamide derivatives were investigated in radioligand binding studies at A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors using [^{3}H]2-chloro-N^6-cyclopentyladenosine ([^{3}H]-CCPA), [^{3}H](*E*)-3-(3-hydroxypropyl)-8-[2-(3-methoxphenyl)-vinyl]-7-methyl-1-prop-2-ynyl-3,7-dihydropurine-2,6-dione ([^{3}H]-MSX-2), [^{3}H]8-((4-(2-hydroxyethylamino)-2-oxoethoxy)phenyl)-1-propylxanthine ([^{3}H]PSB-298), and [^{3}H]2-phenyl-8-ethyl-4-methyl-(8*R*)-4,5,7,8-tetrahydro-1*H*-imidazo[2.1-*i*]purin-5-one ([^{3}H]PSB-11), respectively.[21,39] Rat brain membrane preparations were used for A_1 (cortex) and A_{2A} (striatum) assays. Selected compounds were additionally investigated at human A_1 and A_{2A} receptors recombinantly expressed in Chinese hamster ovary (CHO) cells. For A_{2B} and A_3 assays, human recombinant receptors expressed in CHO cells were used.

Structure−Activity Relationships

Information from several previous structure−activity relationship studies[10,21,40] allowed us to focus this investigation on a well-defined set of compounds, namely, a series of diverse variations of the substituent at the sulfonamide group. Starting from 8-*p*-sulfophenylxanthine derivatives as lead structures, two series of compounds were investigated, 1,3-dimethyl-substituted xanthines derived from **2**, and 1-propyl-3-unsubstituted xanthines derived from **4**. The two lead structures **2** and **4** were selected for sulfonamide formation since these two substitution patterns for the xanthine N1- and N3-position conferred A_{2B} selectivity (see Table 2).[10] The N7-position was unsubstituted because the N7-hydrogen atom appears to be required for hydrogen bond formation with the receptor protein.[40]

All of the compounds showed low affinity for human A_3 ARs as expected. It had been previously shown that the A_3 receptor prefers 1,3-dipropyl-substituted xanthine derivatives,[21] and this was confirmed in the present study. The 1,3-dimethyl-substituted xanthines were generally somewhat less potent at A_{2B} ARs than the 1-propyl-substituted analogues (compare **7**/**15**, **8**/**16**), but no significant difference was observed in the case of the phenylethyl-substituted compounds **6** and **13**, a substituent that was very favorable for high A_{2B} affinity. However, the propyl derivative was still superior due to its higher selectivity versus A_{2A} ARs. Alkyl substitutents at the sulfonamide group (isopropyl, butyl, dipropyl) were tolerated by the A_{2B} AR, but even

Scheme 3. Proposed Mechanism of Aminolysis

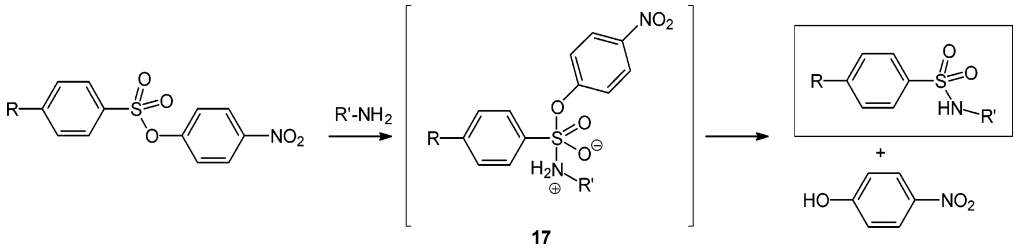
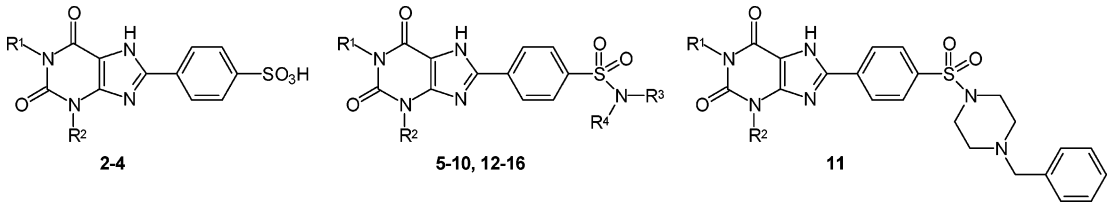


Table 2. Adenosine Receptor Affinity of Sulfonamidophenylxanthine Derivatives and Parent Sulfophenylxanthines



2-4 **5-10, 12-16** **11**

					$K_i \pm$ SEM [nM] (or % inhibition of radioligand binding at indicated concentration)					
compd	R^1	R^2	R^3	R^4	A_1 rat brain cortical membranes vs. [^{3}H]CCPA ($n = 3$)	A_1 human recombinant vs [^{3}H]CCPA ($n = 3$)	A_{2A} rat brain striatal membranes vs. [^{3}H]MSX-2 ($n = 3$)	A_{2A} human recombinant vs [^{3}H]MSX-2 ($n = 3$)	A_{2B} human recombinant vs. [^{3}H]PSB-298 ($n = 3$)	A_3 human recombinant vs. [^{3}H]PSB-11 ($n = 2$)
2	methyl	methyl			14000[43,a]	*g*	14000[43,a]	*g*	1330[40,b]	5890[44,c]
3	propyl	propyl			210[43,a]	*g*	1400[43,a]	*g*	250[40,b]	183[45,c,d]
4	propyl	H			2200[46,a]	>10000[10]	24000[46,a]	*g*	53.4[10,e]	>10000[10]
5	propyl	H	$-CH_2Ph$	H	4.6 ± 0.5	54.8 ± 3.2	26.7 ± 3.2	162 ± 64	4.2 ± 2.5	≥1000 (41%)
6	propyl	H	$-CH_2CH_2Ph$	H	10 ± 2	183 ± 22	297 ± 81	769 ± 206	3.62 ± 0.54	≥10000 (37%)
7	propyl	H	$-CH_2CH_2OH$	H	45 ± 7	*g*	287 ± 15	*g*	27.1 ± 8.0	≥10000 (36%)
8	propyl	H	$-CH_2COOH$	H	100 ± 15	*g*	320 ± 32	*g*	101 ± 35	>10000 (25%)
9	propyl	H	propyl	propyl	5.5 ± 2.0	*g*	42 ± 3	*g*	53.8 ± 36.3[f]	>1000 (18%)
10	propyl	H	phenyl	H	1.8 ± 1.0	*g*	23 ± 13	*g*	31.4 ± 0.9[f]	≥1000 (48%)
11 (PSB-601)	propyl	H	see structure above		260 ± 0	2067 ± 261	93.7 ± 32.1	484 ± 115	3.6 ± 0.4	>1000 (29%)
12	methyl	methyl	isopropyl	H	75 ± 9	*g*	283 ± 13	*g*	102 ± 3	>10000 (27%)
13	methyl	methyl	$-CH_2CH_2Ph$	H	12 ± 1	185 ± 63	113 ± 9	32.6 ± 14	4.48 ± 2.24	1083 ± 25
14	methyl	methyl	butyl	H	27 ± 2	*g*	165 ± 69	*g*	122 ± 20	≥10000 (43%)
15	methyl	methyl	$-CH_2CH_2OH$	H	98 ± 2	*g*	347 ± 37	*g*	250 ± 169	≥10000 (49%)
16	methyl	methyl	$-CH_2COOH$	H	64 ± 4	*g*	182 ± 65	*g*	154 ± 9	≥10000 (41%)

[a] Determined with [^{3}H]*R*-PIA (A_1) and [^{3}H]NECA (A_{2A}) as radioligands. [b] Determined with [^{125}I]ABOPX as radioligand. [c] Determined with [^{125}I]AB-MECA. [d] Determined at the sheep receptor. [e] Determined with [^{3}H]ZM241385 as radioligand. [f] $n = 2$. [g] Not determined.

better by the A_1 AR leading to A_1-selective compounds (**9**, **12**, **14**). Phenyl, benzyl, and phenylethyl substitution was investigated in the 1-propylxanthine series. The phenyl derivative **10** was the most potent A_1 antagonist of the present series (K_i = 1.8 nM, rat A_1 AR); it was 13−17-fold selective versus A_{2A} and A_{2B} and highly selective versus A_3 ARs. Replacement of the phenyl group by a benzyl residue (**5**) increased A_{2B} affinity 7.5-fold, while A_1 affinity was reduced and A_{2A} and A_3 affinities were virtually unaltered leading to a potent A_{2B} antagonist with some selectivity in a comparison of the human receptor subtypes (K_i A_{2B} 4.2 nM, 13-fold selective vs human A_1, 39-fold versus human A_{2A}, >200-fold vs human A_3 ARs). It is interesting to note that the compound is 12-fold more potent at the rat A_1 than at the human A_1 AR and 6-fold more potent at the rat A_{2A} in comparison to the human A_{2A} AR. Further extension of the alkyl chain that connects the aromatic ring by one methylene unit yields the phenylethyl derivative **6**, which was a similarly potent A_{2B} antagonist (K_i 3.62 nM) but showed increased selectivity over the other human AR subtypes (50-fold vs A_1, 212-fold vs A_{2A}, >2700-fold vs A_3). In analogy to the observation with the benzyl derivative **5**, compound **6** was also more potent at rat A_1 as compared to human A_1 (18-fold) and at rat A_{2A} in comparison with human A_{2A} ARs (2.6-fold). Compound **9** was synthesized to investigate whether disubstitution of the sulfonamide nitrogen atom was tolerated. The dipropylamino derivative was moderately potent at A_{2B} (K_i 53.8 nM) and had a reasonable to high affinity for A_{2A} ARs (K_i 42 nM) and A_1 ARs (K_i 5.5 nM).

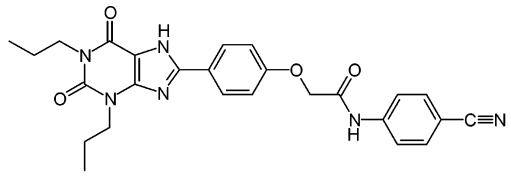
A major problem of many A_{2B} antagonists that have been developed is their frequently very low water solubility, which limits their applicability as drugs or pharmacological tools due to a limited bioavailability. Therefore we introduced polar residues by using functionalized amines for sulfonamide formation, including hydroxyethylamine, aminoacetic acid, and *N*-benzylpiperazine. A hydroxyl group (**7**, **15**) will somewhat increase water solubility, and it would allow for the formation of water-soluble prodrugs, for example, phosphate or amino acid ester prodrugs.[41,42] A carboxylic acid function (**8**, **16**) will be largely deprotonated at physiological pH value and will therefore result in an increased water solubility. The *N*-benzylpiperazine structure (**11**) was chosen due to its basic nitrogen atom, which can be protonated under physiological conditions. The benzyl residue was expected to increase A_{2B} affinity and selectivity since it had been found that an aromatic residue is favorable for selective binding to A_{2B} ARs.[13,26,28] Indeed, both the hydroxyethyl and the acetic acid residue were tolerated by the A_{2B} receptor; however, the compounds were similarly (1-propylxanthine derivatives **7** and **8**) or somewhat more potent (1,3-dimethylxanthine derivatives **15** and **16**) at A_1 ARs.

Our goal was reached with the benzylpiperazinylsulfonamide derivative **11**: the compound showed high affinity for A_{2B} ARs

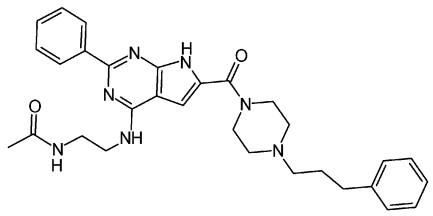
Table 3. Calculated log *P* Values and Polar Surface Areas (PSA) for Compound **11** and Standard A_{2B} Antagonists

compd[a]	calcd log *P* uncharged/protonated	calcd PSA uncharged/protonated
11	3.31/−0.51[b]	127/128[b]
	3.53/0.562[c]	124/125[c]
17	3.18[b]	131[b]
	4.48[c]	134[c]
18	2.58/−1.24[b]	106/105[b]
	3.69/0.527[c]	106/107[b]
19	1.79[b]	144[b]
	3.07[c]	147[c]
20	2.24[b]	126[b]
	3.95[c]	129[c]

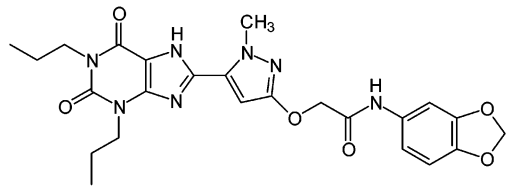
[a] For structures, see Figure 2. [b] Software Marvin tools: www.chemaxon.com; log *P*;[49] PSA.[50] [c] www.molinspiration.com.



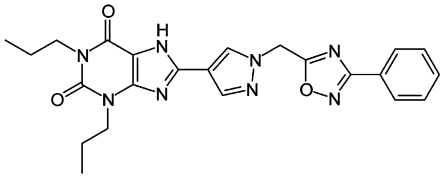
17 MRS1754, K_i values:[26]
hA_{2B}: 1.97 nM
hA_1: 403 nM; rA_1: 16.8 nM
hA_{2A}: 503 nM; rA_{2A}: 612 nM
hA_3: 570 nM



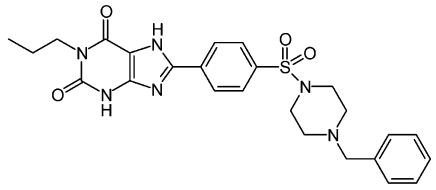
18 OSIP339391, K_i values:[41]
hA_{2B}: 0.5 nM
hA_1: 37 nM
hA_{2A}: 328 nM
hA_3: 450 nM



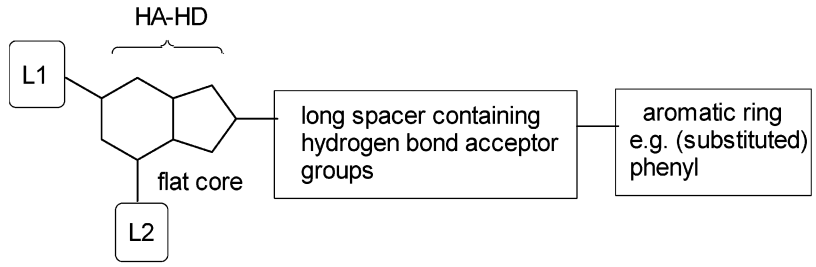
19 MRE2029F20, K_i values:[28]
hA_{2B}: 5.5 nM
hA_1: 200 nM
hA_{2A}: > 1000 nM
hA_3: > 1000 nM



20 CVT compound, K_i values:[54]
hA_{2B}: 1 nM
hA_1: 370 nM
hA_{2A}: 1100 nM
hA_3: 480 nM



11, K_i values:
hA_{2B}: 3.6 nM
hA_1: 2070 nM; rA_1: 260 nM
hA_{2A}: 484 nM; rA_{2A}: 93.7
hA_3: > 1000 nM



HA: hydrogen bond acceptor; HD: hydrogen bond donor
L1, L2: lipophilic domains; flat core: central core structure, mostly heterocyclic

Figure 2. Structures and adenosine receptor affinities of potent adenosine A_{2B} receptor antagonists in comparison with the newly developed sulfonamide derivative **11** and common pharmacophore model: h indicates human; r indicates rat.

(K_i 3.6 nM) combined with high selectivity versus all other AR subtypes, 574-fold versus human A_1, 134-fold versus human A_{2A}, and >278-fold versus human A_3 ARs. Compound **11** shows good A_{2B} selectivity in comparison with the rat A_1 and A_{2A} receptors. Because it is 8-fold more potent at rat A_1 and 5-fold more potent at rat A_{2A} as compared to the orthologous human receptor subtypes, it is even more A_{2B} selective if the therapeutically relevant human subtypes are compared. The piperazine nitrogen atom makes this ligand a weak base similar to many alkaloids (e.g., morphine, atropine), which are known to have excellent pharmacokinetic properties and can penetrate the blood−brain barrier.

Lipophilicity (log *P* value) and polar surface area (PSA) values are two important predictors of peroral bioavailability of drug molecules.[47,48] Therefore we calculated log *P* and PSA values for compound **11** using two different software programs and compared them to the values obtained for a selection of previously published potent and selective A_{2B} antagonists (see Table 3).

Compounds **11** and **18** are both basic molecules, and therefore, we calculated the values for the neutral as well as for the protonated form. The log *P* values calculated with the two different programs differed considerably, the Marvin program generally yielding lower log *P* values. For all compounds the calculated log *P* values were lower than 5, which is the upper limit for drugs to be able to penetrate biomembranes according to Lipinsky's rules. The highest degree of lipophilicity was exhibited by compound **17** (*c* log $P = 3.18$ (Marvin), $= 4.48$ (molinspiration)). The two compounds containing a basic piperazine ring, **11** and **18**, which are largely protonated at pH 7, exhibit the lowest log *P* values in the protonated form, which is an indication for good water solubility. The polar surface area (PSA) is calculated from the surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the PSA is closely related to the hydrogen bonding potential of a compound.[48,51] Both programs that were used to calculate PSA values gave nearly identical results. Neutral and protonated species of a molecule showed only minor

differences as is to be expected from the difference of only one hydrogen atom. Molecules with PSAs of 140 Å^2 or more are expected to exhibit poor intestinal absorption.[48] Table 3 shows that compound **19** is above this limit, while all other molecules, including compound **11**, are below. It has to be kept in mind that log *P* and PSA values are only two — important, although not sufficient — criteria for predicting oral absorption of a drug.[49]

By comparison of the structures of some of the most potent A_{2B} antagonists, a pharmacophore model can be deduced (Figure 2), which partly also applies to antagonists at the other adenosine receptor subtypes. A central core structure (xanthine in many compounds, pyrrolo[2,3-*d*]pyrimidine in **18**)[52] containing a hydrogen bond acceptor−hydrogen bond donor motif has been found to be typical also for A_1 AR ligands.[53] In xanthines, this motif is formed by the C6-carbonyl group (acceptor) and the N7-hydrogen (donor). In compound **18**, a pyrimidine ring nitrogen atom and the pyrrole N−H function form the same motif (Figure 2). A lipophilic pocket (L1) can be filled with an alkyl (preferably propyl) or a phenyl residue. A second pocket (L2) is present, but this is more important for A_1 and A_3 ARs and therefore reduces selectivity.[10] Since a free, unsubstituted N3−H atom in xanthines not only increases A_{2B} selectivity but also affinity,[10] it can be speculated that the A_{2B} AR prefers a hydrogen donor group in that positon (N3−H in **11**, exocyclic NH in **18**). Connected to C8 of xanthine derivatives or to the respective position in the pyrrolopyrimidine is a long spacer, ca. 7−10 atoms long, that may contain cyclic, aromatic, or nonaromatic structures, as well as various hydrogen bond-accepting functional groups. At the terminus of the spacer, an aromatic ring is attached, and this appears to increase selectivity for the A_{2B} AR. In the new sulfonamide derivative **11**, the spacer is sterically highly restricted due to the piperazine ring connected via a sulfone to the 8-phenyl residue.

Conclusions

In conclusion, we have developed a new strategy for the preparation of sulfonamides using *p*-nitrophenoxide as a leaving group in nucleophilic substitution of 8-[4-[[[*p*-nitrophenyl]oxy]-sulfonyl]phenyl]xanthine by amines. The new method allowed the preparation of xanthin-8-yl-benzenesulfonamides that could not be obtained at all or only in very low yields by standard synthetic procedures. It may not be limited to xanthinylbenzenesulfonamides, but generally applicable and it thereby extends the current repertoire of methods for preparing sulfonamides, one of the most important classes of drugs. The new method allowed us to synthesize a series of xanthin-8-ylbenzenesulfonamides and to investigate their structure−activity relationships at adenosine receptors with the goal to improve affinity and selectivity for A_{2B} ARs. A highly potent and selective A_{2B} AR antagonist (**11**) was identified, which contains a basic piperazine partial structure that can be protonated at physiological pH values conferring increased water solubility.

Experimental Section

General Procedure for the Preparation of Sulfonamides 5−16. To a stirred solution of 1-propyl-8-[4-[[[*p*-nitrophenyl]oxy]-sulfonyl]phenyl]xanthine[21] (1 equiv) for **5**−**11** or 1,3-dimethyl-8-[4-[[[*p*-nitrophenyl]oxy]sulfonyl]phenyl]xanthine[21] (1 equiv) for **12**−**15** in DMSO (5 mL) the appropriate amine (10−50 equiv) was added at room temperature. In method A, the reaction mixture was stirred for 30 min at room temperature, then heated under reflux for 3−5 h. In method B, the mixture was heated at 150 °C for 5 h. In method C, the mixture was stirred for 72 h at r.t. under an atmosphere of argon. In method D, DMF instead of DMSO was used as a solvent. The reaction mixture was stirred for 48 h at r.t. followed by heating under reflux for 1 h. The progress of all reactions was monitored by TLC. After the starting xanthines had been consumed, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (40:1 for compounds **5**, **6**, **9**, and **11**−**13**, 20:1 for compounds **7**, **8**, **10**, **15**, and **16**, or 9:1 for **11**). All compounds gave only a single spot on TLC.

8-[4-(Benzylamidosulfonyl)phenyl]-1-propylxanthine (5). Preparation via the Chlorosulfonate (Standard Procedure). 1-Propyl-8-*p*-sulfophenylxanthine[21,46] (0.57 mmol) was dissolved in chlorosulfonic acid (5 mL) and stirred overnight. The reaction mixture was poured into ice water; the formed white precipitate was filtered off and dried affording the corresponding sulfonyl chloride derivative. 1-Propyl-8-*p*-chlorosulfophenylxanthine (0.49 mmol) was dissolved in anhydrous DMF/pyridine (1:1, 25 mL), benzylamine (1.46 mmol) was added, and the reaction mixture was stirred under argon for 3 days and then refluxed for 2 h. The solvent was distilled off in vacuo, and the residue was suspended in a small amount of methanol and filtered off. The product was purified by column chromatography on silica gel using dichloromethane/methanol (9:1) to give compound **5**.

8-[4-(Benzylamidosulfonyl)phenyl]-1-propylxanthine (5). Mp 292 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.40 Hz, 3H), 1.58 (m, J = 7.40 Hz, 2H), 3.82 (t, J = 7.40 Hz, 2H), 4.03 (s, 2H), 7.21 (m, 5H), 7.87 (d, J = 8.50 Hz, 2H), 8.23 (d, J = 8.50 Hz, 2H), 12.05 (s, 1H), 13.88 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 11.31, 21.01, 41.60, 46.30, 108.69, 126.92, 127.26, 127.30, 127.74, 128.36, 132.50, 137.69, 141.69, 147.69, 148.42, 151.11, 155.14. Anal. ($C_{21}H_{21}N_5O_4S\cdot 0.2H_2O$) C, H, N.

8-[4-(Phenylethylamidosulfonyl)phenyl]-1-propylxanthine (6). Mp >300 °C. HRMS ($C_{22}H_{23}N_5O_4S$) calcd, 453.1470; found, 453.1469.

8-[4-(2-Hydroxyethylamidosulfonyl)phenyl]-1-propylxanthine (7). Mp >300 °C. Anal. ($C_{16}H_{19}N_5O_5S\cdot 2.5\ H_2O$) C, H, N.

4-(1-Propylxanthin-8-yl)phenylsulfonamidoacetic Acid (8). Mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.41 Hz, 3H), 1.58 (m, 2H), 2.44 (s, J = 5.04 Hz, 2H), 3.84 (t, J = 7.4 Hz, 2H), 7.51 (t, 1H), 7.89 (d, J = 8.51 Hz, 2H), 8.30 (d, J = 8.2 Hz, 2H), 11.94 (s, 1H). Anal. ($C_{16}H_{17}N_5O_6S$) C, H, N calcd, 17.19; found, 18.02.

8-[4-(Dipropylamidosulfonyl)phenyl]-1-propylxanthine (9). Mp >300 °C. HRMS ($C_{20}H_{27}N_5O_4S$) calcd, 433.1784; found, 433.1787.

8-[4-(Phenylamidosulfonyl)phenyl]-1-propylxanthine (10). Mp >300 °C. HRMS ($C_{20}H_{19}N_5O_4S$) calcd, 425.1157; found, 425.1145.

8-[4-(4-Benzylpiperazide-1-sulfonyl)phenyl]-1-propylxanthine (11). Mp >300 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88 (t, J = 7.40 Hz, 3H), 1.58 (sext, J = 7.40 Hz, 2H,), 2.41 (bs, 4H), 2.94 (bs, 4H), 3.44 (s, 2H), 3.82 (t, J = 7.40 Hz, 2H), 7.22 (m, 5H), 7.83 (d, J = 8.51 Hz, 2H), 8.32 (d, J = 8.50 Hz, 2H), 11.93 (s, 1H), 13.90 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 11.32, 21.00, 41.63, 46.30, 51.56, 61.46, 108.81, 127.07, 127.12, 128.30, 128.39, 128.83, 128.97, 133.25, 135.77, 137.79, 147.70, 148.16, 151.09, 155.12. Anal. ($C_{25}H_{28}N_6O_4S\cdot 0.5\ H_2O$) C, H, N.

8-[4-(Isopropylamidosulfonyl)phenyl]-1,3-dimethylxanthine (12). Mp >300 °C. Anal. ($C_{16}H_{19}N_5O_4S$) C, H, N calcd, 18.58; found, 18.04.

8-[4-(Phenylethylamidosulfonyl)phenyl]-1,3-dimethylxanthine (13). Mp >300 °C. Anal. ($C_{21}H_{21}N_5O_4S$) C, H, N.

8-[4-(Butylamidosulfonyl)phenyl]-1,3-dimethylxanthine (14). Mp >300 °C. Anal. ($C_{17}H_{21}N_5O_4S$) C, H, N.

8-[4-(2-Hydroxyethylamidosulfonyl)phenyl]-1,3-dimethylxanthine (15). Mp >300 °C. Anal. ($C_{15}H_{17}N_5O_5S\cdot 0.8\ H_2O$) C, H, N calcd, 17.78; found: 17.33.

4-(1,3-Dimethylxanthin-8-yl)phenylsulfonamidoacetic Acid (16). Mp >300 °C. Anal. ($C_{15}H_{15}N_5O_6S$) C, H, N.

Biological Studies. Radioligand binding studies were performed as recently described.[21,39]

Computer Calculations. The molecules were built with the SYBYL software, version 7.0 (Tripos, Inc., St. Louis, MO). The structures were energy-minimized using the maximin2 minimizer

in SYBYL running on default options. Minimization was terminated either after 1000 iterations or when a gradient of less than 0.05 kcal/(mol·Å) was attained. To find conformations with low energy, the systematic search intergrated in SYBYL was performed. Partial electrostatic potentials were calculated using the Gasteiger−Hückel method. Low-energy conformations were used for calculations of log *P*[49] and PSA values[50] with Marvin (www.chemaxon.com), while calculations with molinspiration (www.molinspiration.com) could only be performed using nonoptimized structures.

Acknowledgment. L.Y. was supported by a STIBET scholarship by the Deutscher Akademischer Austauschdienst (DAAD). We thank the Deutsche Forschungsgemeinschaft for support (Grant GRK677, scholarships for D.C.G.B. and H.M.).

Supporting Information Available: ^{1}H and ^{13}C NMR spectral data, elemental analyses, and HRMS data for the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM060277V