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8-Aryl Xanthines Potent Inhibitors of Phosphodiesterase 5

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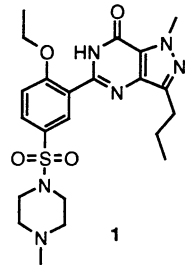
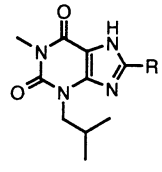
Abstract—In clinical studies, several inhibitors of phosphodiesterase 5 (PDE5) have demonstrated utility in the treatment of erectile dysfunction. We describe herein a series of 8-aryl xanthine derivatives which function as potent PDE5 inhibitors with, in many cases, high levels of selectivity versus other PDE isoforms.

Inhibition of phosphodiesterase 5 (PDE5) is a clinically proven concept for treatment of male erectile dysfunction (MED), with the PDE5 inhibitor sildenafil **1** launched in 1998, and great recent interest in the development of new PDE5 inhibitors.[1,2]

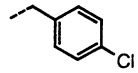


1

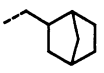


2a, R=H (IBMX)

2b, R=



2c, R=



Despite the clear utility of **1**, adverse effects such as headaches, flushing and visual disturbance have been noted in a small number of MED patients taking sildenafil,[3] some of which could be associated with cross reactivity on other PDE isoforms. Competitive inhibition of PDE6, which controls function of rod and cone cells within the eye, may be responsible for some of the ocular side effects observed.[4] In this communication, we disclose the discovery of novel xanthine-based PDE5 inhibitors which exhibit good levels of in vitro potency and differing selectivity over other PDE isoforms, including PDE6.

3-Isobutyl-1-methylxanthine (IBMX) **2a** has been long known as a general, non-selective PDE inhibitor.[5] More recently, Corbin[6] described a series of 8-substituted derivatives of IBMX such as **2b** and **2c**, which exhibited low nM potency against PDE5 and modest selectivity against PDE1. In searching for a selective PDE5 inhibitor, one strategy we employed involved a comparative investigation of the similarity of xanthine templates related to **2** and known PDE5 inhibitors such as sildenafil **1**. The absolute binding conformations of these molecules are unknown, and therefore it was sought to determine those common features of known PDE5 inhibitors which were most likely to give rise to their activity at this receptor. Using Catalyst©[7] in *hip-hop* mode, common features in 3-D space were identified and aligned. This confirmed manual attempts at overlaying our compounds where the 6 membered ring of the pyrazolopyrimidine template was overlaid with the five-membered ring of the xanthine template (Fig. 1). The similarities between these two templates prompted the design and subsequent synthesis of novel hybrid **3a**.

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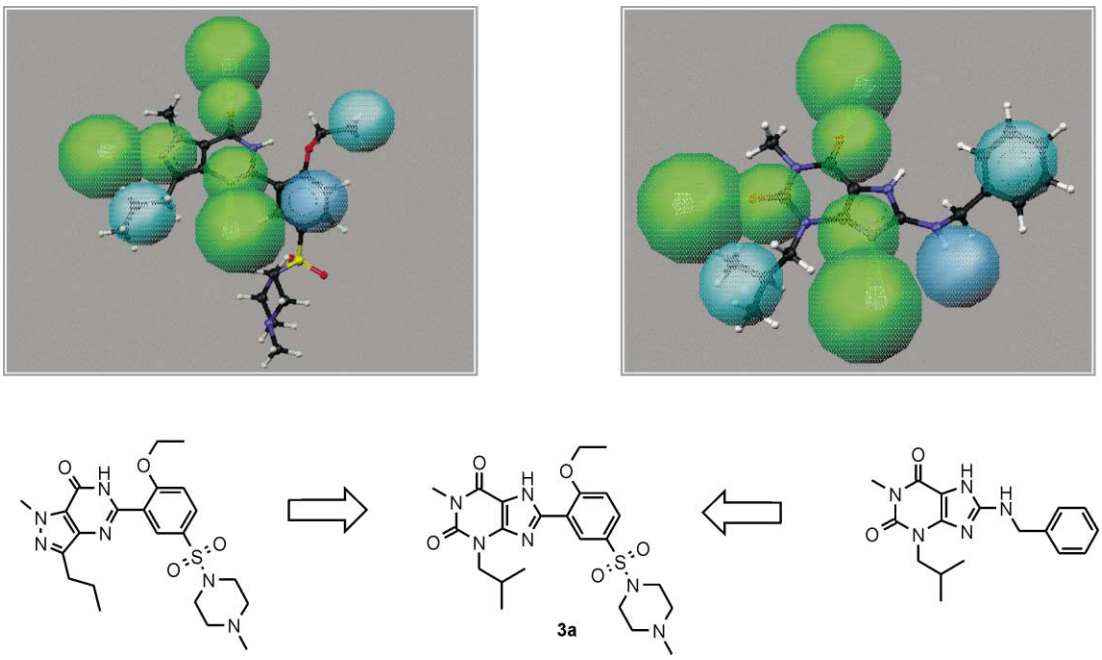
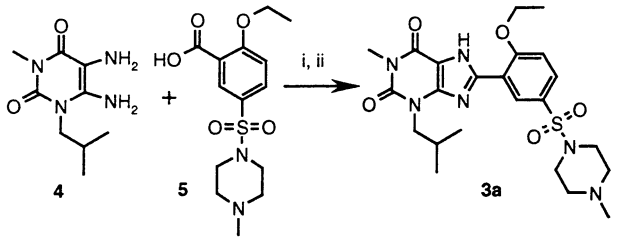


Figure 1. Schematic overview of the common features hypothesis methodology utilised to generate a hypothetical PDE5 inhibitor.

8-Substituted xanthine **3a** was prepared by condensation of the known uracil **4**[8] and benzoic acid **5**[9] (Scheme 1). We were pleased to discover that the desired xanthine sildenafil hybrid **3a** was a potent PDE5 inhibitor (human platelet PDE5 IC_{50} 20 nM)[10] and displayed similar selectivity to sildenafil versus PDEs1, 2, 3, 4 and 6. Its suitability as a lead structure was further assessed (Fig. 2). Lipophilicity, permeability and solubility were in acceptable ranges for an oral drug however clearance was relatively high and the relatively high molecular weight and polar surface area (PSA)[11] were potentially limiting for lead optimisation. Nevertheless given the relative ease of synthetic access a modest lead optimisation programme was initiated.



Scheme 1. Reagents and conditions: (i) acid, HATU or EDC; DIPEA, DMF, rt; (ii) NaOH, MeOH, H_2O, 60 °C.

Physical properties	MWt 504.6 PSA 90.56 A^2 Log P 3.26 Log D (pH 7.4) 3.15
Kinetic solubility	pH 5.9 > 160mg/L pH 6.9 ca 30mg/L
Caco-2 permeability	P_{app} 2.5x 10^{-5} cm s-1
Rat *in vivo* Pharmacokinetics	$t_{1/2}$ 92 ± 8 min Vss 9.7 ± 0.5 L/kg CL 94 ± 6 mL/kg BAV i.d. 11%

Figure 2. Physical chemistry and pharmacokinetic properties of **3a**.

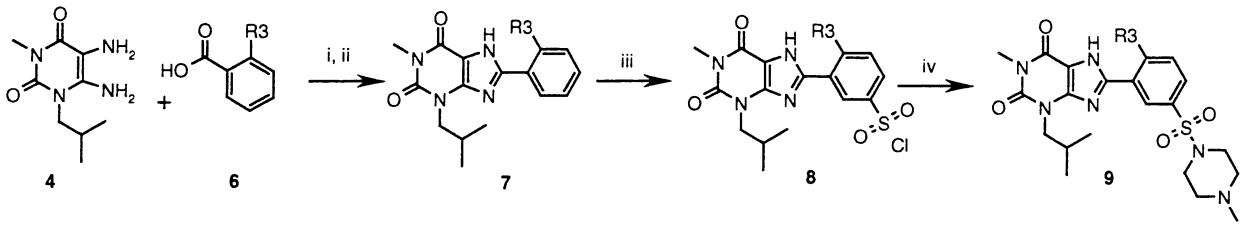
The N1 methyl and N3 isobutyl groups of xanthine **3a** originate from IBMX **2a** and have been found to be relatively optimal for broad spectrum PDE inhibitory potency.[6] We were interested to determine whether this relationship would be maintained in our new series. Synthesis of the required N1, and N3 analogues of **3a** followed in direct analogy to Scheme 1, the required diaminouracils analogous to **4** being either known compounds or prepared using similar methodology.[8]

Removal of the N1 methyl lowered potency (Table 1). Conservative modification at N3 largely retained activity with 4–5 carbon atom substituents being favoured for potency at PDE5. Some potential for increased selectivity versus PDE6 was noted for the larger R2 groups.

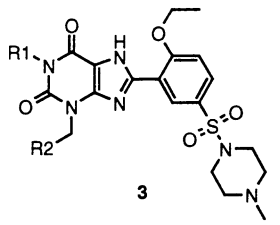
Table 1. PDE5 activity of **3a** and derivatives

Compd	R_1	R_2	hPDE5	bPDE6	bPDE1	hPDE3
3a	Me	*i*Pr	0.020	0.10	3.38	>10
3b	H	*i*Pr	0.315	—	>10	>10
3c	H	H	>10	—	—	—
3d	H	Et	1.36	—	—	—
3e	Me	Et	0.10	0.345	—	—
3f	Me	Vinyl	0.10	5.6	>10	>10
3g	Me	*c*Pr	0.028	0.217	>10	>10
3h	Me	*t*Bu	0.091	2.38	—	5.57
3i	Me	CHMeEt	0.009	0.083	>10	6.03
3j	Me	*n*Pn	0.13	—	—	—
3k	Me	*c*Hexyl	0.16	—	—	—
3l	Me	4-Methoxyphenyl	0.059	1.21	4.52	>10

IC_{50} values are reported in μM. Source of PDEs: human platelet PDE5, bovine retina PDE6, bovine heart PDE1, human platelet PDE3.



Scheme 2. Reagents and conditions: (i) WSCD, HOBt, CH_2Cl_2, H_2O, 40 °C; (ii) NaOH, MeOH, H_2O, 60 °C; (iii) neat $ClSO_3H$, 40–60 °C, 30 min; (iv) amine, DMF, RT, 18 h.



We next probed the effect of variation of the 8-aryl group substituents. Planning to later synthesise a range of sulphonamides suggested a more attractive route to the derivatives wherein the sulphonamides could be introduced in the final step of the synthesis (Scheme 2). Ortho substituted benzoic acids **6** were either commercially available or synthesised by alkylation of salicylic acid methyl ester with the corresponding alkyl bromide and saponification. Condensation of **6** with diamino uracil **4** gave the simple C8 aryl xanthines **7**. An initial appraisal of the PDE5 inhibitory activity of the various 8-aryl xanthines **7** was made (Table 2) before preferred compounds (**7d**, **e**, **f**, and **g**) were converted to the reactive sulphonyl chlorides **8** and thence to the sulphonamides **9**. *O*-Dealkylation was problematic during chlorosulphonic acid treatment of **7f**, presumably due to the greater stability of the *i*Pr cation, hence an alternative sequence analogous to Scheme 1 was used for the preparation of **9f**.

Table 2. PDE5 activity and isoform selectivity: variation of substituents at C2′ of the 8 phenyl IMBX skeleton

Compd	R_3	hPDE5	bPDE6	Ratio PDE5/PDE6
7a	H	>10	—	—
7b	OH	>10	—	—
7c	OMe	1.81	—	—
7d	OEt	0.073	0.227	3.1
7e	O-*n*Pr	0.060	0.087	1.4
7f	O-*i*Pr	0.077	0.214	2.8
7g	O-*n*Bu	0.135	0.436	3.2
7h	O-*i*Bu	0.105	0.073	0.7
7i	O-*n*Pn	0.551	—	—
7j	OCH_2Ph	>10	—	—
7k	OCH_2CH_2OMe	1.50	—	—
7l	F	>10		
7m	NHMe	>10		
7n	NMe_2	>10		
7o	SMe	5.42		

IC_{50} values are reported in μM.

Table 3. PDE5 activity and isoform selectivity: variation of substituents at C2′ of the sildenafil–IBMX hybrid skeleton

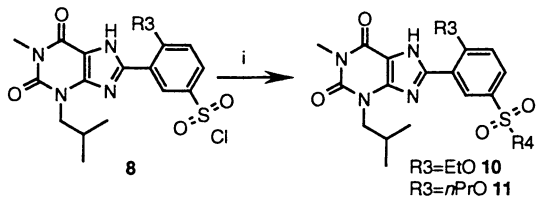
Compd	R_3	hPDE5	bPDE6	Ratio PDE5/PDE6
3a	OEt	0.020	0.100	4.9
9e	O-*n*Pr	0.010	0.006	0.6
9f	O-*i*Pr	0.016	0.077	5.0
9h	O-*i*Bu	0.093	0.102	1.1

IC_{50} values are reported in μM.

For derivatives **7**, optimal PDE5 potency is achieved when R3 is a small alkyl ether which is a similar trend to that disclosed by Terrett et al. in the optimisation of sildenafil.[2a] Interestingly, ethers appear preferred over thioethers (**7c** vs **7o**) both of which have higher potency that the nitrogen substituents (**7m** and **7n**). Introduction of an additional hetero atom into the alkyl group results in a substantial loss of activity (**7g** vs **7k**). These compounds show little selectivity over PDE6. Again, similarly to sildenafil, introduction of the piperazinyl sulphonamide increased potency at PDE5, however, little obvious trend in selectivity for PDE6 was apparent (Table 3). Interestingly these SAR trends also mimic that of sildenafil[2a] providing additional convincing evidence to support our overlay hypothesis.

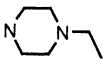
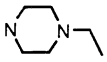
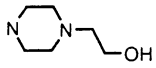
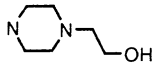
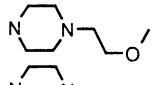
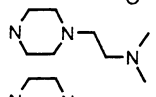
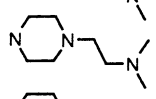
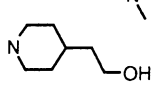
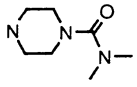
The ethyl and propyl ethers were selected for further optimisation at the sulphonamide group. Key intermediates **8** (R = OEt and O*n*Pr) were synthesised on gram scale and a library of sulphonamides prepared in 96-deep-well plates, with purification by preparative HPLC (Scheme 3). Representative examples are shown Table 4. In general the most potent PDE5 inhibitors contained a propyl ether at C2′ (e.g., **3a** vs **11d**, **11e** vs **10e**, **11f** vs **10f** and **11h** vs **10h**). In the case of piperazinylsulphonamides selectivity over PDE6 was generally poor, the simpler derivatives showing best selectivity (up to 7.5-fold) when R3 = OEt. High potency and improved PDE6 selectivity could nevertheless be obtained with *N*-dimethyl-ethylaminosulphonamides, for example **11c**.

Biopharmaceutical charaterisation of some representative derivatives is presented in Table 5. Potent com-



Scheme 3. Reagents and conditions: (i) amine, DMF, rt, 18 h.

Table 4. PDE5 activity and isoform selectivity: variation of substituents at C5′ of the 8 phenyl IMBX skeleton

Compd	R_4	hPDE5	bPDE6	Ratio PDE6/PDE5
11a	NH_2	0.005	0.016	3
11b	$NEt(CH_2CH_2NMe_2)$	0.011	0.242	22
11c	$NMe(CH_2CH_2NMe_2)$	0.016	1.15	72
11d		0.010	0.006	0.6
11e		0.0055	0.003	0.5
10e		0.026	0.203	7.5
11f		0.0035	0.015	4
10f		0.019	0.068	3.5
11g		0.012	0.091	7.5
11h		0.024	0.037	1.5
10h		0.063	0.146	2.5
11i		0.003	0.017	5.5
11j		0.0035	0.014	4.0

IC_{50} values are reported in μM.

Table 5. Biopharmaceutical properties of selected PDE5 inhibitors

	3i	**11j**	**11i**	**11c**
Physical properties				
M_r	518.6	575.7	547.7	534.7
cLog P	3.81	4.04	3.67	3.90
PSA	92.9	107.3	115.1	96.6
Kinetic solubility				
pH 7.4 (mg/L)	ca. 100	ca. 25	ca. 5	—
pH 5 (mg/L)	>200	ca. 25	ca. 5	—
Caco2 permeability				
$P_{app} \times 10^{-5}$ cm s^{-1}	3.45	2.29	1.32	0.03
In vitro microsome metabolism Cl_{int}:				
(μL/min/mg) rat	178	185	226	—
human	114	71	High	—
Rat in vivo PK				
$t_{1/2}$ (min)	92±8	22±3	[a]	—
Vss (L/kg)	9.7±0.5	3.4±0.5	[a]	—
CL (mL/kg)	94±6	140±10	[a]	—
BAV id	11%	0%	0%	—

[a]Clearance too fast to determine reliably.

pounds were associated with high PSA values; however, this did not always result in poor permeability. Xanthines containing a basic amino residue gave significantly better solubility. A more recurrent problem was high intrinsic and in vivo clearance resulting in short half-lives and poor bioavailability. We felt that this together with the high molecular weight of the template precluded likely progression of this series. Shortly after the termination of our studies a closely related series of compounds was published by workers from Almirall Prodespharma.[12]

In conclusion, we have shown that xanthines containing an 8-(2-alkyloxy-5-aminosulphonyl) phenyl substituent can serve as potent inhibitors of PDE5. Small alkyl groups are favoured substituents at the N1 and N3 positions of the xanthine whereas a large variety of sulphonamides are tolerated at C5′ of the 8 aryl group. Variation at this position provides potent PDE5 inhibitors and allows selectivity up to 70-fold to be achieved versus the closely related PDE6 isoform.

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