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A Solid-Phase Approach Towards the Synthesis of PDE5 Inhibitors

David Beer, Gurdip Bhalay,* Andrew Dunstan, Angela Glen, Sandra Haberthuer and Heinz Moser

Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB, UK

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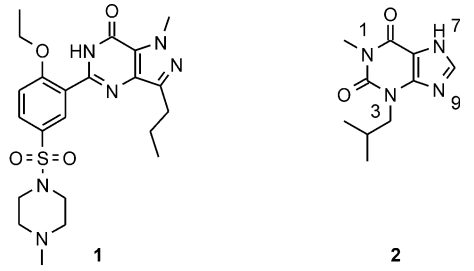
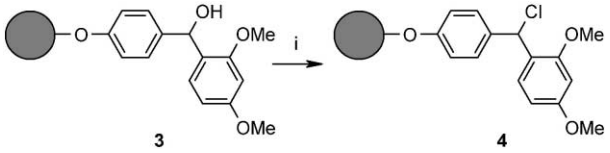
Abstract—PDE5 inhibitors based upon the xanthine scaffold **8** have been expediently synthesized using a solid-phase route. Attachment of the xanthine scaffold **8** using the Rink chloride linker **4** and *N*-1 functionalization using Mitsunobu chemistry is described. A library of compounds was produced in multi-milligram quantities with excellent purities and acceptable yields. The compounds were tested for their PDE5 inhibitory activity.

Erectile dysfunction[1] (ED) is defined as the inability to achieve and maintain an erection to permit satisfactory sexual intercourse. The major contributors to this condition include: age, diabetes, heart disease, hormone levels, hypertension, psychological influences and physical injury such as damage to the spinal cord. ED is a common and important problem; it has been estimated that in the United States alone up to 30 million men suffer from ED.[2] Investigations to elucidate the mecanism of ED have revealed the importance of the enzyme phosphodiesterase 5 (PDE5). The cyclic nucleotide phosphodiesterases (PDEs) are a super family of enzymes that catalyze the hydrolysis of cyclic nucleotides, cAMP and cGMP to their 5′-nucleoside monophosphates via cleavage of the phosphodiester bond. PDE5 is the principal cGMP hydrolyzing enzyme found in smooth muscle (*corpus cavernosum*) in the penis. Upon sexual stimulation and under normal physiological conditions the neurotransmitter nitric oxide is released from non-adrenergic, non-cholinergic neurons from nerve endings in the penis. This results in the activation of soluble guanylyl cyclase, which converts GTP to cGMP. Therefore the inhibition of PDE5 leads to the elevation of cGMP levels, which produces greater relaxation of smooth muscle, producing an increased blood flow in to the *corpus cavernosum* tissue resulting in an erection.

Sildenafil[3] **1** (Viagra™) is an efficacious PDE5 inhibitor used for the treatment of male ED and made an enormously successful launch in 1998. Despite its great success, for some patients there are some side-effects associated with its use. Some of the problems have been associated with: headaches, visual disturbances, nausea, facial flushing and dyspepsia. These are thought to arise from the inhibition of other PDEs. The search for more selective[4] PDE5 inhibitors is of interest to us and others. We decided to start our program by investigating the xanthine structural motif. From previous work, it was known that 3-isobutyl-1-methylxanthine[5] (IBMX) **2** is a potent and non-selective inhibitor of PDE (Scheme 1). We were interested in this class of compounds as a potential source of selective PDE5 inhibitors (Scheme 2).



Scheme 1. Sildenafil **1** and isobutyl methylxanthine (IBMX) **2**.



Scheme 2. Preparation of the Rink chloride linker. Reagents: (i) C_2Cl_6, PPh_3, THF, rt, 6 h.

*Corresponding author. E-mail: gurdip.bhalay@pharma.novartis.com

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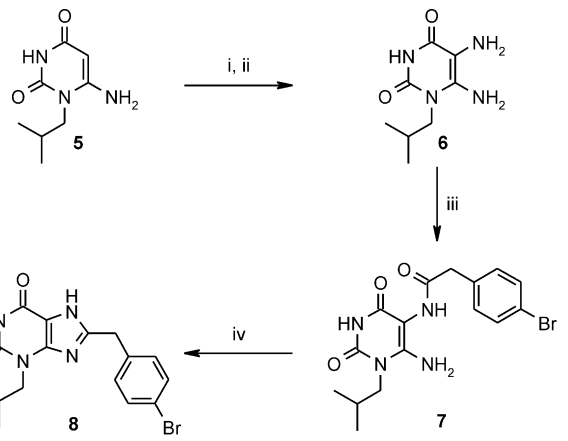
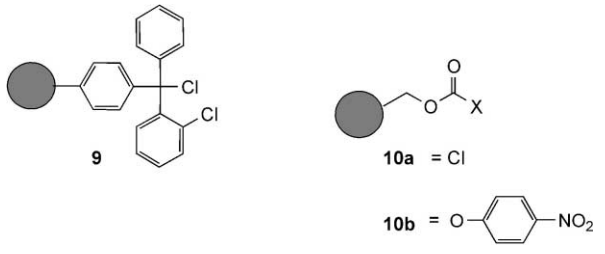
Synthesis of the desired xanthine scaffold[6] **8** (Scheme 3) started from the uracil **5**. Reaction with sodium nitrite in acetic acid and aqueous ethanol at 0 °C for 1 h produced the nitroso intermediate (75%), which was subjected to a dithionite reduction using sodium thiosulphite in water giving the diamino uracil **6** (97%). The amide **7** was produced by direct condensation of 4-bromophenylacetic acid and the diamino uracil **6** by heating the powdered mixture at 140 °C to achieve molten form and held there for 1 h (80%). Finally, the construction of the xanthine heterocycle was completed by heating **7** with a solution of sodium hydroxide and methanol, giving the xanthine product **8** (75%) (Scheme 4). To initiate the program and to provide a rapid understanding of the SAR of **8** we required a robust method which would allow for the swift generation of xanthine **8** analogues differing at R1 (Scheme 5). In order to construct a series of compounds that differed at *N*-1 (xanthine numbering, see **2**) we first attempted to attach xanthine **8** to commercially[7] available 2-chlorotrityl chloride resin **9** (Scheme 4) by treating with a solution[9] of **8** in DMF and Hunig's base. Under these conditions we failed to anchor **8** to the solid support. Similar disappointment was borne using **10a** and **10b**. In the case of **9** we reasoned that the steric challenge posed by the 2-chlorotrityl chloride linker **9** was the primary reason for this failure, so we turned our focus towards the Rink chloride linker[8] **4** (Scheme 2). Transformation of the Rink amide linker **3** to the chloro analogue **4** (Scheme 2) was achieved following a reported[8] method using a mixture of hexachloroethane and triphenylphosphine in THF (rt, 6 h). This was followed by the addition of a solution[9] of xanthine **8**. Evidence for the attachment of the xanthine **8** was obtained using FT-IR spectroscopy, which showed a C=O stretch at 1687 cm^{-1}. To determine loading, the support bound xanthine **11** was cleaved from the resin by exposing **11** to a solution of TFA in DCM (5% v/v) for 30 min at rt. This gave the expected xanthine **13** (R1 = H) as the trifluoroacetate salt. The loading was calculated through mass balance and typically ranged between 40 and 50%.

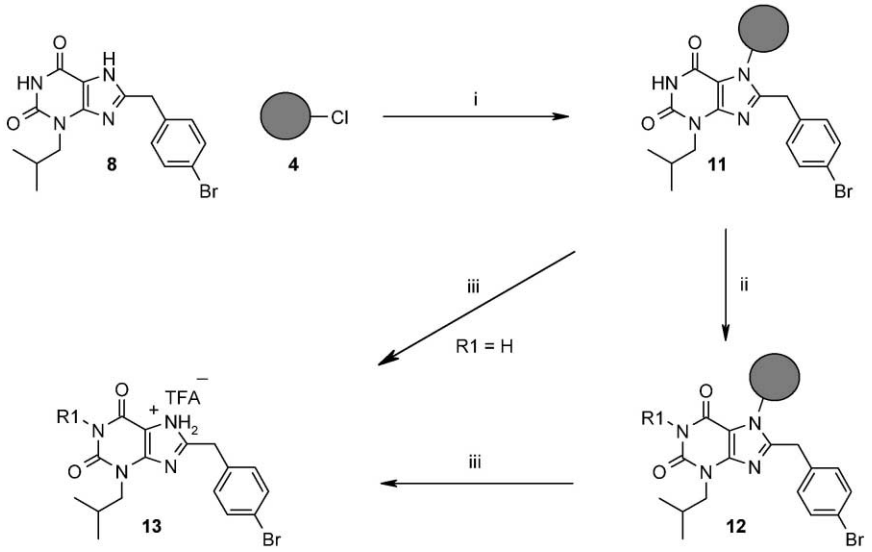


Scheme 3. Synthesis of xanthine **8**. Reagents: (i) $NaNO_2$, AcOH/EtOH/H_2O (1:3:2 v/v/v)), 0 °C, 1 h; (ii) $Na_2S_2O_4$, H_2O, 85 °C, 1 h; (iii) 4-bromophenylacetic acid, 140 °C, 1 h; (iv) NaOH (2 M), MeOH/H_2O (7:1 v/v), 70 °C, 3 h.



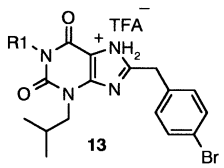
Scheme 4. Linkers that failed to tether the xanthine scaffold **8**.

The loading is remarkable considering the highly dilute conditions[9] necessitated by the poor solubility of the xanthine scaffold **8**. The point of attachment of xanthine **8** with the solid support could be via *N*-7 or *N*-9 (xanthine numbering, see **2**). Either way, it provides for an anchored scaffold which upon cleavage from the solid support releases the compound. The preparation



Scheme 5. Solid-phase route for the synthesis of **13**. Reagents: (i) DMF, Hunig's base, RT, 6 h; (ii) R1-OH, DBAD, PPh_3, THF, rt, 1 h; (iii) TFA 5% in DCM, rt, 30 min.

Table 1. PDE 5% inhibition data for the R1 derivatives of **13** tested at 1 μmol and also showing chemical yields and purities



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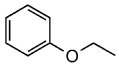
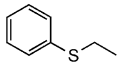
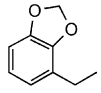
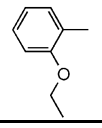
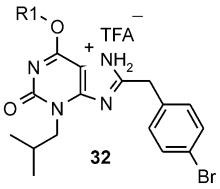
No	R1	PDE5 Inhibition (%)[10]	Yield (%)[11]	Purity (%)[12]
14	H	42	47	97
15	Me	93	45	98
16		93	47	97
17		57	44	97
18		68	46	98
19		35	46	96
20		4	45	96
21		42	46	97
22		88	44	97
23		38	46	96
24		41	45	98
25		59	45	98
26		22	46	97
27		20	47	97
28		33	46	97
29		15	46	98
30		13	45	96
31		38	44	97

of the *N*-1 derivatives **14**–**31** (Table 1) was achieved by reaction of the solid supported xanthine **11** (Scheme 5) under the Mitsunobu[13] conditions of triphenylphosphine, di-*tert*-butyl azodicarboxylate in THF (rt, for 1 h) and the appropriate alcohol[14] giving **12**. Resin **12** was then exposed to the cleavage solution [TFA (5% v/v), 30 min, RT] releasing the required products in useful yields and high purities (Table 1).



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Scheme 6. *O*-Alkylated 'by-product'.

Under the Mitsunobu conditions used for *N*-1 alkylation, we were prepared for the possibility of *O*-alkylation. Pleasingly we saw no evidence (using ^{1}H NMR and ^{13}C NMR) for the production of the unwanted *O*-alkylated product **32** (Scheme 6).

From the percentage PDE5 inhibition data (Table 1), some interesting features are evident. The unsubtituted xanthine **14** shows moderate activity and it is clear that small alkyl groups are favoured, with methyl **15** and ethyl **16** analogues displaying the same value (93%). Short chain bulk, as in the cyclobutyl derivative **20** and heteroaromatic derivatives **26**, **27** have a deleterious effect on inhibition. Derivatives **22**–**25** showed an improved solubility profile in a range of solvents, but only the alcohol derivative **22** retained good activity.

In conclusion, we have broadened the utility of the Rink chloride linker to allow for the loading of xanthine heterocycles. And using Mitsunobu chemistry we have been able to synthesize a range of analogues differing at *N*-1. Moreover, using an appropriate scaffold this methodology could be used to perform further changes on the heterocycle. The preliminary data suggest that xanthines containing a methyl, ethyl or hydroxymethyl substituent (**15**, **16** and **22**, respectively) at *N*-1 may serve as potent inhibitors of PDE5. Further work will be reported in due course.

References and Notes

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9. The xanthine **8** was poorly soluble in DMF and required the addition of Hunig's base to aid dissolution.
10. Inhibition of PDE5 enzyme activity was determined with a [^{3}H]cGMP scintillation proximity assay using yttrium silicate beads (Amersham Pharmacia Biotech). % inhibition values quoted were obtained from testing at 1 μmol.
11. Yield calculated using mass balance.
12. Purity calculated using HPLC 254 nm.
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14. For **22** and **23**, 2-*tert*-butoxyethanol and 2-(hydroxyethyl) carbamic acid *tert*-butyl ester were used respectively in the Mitsunobu reaction. With the initial product off resin, the final compound was obtained by treatment with 95% TFA in DCM for 1 h (rt).