An efficient route to xanthine based A_{2A} adenosine receptor antagonists and functional derivatives†

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A one-pot route to 8-substituted xanthines has been developed from 5,6-diaminouracils and carboxaldehydes. Yields are good and the process applicable to a range of substrates including a family of A_{2A} adenosine receptor antagonists. A new route to the KW-6002 family of antagonists is presented including a pro-drug variant, and application to related image contrast agents developed.

Introduction

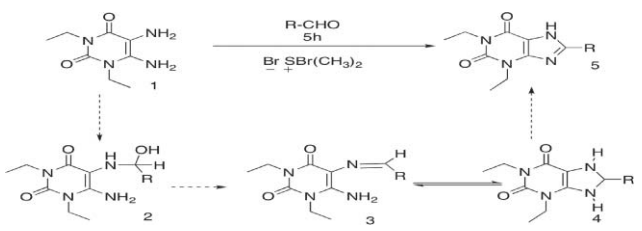
Due to pathway interactions between A_{2A} and D_2 receptors, antagonists of the adenosine receptor have become major targets in CNS drug discovery.[1] Lead compounds based on the xanthine skeleton, including the chlorostyryl caffeine CSC,[2] the thienylated xanthine DMPTX,[3] and the dimethoxystyryl xanthine KW-6002 have been investigated.[4] Based on promising results obtained with co-administration of levodopa, KW-6002 (Istradefylline®), is a clinical candidate for Parkinson's disease.[5] Several annulation strategies have been explored in the construction of the xanthine backbone, most commonly *via* disconnection to the corresponding amino-acylaminouracil,[6] or closure of the 6-amino-5-iminouracils, typically utilizing oxidative methods.[7]

Results and discussion

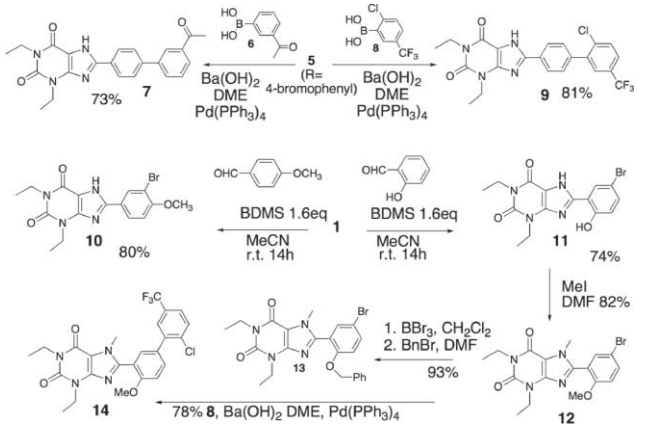
Given the importance of the xanthine class we became interested in developing a one-pot method through direct coupling of carboxaldehydes with readily available 5,6-diaminouracils **1** under mild conditions.[8]

Under stoichiometric conditions, simple aldehydes coupled with **1** to produce high yields of xanthines **5** presumably *via* the imine intermediate **3** and/or its aminal form **4** (Scheme 1).[9] Attempts to isolate presumed intermediates **2** and **4** were unsuccessful but at 10 mol% BDMS substantial buildup of imine **3** occurs. Nonetheless, using 0.6 equivalents of BDMS very high yields of the product xanthines **5** are attainable, suggesting the BDMS is regenerated during the cycle. Under closer scrutiny, DMSO, Me_2S, HBr and H_2O can all be detected during the reaction. DMSO, formed either directly through oxidative elimination from **2** with BDMS or *via* attack of Me_2S by *in situ* generated HOBr, can be reconverted to BDMS by reaction with $HBr/Br_2/H_2O$. Me_2S and HBr could in turn be released by BDMS in facilitating dehydrogenation of aminal **4**, either through collapse of an N-bromo intermediate, or *via* bromide induced dehydrogenation, with the aminal C–H departing as hydride to capture the bromonium ion of the BDMS. Clearly, the intricacies of the process warrant further investigation and thorough kinetic analysis, given the high efficiency of the method. The process proved amenable to a broad range of substrates (Chart 1), and requires only trivial purification of products **5**.

The utility of the bromo-substituted products for subsequent transformations was readily demonstrated through Pd mediated coupling to give analogs **7** and **9** (Scheme 2). Given the ease of coupling we were motivated to investigate the potential for *in situ* tandem ring closure and bromination, and after some effort determined that utilization of 1.6 equivalents of the reagent (0.5 for 4 h then and additional 1.1 eq. for 10 h) effected conversion of *p*-methoxy benzaldehyde and salicylaldehyde into **10** and **11** respectively. The utility of the phenolic functionality was further



Scheme 1 BDMS accelerated condensation in synthesis of the xanthine core



Scheme 2 Pd coupling and *in situ* dehydration-aryl bromination en route to functionalized xanthines

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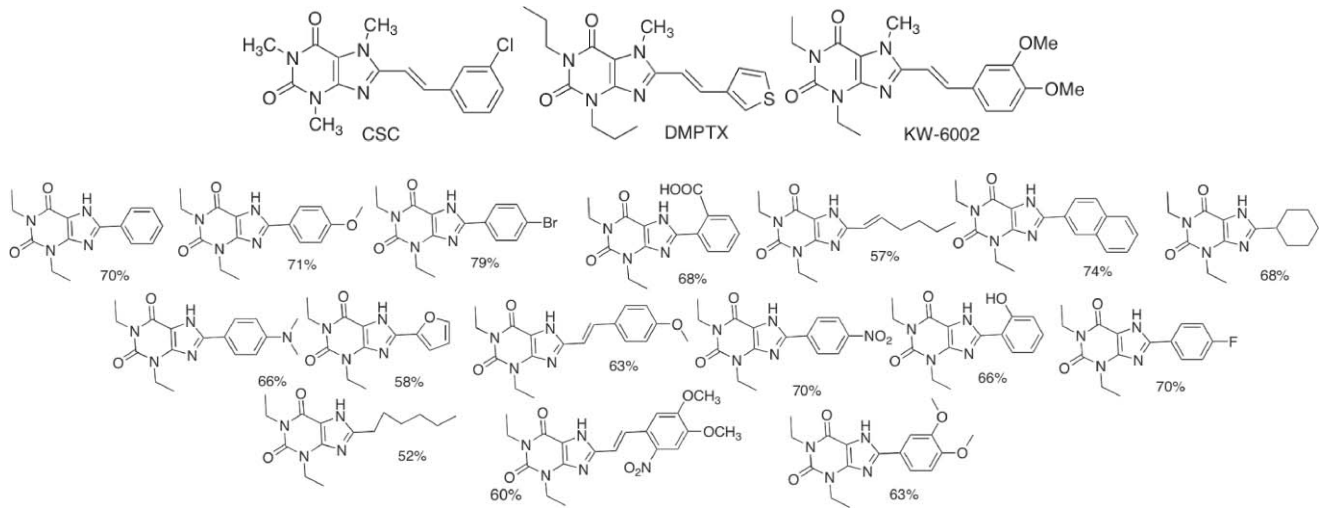
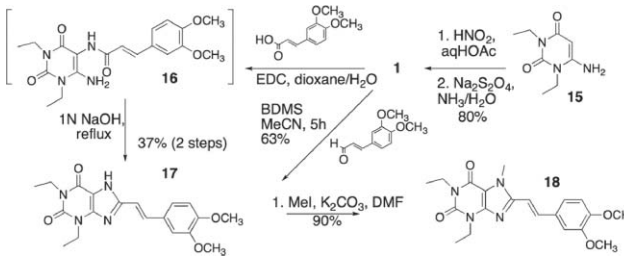
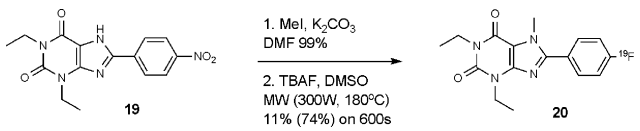


Chart 1 Xanthines accessible *via* BDMS route



Scheme 3 Application of BDMS methodology to synthesis of KW-6002.



Scheme 4 Fluorodenitration route to potential labeled PET imaging agents

demonstrated through conversion to **12** and **13**, and the bromo group through Suzuki coupling of **12** to produce **14** (Scheme 2).

Microwave accelerated conditions to expedite the ring closing process were also investigated, 4-bromobenzaldehyde reacting (CEM Discover, 150 W, 110 °C, 100 psi, CH_3CN) to produce the corresponding xanthine in 72% yield ***within 30 min***. This result bodes well for the application of the method for the rapid production of libraries of xanthine derivatives under automated conditions.[10]

In order to demonstrate the effectiveness of our approach, we conducted a comparative synthesis of KW-6002 (**18**, Scheme 3) from **1**. As can easily be seen the direct route to key intermediate **17** is superior, and opens the prospect of targeted library design for the class. Given the importance of the KW-6002 agents in modulating CNS related pathways, methods to allow *in vivo* imaging will likely become of significance. A route to a ^{11}C labeled version has been reported,[11a] and given its time-to-peak plasma concentration of 2–5 h,[11b] a suitably functionalized ^{18}F labeled derivative would presumably offer considerable utility in extended PET imaging studies of this class of agent.[11c]

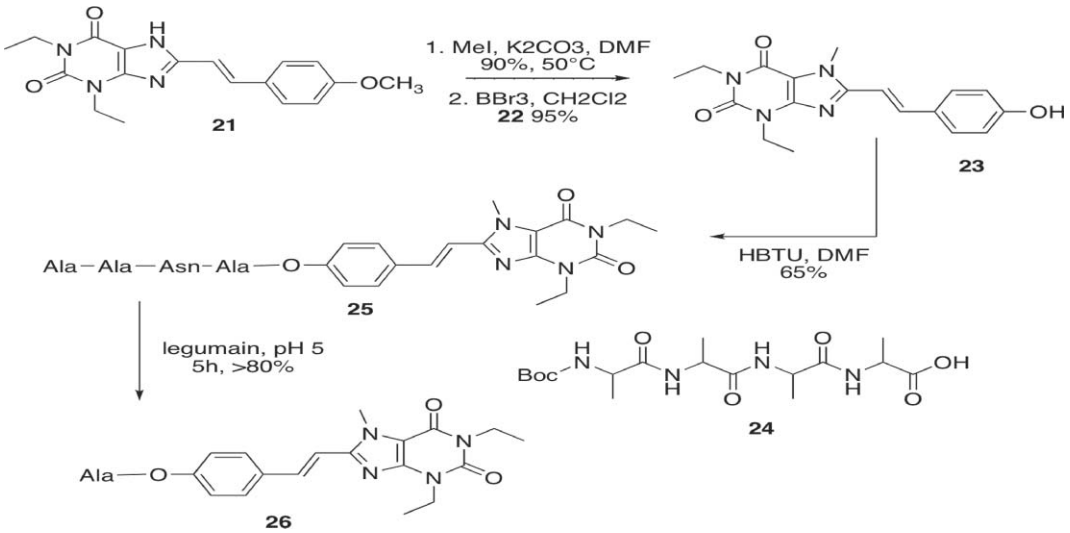
To demonstrate proof-of-principle, nitrosubstituted xanthine **19** was *N*-methylated then subjected to microwave accelerated fluorodenitration using anhydrous TBAF giving appreciable quantities of **20** in <10 min (Scheme 4).[12]

Given the half life of ^{18}F (120 min), we expect cyclotron derived ^{18}F variants of this process to be useful in preparation of agents for direct PET imaging of KW-6002.[13]

In addition to use in CNS disorders, KW-6002 has shown promise as an antitumoral agent, but suffers from poor water solubility *in vivo*.[14] Accordingly we sought to synthesize a hydrophilic variant in the form of a prodrug, as the hydrophobic xanthine core imparts A_{2A} receptor affinity.[15] After consideration, a tetrapeptide substrate for the enzyme legumain was designed, being the only asparaginyl endopeptidase of the mammalian genome, and over expressed in neoplasms.[16] Alkylation and *O*-demethylation of substrate **21** allowed phenolic coupling of **23** with the boc protected tetra-peptide **24** (Scheme 5).[17] A series of enzymatic digests were examined on substrate **25**, which gave clean conversion to alanine conjugate **26** within 5 h. This promising prodrug, which presumably does not cross the blood brain barrier effectively is now the subject of extensive *in vitro* and *in vivo* antitumoral assays.

Conclusions

In summary, a direct route to the xanthine class of adenosine receptor antagonists has been developed. The process is efficient, scalable, and can be applied to versatile and diverse library construction. In the case of aryl aldehyde substrates tandem *in situ* bromination of the products is an effective adaptation of the process, and promises to extend the versatility in the form of heavily substituted xanthine derivatives. Potential use of xanthine derived A_{2A} antagonists for *in vivo* imaging and as antitumorals may be facilitated by synthesis of derivatives bearing radiolabels and enzyme substrates, using additional methodology outlined herein.



Scheme 5 Preparation and functionalization of xanthine prodrug conjugates.

Representative experimental procedure

Synthesis of 8-(5-bromo-2-hydroxyphenyl)1,3-diethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

(Bromodimethyl)sulfonium bromide (0.879 g, 4.0 mmol) was added (in two portions) to a mixture of *p*-methoxybenzaldehyde (0.3053 g, 2.5 mmol) and 1,3,-diethyl-5,6-diaminouracil (0.495 g 2.5 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 14 h. The precipitate formed was collected by vacuum filtration, washed with ethyl acetate and dried *in vacuo*. The crude solid was purified by recrystallization from DMSO and water to yield the title compound (0.66 g, 73%) as a white solid m.p. 315–317 °C; TLC (dichloromethane–methanol = 19 : 1): R_f 0.30; ^{1}H NMR (500 MHz, d6-DMSO): δ 13.80–14.20 (brs, 1H), 11.75–12.10 (brs, 1H), 8.29 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.5, 2.5 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 4.08 (q, J = 7.5 Hz, 2H), 3.96 (q, J = 7.5 Hz, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, d6-DMSO): δ 156.6, 154.4, 150.7, 150.6, 148.1, 135.1, 129.7, 120.2, 118.0, 115.3, 111.3, 55.6, 39.2, 36.7, 13.9; HRMS (ESI) m/z calcd for $C_{15}H_{16}BrN_4O_3$ $(M+H)^+$: 379.0406, found, 379.0401.

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