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Imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones, a New Class of Potent PDE 5 Inhibitors

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Abstract—2-aryl-substituted imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones represent a new class of potent cGMP-PDE 5 inhibitors that prove to be superior to other purine-isosteric inhibitors. Subnanomolar inhibitors of PDE 5 with activity in in vivo models for erectile dysfunction have been identified. BAY 38-9456 (Vardenafil-hydrochloride) has been selected for clinical studies in the indication of erectile dysfunction.

Introduction

The intracellular level of cyclic guanosine monophosphate (cGMP) is regulated by synthesis (via guanylatcyclase) and by degradation to GMP by the phosphodiesterase (PDE) family of isoenzymes. Among the plethora and still increasing number of PDEs, several types selectively hydrolyze either cGMP (PDE 5, PDE 6, PDE 9) or cyclic adenosine monophosphate (cAMP) (PDE 3, PDE 4, PDE 7, PDE 8), whereas other isoenzymes are more promiscuous and accept both cyclic nucleotides as a substrate (e.g., PDE 1, PDE 2, PDE 10, PDE 11). The NO/cGMP system plays a central role in the hemodynamic process of erection.[1–6] The PDE mainly responsible for cGMP degradation in penile tissue is PDE 5 (cGMP specific PDE).[7] Selective inhibitors of this isoenzyme increase the cGMP level in the corpus cavernosum, cause erection via relaxation of the penile arterioles.[8–10] and minimize potential side effects.

It is well known that suitably substituted purinones as analogues of cGMP are potent PDE inhibitors in vitro.[11,12] Xanthineoxidase plays a major role in metabolizing the purinone system of xanthine by hydroxylation of the 8-position in the imidazole part of the molecule[13] (Fig. 1).

We hypothesized that blockage of the metabolically labile position by substitution of the carbon atom for a heteroatom may render the heterocyclic core metabolically more stable (Fig. 2).

A great variety of purine-isosteric heterocyclic systems has been reported in the literature.[14–21] Among those systems, the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones (Fig. 3) until now have attracted only limited attention as cAMP PDE inhibitors.[22]

Figure 1. Metabolic degradation of purines.

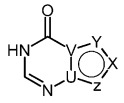

Figure 2. Blockage of metabolic degradation via heteroatom substitution.

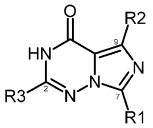

Figure 3. Imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones.

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Herein, we show that 2-aryl-substituted imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones represent a new class of potent inhibitors of cGMP-metabolizing PDE 5. Subnanomolar inhibitors of PDE 5 with excellent in vivo activity have been identified in this new class of PDE inhibitors.

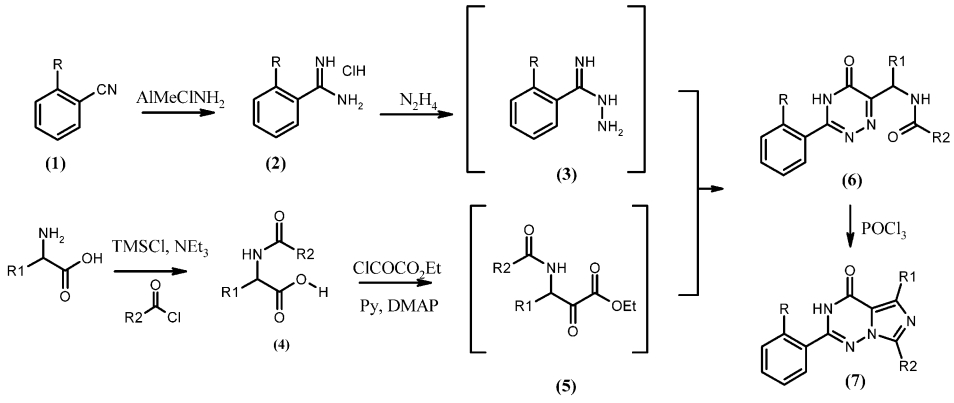
Results and Discussion

Imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones are purine-isosteric heterocyclic systems that were first described in the patentliterature[22] as bronchodilators.[22–28] Furthermore, products of their synthesis have been described as C-nucleoside isosteres[29–32] and purine analogues.[33]

The synthesis of 2-aryl-substituted imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones is shown below (Scheme 1):[34] Dakin–West reaction of the acylated amino-acid (**4**) yields the corresponding α-oxoamino-acid ester (**5**), which is condensed with the carboxymidohydrazide (**3**) to give intermediate (**6**). The required imidamide (**2**) can be obtained via a reaction between the corresponding nitrile and $AlMeClNH_2$,[35] prepared from $AlMe_3$ and NH_4Cl. Intermediate (**6**) is cyclized to the final heterocyclic system (**7**) using $POCl_3$. Highest yields for (**7**) were achieved (approximately 30%), when the intermediates (**3**), (**5**), and (**6**) were taken to the next step without isolation or purification. The α-oxoamino-acid ester (**5**) proved to be the most capricious intermediate and could never be obtained in a purity greater than 50%.

At this stage, it became obvious that the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones were ideal heterocyclic core systems for PDE 5 inhibitors (Fig. 4): In comparison to known isosteric heterocycles (e.g., **10**, **12**), superior IC_{50} values and improved selectivity for PDE 5 were obtained.[11,12,36,37]

Attachment of polar substituents on the aromatic ring improves PDE 5 inhibitory activity. Putatively, these



Scheme 1. Synthesis of imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones.

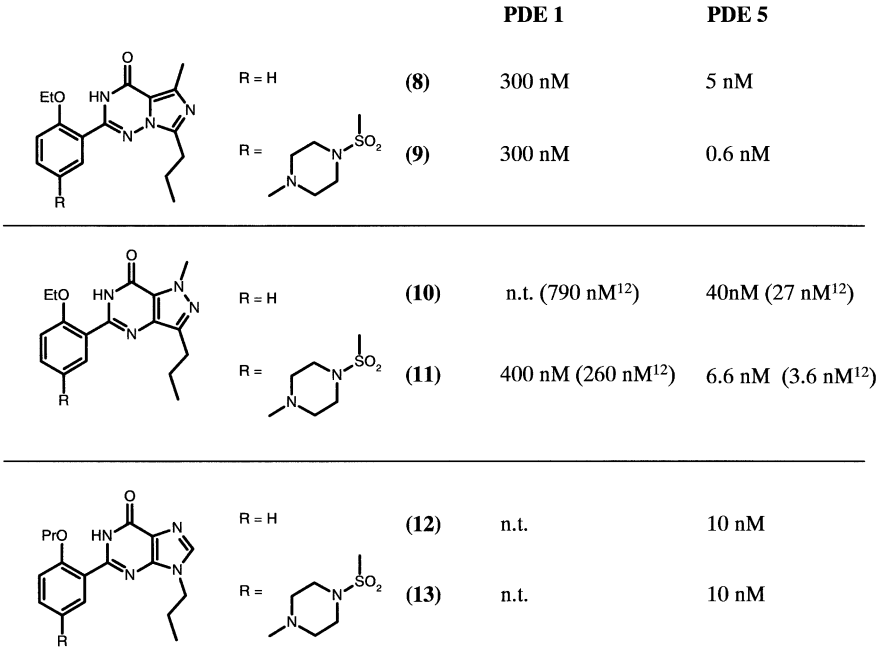


Figure 4. Comparison of PDE enzyme inhibition by different 2-alkoxyaryl and 5′-sulfonamidoalkoxyaryl purine isosteres.

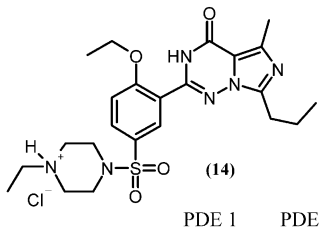


Figure 5. Vardenafil-hydrochloride, a clinical candidate for the treatment of erectile dysfunction.

polar substituents occupy space usually filled with the phosphate group of cGMP.[12]

In the case of R = OEt, the activated aromatic ring can be substituted selectively with various electrophiles at the 5′-position. The superior potency and increased selectivity of the imidazotriazinone heterocycle for PDE 5 inhibition is also observed in the sulfonamide analogue series (Fig. 4).

In comparison to the known pyrazolo[4,3-*d*]pyrimidin-7-one PDE inhibitors (e.g., Sildenafil)[12] and the dihydropurinones,[11,38–40] the imidazotriazinones show substantially improved PDE 5 inhibition and improved selectivity over PDE 1. The piperazine-sulfonamide residue renders these PDE inhibitors highly soluble and hydrophilic.

The *N*-ethylpiperazino derivative Vardenafil (**14**, Fig. 5) shows excellent PDE inhibitory activity and was selected as a potential candidate for further in vivo studies. It shows in vivo activity in a conscious rabbit model with a minimal effective dose of 3 mg/kg (po administration).[41]

All compounds of the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one type mentioned above are highly cGMP-PDE 5 selective and show IC_{50} values for PDE 3 and PDE 4 greater than 500 nM.

Summary

We have shown that with the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one heterocyclic system, highly potent inhibitors of cGMP-metabolizing PDE 5 can be obtained with superior in vitro potency and selectivity to other known purine-isosteric systems. BAY 38–9456 (Vardenafil-hydrochloride), a highly potent and selective PDE 5 inhibitor has been submitted to the FDA for approval for the treatment of erectile dysfunction.

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