Bioorganic & Medicinal Chemistry Letters 21 (2011) 5684–5687

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of PF-184563, a potent and selective V1a antagonist for the treatment of dysmenorrhoea. The influence of compound flexibility on microsomal stability

Patrick S. Johnson [a], Thomas Ryckmans [a,*], Justin Bryans [a], Dave M. Beal [a], Kevin N. Dack [a], Neil Feeder [b], Anthony Harrison [c], Mark Lewis [c], Helen J. Mason [a], James Mills [a], Julie Newman [a], Christelle Pasquinet [a], Dave J. Rawson [a], Lee R. Roberts [a], Rachel Russell [d], Deborah Spark [d], Alan Stobie [a], Toby J. Underwood [a], Robin Ward [d], Simon Wheeler [a]

[a] Pfizer Worldwide Medicinal Chemistry, Ramsgate Road, Sandwich Kent CT139NJ, UK
[b] Pfizer Pharmaceutical Development, Ramsgate Road, Sandwich Kent CT139NJ, UK
[c] Pfizer Department of Pharmacokinetics, Distribution and Metabolism, Ramsgate Road, Sandwich Kent CT139NJ, UK
[d] Pfizer Discovery Biology Ramsgate Road, Sandwich Kent CT139NJ, UK

ARTICLE INFO

Article history:
Received 11 July 2011
Accepted 6 August 2011
Available online 12 August 2011

Keywords:
V1a antagonists
Triazoles
LiPE
Lead optimisation
Number of rotatable bonds

ABSTRACT

The V1a receptor has emerged as an attractive target for a range of indications including Raynaud's disease and dysmenorrhoea. As part of an effort to discover a new class of orally active V1a antagonist, we optimised a highly lipophilic, metabolically unstable lead into a range of potent, selective and metabolically stable V1a antagonists. In this communication, we demonstrate the series-dependent effect of limiting the number of rotatable bonds in order to decrease Cytochrome P450-mediated metabolism. This effort culminated in the discovery of PF-184563, a novel, selective V1a antagonist with excellent in vitro and in vivo properties.

Vasopressin (AVP) is a small peptide that exerts its effects through the V1a, V1b, V2 and Oxytocin (OT) receptors.[1,2] The V1a receptor is expressed inter alia in smooth muscles, and its overactivation by elevated levels of AVP has been linked to both Raynaud's disease[3] and dysmenorrhoea. Clinical evidence shows that blockade of the V1a receptor by Relcovaptan **1** alleviates the symptoms of both these conditions.[3,4] As part of an effort to discover a new agent for the treatment of dysmenorrhoea, the triazole **2** attracted our interest as a novel V1a antagonist. An analog of this compound had been disclosed as a V1a antagonist.[5] (Fig. 1).

Despite modest potency and very high lipophilicity, compound **2** displayed a relatively high Ligand Efficiency[6] (LE) owing to its low molecular weight. Furthermore this chemotype is synthetically enabled, for example, each substituent on the triazole core can be introduced from widely available monomers (carboxylic acids and amines) using well-established methods. Early optimisation efforts on this lead focused on reducing the lipophilicity of the series, as high lipophilicity has been linked to a range of issues in development candidates, such as low solubility, high metabolic clearance, promiscuity and overall toxicity.[6,7]

The first key modification in this series was the replacement of the biaryl moiety of **2** with a 2-piperidyl pyridine group, resulting in compound **3**. Pleasingly, this compound proved to be only slightly less potent than **2** with a similar LE, and a *c*Log*P* reduced by 3 units. This translated into a much higher LiPE (4.4), a measure of binding efficiency per unit of lipophilicity and of overall lead quality.[8] Using this optimised 2-piperidyl pyridine scaffold, derivatives were prepared to further explore the SAR of the substituents at the 3- and 5-positions of the triazole.

Chemistry: The synthesis of compound **3** (R_1 = H) exemplifies the route to our final compounds **7a–f** and **8a–j**. Formation of bis-hydrazide **5** from the acid **4** was followed by a dehydrative cyclisation to oxadiazole **6**. Reaction of this oxadiazole with aniline formed the final triazole **3** in good yields. The full experimental details for the preparation of these compounds have been disclosed.[9,10] (Scheme 1).

Compounds **8a–d** were similarly obtained from the corresponding benzylamines; compound **8e** was prepared using butyryl hydrazide in step (a), while compounds **8f–j** were prepared by nucleophilic substitution from the corresponding 5-chloromethyl

* Corresponding author. Tel.: +44 1304 643 735; fax: +44 1304 651 817.
E-mail address: Thomas.ryckmans@gmail.com (T. Ryckmans).

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doi:10.1016/j.bmcl.2011.08.038

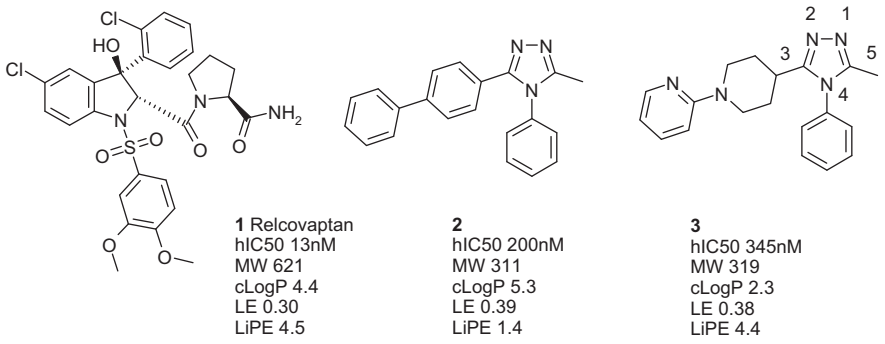


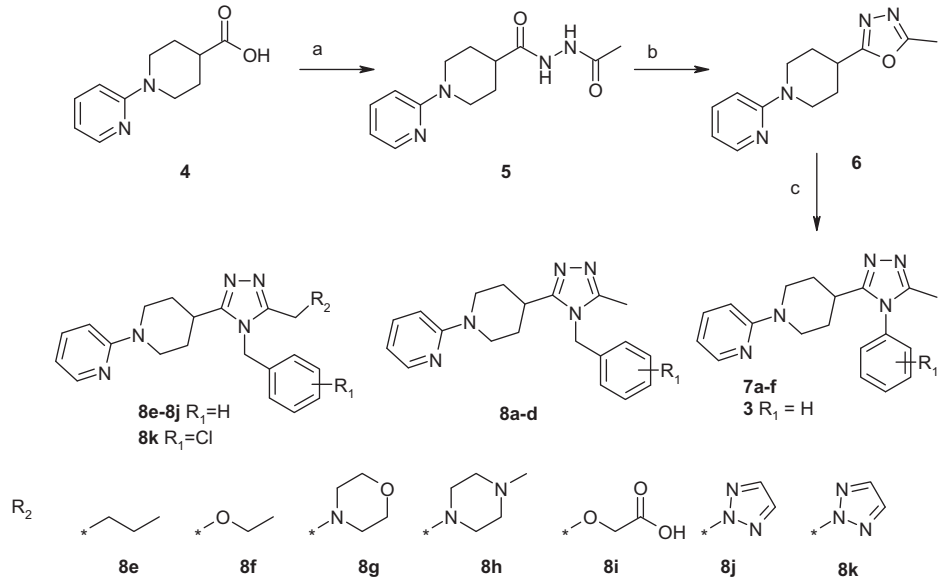
Figure 1. Structure of Relcovaptan **1** and lead **2**.

oxadiazole **9** (see Scheme 2) followed by step (c) using benzylamine.[9–11]

Results and discussion: Selected examples are presented here. For *N*-phenyl derivatives **7**, substituents such as 4-methoxy (**7a**), 4-methyl (**7c**) and 4-chloro (**7f**) proved beneficial to potency at the V1a receptor, with a concomitant increases in LiPE. The 4-CN and 4-CF_3 groups were poorly tolerated. Disappointingly, our most potent compound **7f** suffered from significant metabolic instability as measured in Human Liver Microsomes (HLM). Next, a series of *N*-benzyl derivatives was prepared. In this case, the 3-chloro compound (**8c**) displayed interesting potency but with similar metabolic liability to **7f**. Modification of the side chain at the 5-position of the triazole demonstrated that while basic (**8h**) and acidic (**8i**) groups were poorly tolerated, both lipophilic and polar side chains were beneficial to potency (compare **8a** with **8e** and **8f**). The best LiPE value was achieved with compound **8j**. Combination of the features of **8c** (R_1 = 3-Cl) and **8c** (R_2 = 2*H*-[1,2,3]triazolyl–) in **8k** proved to be additive in terms of potency, but also resulted in high metabolic instability. All potent derivatives **8** proved metabolically unstable despite their low *c*Log*P* values (Table 1).

In order to define a strategy to reduce microsomal clearance, we sought to find a correlation between HLM clearance and physicochemical properties using a larger dataset (60 compounds). Attempts to correlate *c*Log*P* with HLM clearance (a well established trend) were not successful, possibly because of the limited range of lipophilicity exemplified (85% of prepared compounds had *c*Log*P* values between 1 and 3). Another molecular descriptor linked to microsomal clearance is the number of rotatable bonds (NRB); compounds with high NRB (high flexibility) are more likely to adopt a conformation recognised by Cytochrome P_{450}. Indeed, plotting HLM clearance binned between low ($Cl_{int} < 10$), medium ($10 \leqslant Cl_{int} \leqslant 20$) and high ($Cl_{int} > 20$) values against NRB values showed that all stable compounds bar one (with a low *c*Log*P* of 0.6) had a NRB count below 5. Conversely, all compounds with a NRB > 7 displayed a high clearance, even at low *c*Log*P* values. (Fig. 2)

This analysis, albeit based on a limited dataset, led us to design a series of compounds in which conformational restriction was achieved by tethering the 3- and 5-substituents of the triazole. Reaction of chloromethyl oxadiazole **9** with bis nucleophiles **10** afforded the adduct **11**, which was cyclised under acidic conditions to give tethered compounds **12** and **13**. Full experimental details for the preparation of these compounds have been disclosed.[11–13] Cyclic ethers **12** proved mostly equipotent to their non-cyclic analogs, but generally displayed a trend toward higher metabolic stability (compare **12a** and **3**, **12c** and **7a**, **12d** and **7f**). This trend can be attributed to either (or both) the reduction in *c*Log*P* or NRB count for compounds **12a–d** compared with compounds **3** and



Scheme 1. Typical procedure for the synthesis of compound **6**. Reagents and conditions (a) oxalyl chloride (2 equiv), DCM, 25 °C, 16 h then acetylhydrazide (2 equiv), DCM, 25 °C, 16 h, 39%; (b) $POCl_3$ (excess), 100 °C 2 h 95%; (c) aniline or benzylamine (4 equiv), anhydrous $MgCl_2$ (0.3 equiv), 150 °C 18 h 75%, or xylene, *p*TSA (0.01 equiv), reflux 18 h.