Bioorganic & Medicinal Chemistry Letters 22 (2012) 1944–1948

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of 4-hydroxy-1,6-naphthyridine-3-carbonitrile derivatives as novel PDE10A inhibitors

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ARTICLE INFO

Article history:
Received 8 December 2011
Revised 12 January 2012
Accepted 13 January 2012
Available online 26 January 2012

Keywords:
PDE10A
Phosphodiesterase
Hit to lead
Enzyme inhibitor
Naphthyridine

ABSTRACT

A series of 1,6-naphthyridine-based compounds was synthesized as potent phosphodiesterase 10A (PDE10A) inhibitors. Structure-based chemical modifications of the discovered chemotype served to further improve potency and selectivity over DHODH, laying the foundation for future optimization efforts.

The cyclic nucleoside monophosphates cAMP and cGMP serve as critical intracellular signaling agents. Signal termination is regulated by hydrolytic cleavage of cAMP and cGMP by members of the phosphodiesterase (PDE) family of enzymes. Among the 11 PDE families, PDE10A has received significant attention as a possible target for new anti-psychotic or -diabetic drugs.[1–3] First generation, selective PDE10A inhibitors have been tested in animal models to explore the biochemical and behavioral consequences of inhibiting this molecular target. Papaverine and TP-10 (Fig. 1) are active in a number of models that predict anti-psychotic behavior[4,5] at doses that overlap the biochemical changes, suggesting a link between PDE10A inhibition and desired behavioral outcomes. These results are consistent with earlier studies testing PDE10A knockout mice in behavioral models.[6] Furthermore, papaverine and TP-10 demonstrated efficacy in rodent models of negative symptoms and cognition,[4] suggesting the potential for broad efficacy in schizophrenia with PDE10A inhibitors. Recent data suggest that β-cell PDE10A plays a role in regulating cAMP-induced glucose-stimulated insulin secretion (GSIS). Inhibition of PDE10A resulted in an increase in insulin release in vitro and was associated with improved glucose tolerance in vivo.[7] Moreover, inhibition of PDE10A had beneficial effects on weight loss. PDE10A KO mice challenged with a high fat diet were resistant to obesity, and administration of PDE10A selective inhibitors to diet-induced obese (DIO) mice resulted in weight loss.[8] Accordingly, PDE10A inhibition could provide an alternative therapeutic approach for the treatment of obesity and diabetes.

Several classes of structurally diverse PDE10A inhibitors have been described and examples are shown in Figure 1. Starting points have originated from the natural product papaverine,[3] random screening (TP-10, **1** and **2**),[9,10] and from fragment screening.[11]

In this paper, we describe the use of known ligand information applied to the discovery of PDE10A inhibitors. Starting from **2**, a hit-to-lead program was initiated with the intent to reduce its lipophilicity, whilst securing adequate PDE10A potency. Replacement of the D-alanine moiety of **2** was of particular importance, in order to minimize acylglucuronide formation and the potential risk for toxicity. We thus reasoned that a scaffold hop from quinoline to 4-hydroxy-1,6-naphthyridine (Fig. 1) would increase the overall polarity of the ligands and avoid the amino acid side chain of **2**, whilst enabling chemical variation of the substitution pattern. Accordingly, a number of initial compounds were synthesized (**3**–**4**, Scheme 1, and **5**–**6**, Scheme 2) to validate this hypothesis. The results are summarized in Table 1.

The hypothesized scaffold hop (**5**, PDE10A IC_{50}: 12 nM) offered an improvement in ligand efficiency (LE) and ligand lipophilicity efficiency (LLE) over **2**, while a 4-methoxy substituent (**6**) significantly decreased PDE10A potency (Table 1). The 3-cyano substituent was essential for significant PDE10A affinity (cf. **5** and **6**, Table 1).

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doi:10.1016/j.bmcl.2012.01.046

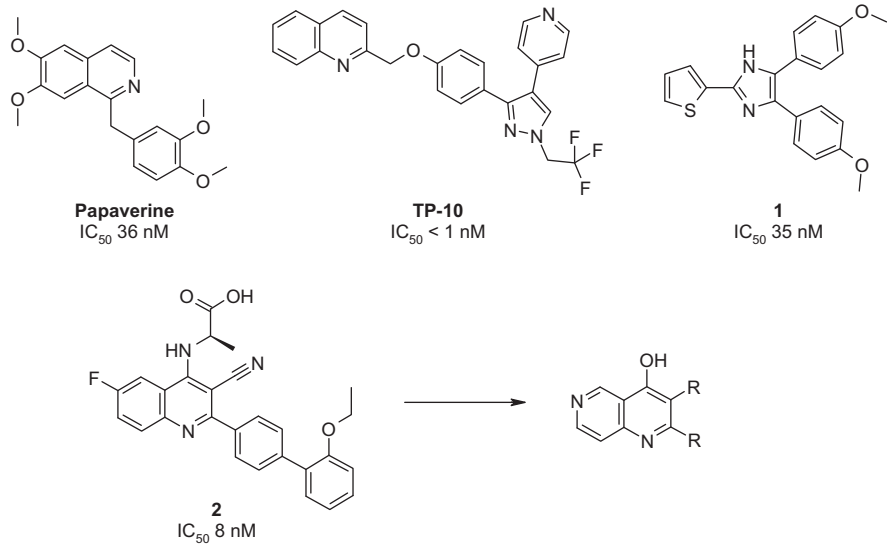
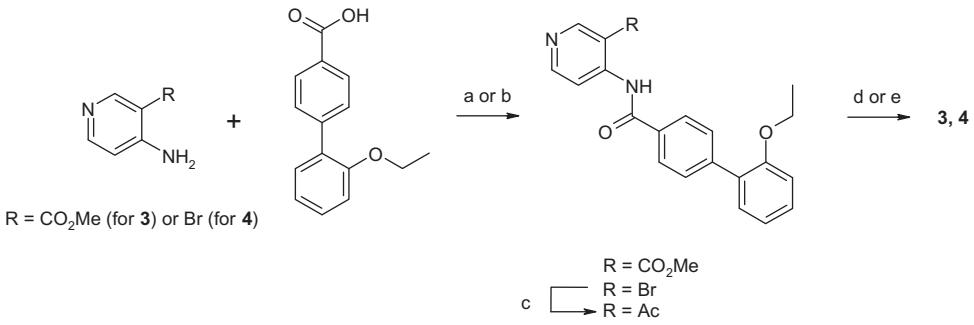


Figure 1. Selected examples of PDE10A inhibitor leads and initial scaffold hopping hypothesis.

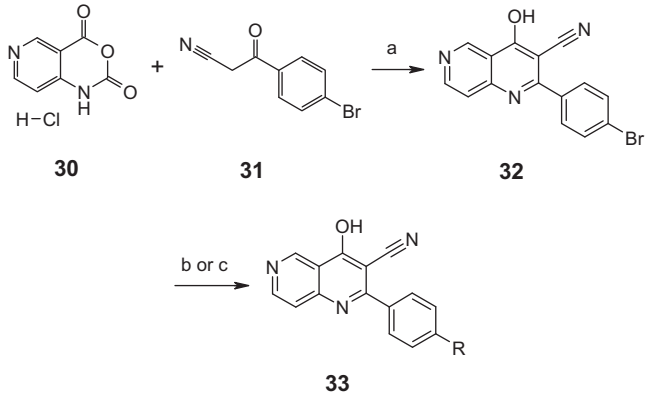


Scheme 1. Reagents and conditions: Synthesis of 3: R = CO_2Me, (a) TBTU, NEt_3, DCM, reflux, 3 d; (d) NH_3, MeOH, 160 °C, 4 h. Synthesis of 4: R = Br, (b) oxalylchloride, DCM, rt, 0.6 h, then NEt_3, DCM, rt, 2 h; (c) *n*-BuLi, THF, −78 °C to −30 °C, 1 h, then $CH_3CON(CH_3)OCH_3$, −30 °C to rt, 70 min, then aq HCl; (e) NaOH, dioxane, reflux, 35 min.

Having successfully simplified the ligand, we investigated whether PDE10A potency and LLE could be further improved over **5**. Based on the predicted, and subsequently experimentally determined (vide infra), three-dimensional molecular interaction between **5** and PDE10A, the distal phenyl ethoxy substituent was systematically modified, as shown in Table 2. Compounds **7**–**20** were synthesized following Scheme 2.

In general, ether substituents (**5**, **8**–**10**) afforded good PDE10A potency, with the bulky trifluoromethyl showing the best inhibition (**9**, PDE10A IC_{50}: 1 nM).[12] Small, electron-withdrawing (**11**–**14**) and electron-donating (**15**–**16**) groups displayed a PDE10A potency increase dependent on their volume (Table 2). Introduction of markedly polar substituents such as phenol (**7**), alcohol (**17**) and amines (**18, 19**) was not favoured, as shown in Table 2.

X-ray crystallography of the complex formed between compound **5** and PDE10A (Fig. 2, PDB code is 4ael) showed an atypical binding mode, with a papaverine-type hydrogen-bonding interaction with Q726 not observed.[13] The only polar interaction is a hydrogen-bond between Y693 and the N-1 of the naphthyridine ring system and disrupting this interaction led to a loss of potency. When R^2 (Table 2) is electron-withdrawing (e.g. nitrile), the enol tautomer of the 4-hydroxynaphthyridine is favoured,[14] thus N-1 acts as a hydrogen-bond acceptor and interacts with Y693. Non electron-withdrawing groups (e.g. $R^2 = CH_3$, compound **20** or $R^2 = H$, compound **4**) lead to a preference for the keto tautomer, thus N1 becomes a hydrogen-bond donor and is no longer available for interaction with Y693. The R^1 substituent on the distal



Scheme 2. Reagents and conditions: (a) DMA, NaH (2.6 equiv), 0–120 °C, 2 h, 74%. (b) RB(OR′)2 (1.1–1.5 equiv), PPh_3 (20 mol %), $Pd(OAc)_2$ (10 mol %) or 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (10 mol %), sodium carbonate (3 equiv), THF or ACN, water, 30 min, 150 °C microwave. (c) $(PinB)_2$, $Pd(dppf)_2Cl_2$, potassium carbonate (3.3 equiv), DMF, 30 min, 130 °C, then R–I (1.3 equiv), $Pd(dppf)_2Cl_2$, sodium carbonate hydrate, 1 h, 100 °C.

phenyl ring reduces rotational freedom in the biphenyl moiety, thus stabilizing the bioactive conformation. R^1 also occupies a relatively hydrophobic pocket formed by L635, M713 and F729. The central phenyl ring is sandwiched between Q726 and F729,