Bioorganic & Medicinal Chemistry Letters 20 (2010) 1858–1860

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design of two new chemotypes for inhibiting the Janus kinase 2 by scaffold morphing

Pascal Furet *, Marc Gerspacher, Carole Pissot-Soldermann

Novartis Institutes for BioMedical Research, WKL-136.P.12, CH-4002 Basel, Switzerland

ARTICLE INFO

Article history:
Received 18 December 2009
Revised 26 January 2010
Accepted 29 January 2010
Available online 4 February 2010

Keywords:
Scaffold morphing
Kinase inhibitor design

ABSTRACT

JAK2 is a target of high interest in chronic myeloproliferative disorders drug research. Starting from a screening hit, two new JAK2 inhibitor chemotypes were designed by scaffold morphing. The prototype compounds of these new series showed nanomolar inhibition of the kinase.

Inhibition of the Janus kinase 2 (JAK2) is considered as a promising therapeutic approach in the treatment of chronic myeloproliferative neoplasms.[1] Consequently, medicinal chemistry efforts aiming at the discovery of chemical inhibitors of this kinase are currently pursued.[2–4] We initiated our own efforts in this direction by screening an internal collection of kinase inhibitors using a biochemical JAK2 enzymatic assay in a search for chemical starting points. The screening resulted in the identification of compound **1**, belonging to a series of pyrrolopyrimidines synthesized in the course of a focal adhesion kinase (FAK) inhibitor program,[5] as a potent inhibitor of JAK2. Here, we report the design of two new JAK2 inhibitor chemotypes by scaffold morphing starting from compound **1** (see Fig. 1). The synthesis, structure–activity relationships, selectivity profiles, and pharmacokinetic properties of these new series of JAK2 inhibitors are reported elsewhere.[6,7]

Designing molecular mimics of known biologically active molecules, a process currently termed scaffold morphing, can be an effective way to generate new chemotypes in medicinal chemistry. In this process, the chemical functions conferring the desired biological activity are introduced in new, different, molecular frameworks that can present advantages over the reference molecule in terms of synthetic access, profile of selectivity or ADME properties. However, this is a very difficult exercise requiring a deep understanding of the structural determinants of binding affinity for the protein target coupled with innovative thinking in the design since no standard procedure or technology exists to accomplish this task with guaranteed success.

To establish a solid basis to the scaffold morphing of **1**, the compound was docked in the ATP pocket of an available crystal structure of the kinase domain of JAK2.[8] The resulting docking model is shown in Figure 2.[9] Inspection of the possible orientations of **1** in the ATP pocket of JAK2 led to the conclusion that the compound most probably binds to this kinase with the same mode of interaction as that observed in its co-crystal structure with FAK.[5] Thus, in the JAK2 model, its pyrimidine N1 atom and 2-amino group form bidentate hydrogen bonds with the backbone of the hinge residue L932.[10] These position the trimethoxyphenyl moiety of the inhibi-

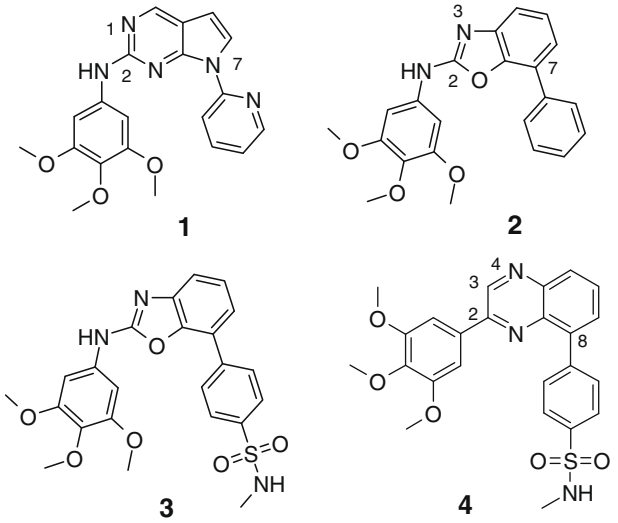

Figure 1. Chemical structures of the screening hit and designed compounds.

* Corresponding author. Tel.: +41 61 696 79 90; fax: +41 61 696 48 70.
E-mail address: pascal.furet@novartis.com (P. Furet).

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doi:10.1016/j.bmcl.2010.01.151

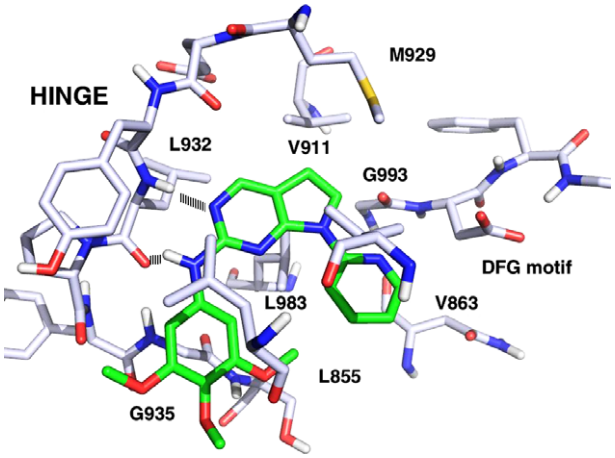

Figure 2. Model of compound **1** docked in the ATP pocket of JAK2. Key hydrogen bonds appear as dashed lines.

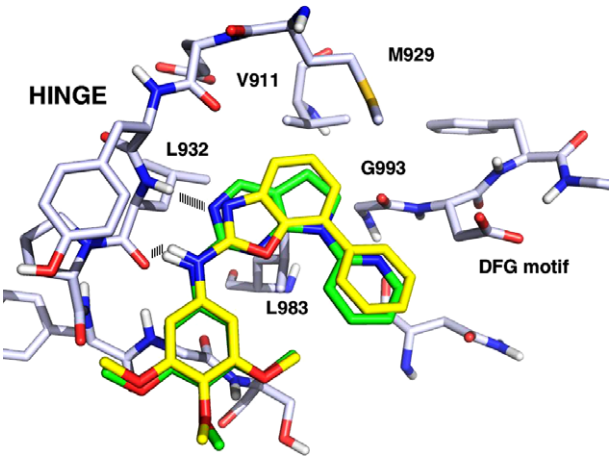

Figure 4. Model of prototype compound **2**. (yellow) docked in the ATP pocket of JAK2. The mimicked compound **1** appears in green. Key hydrogen bonds are represented as dashed lines.

tor in the hydrophobic channel formed by residues G935 and L855 at the entrance of the cavity while placing its pyrrole ring in the hydrophobic environment provided by V911, G993, and the gate keeper residue M929[10] at the bottom of the pocket. This orientation allows, in addition, a favorable hydrophobic interaction to occur between its pyridine ring and residue V863 of the kinase P-loop.

Examination of the above docking model, inspired the original idea to invert the six-membered and five-membered rings in the pyrrolopyrimidine hinge binding moiety of **1**. This implied that the hydrogen bond acceptor functionality interacting with the backbone N–H group of residue L932 should be introduced in the five-membered ring while the six-membered ring would mimic the pyrrole ring of **1** in its hydrophobic interactions with residues V911, G993, and M929. The 2-amino-aryl-7-aryl-benzoxazole scaffold shown in Figure 3 was designed by interactive molecular modeling following this concept. The binding model of the prototype molecule of this series, compound **2**, is represented in Figure 4. As can be seen, the inversion of the pyrrolopyrimidine five- and six-membered rings to give a benzoxazole bicycle provides an excellent molecular mimic of **1**. The N3 atom of the benzoxazole core can form the expected hinge hydrogen bond interaction while the attached 2-amino-aryl and 7-aryl moieties match exactly the positions of those of the pyrrolopyrimidine inhibitor in the ATP pocket.[11] The prototype compound **2** was synthesized.[6] Very encouragingly, **2** turned out to potently inhibit JAK2 with an IC_{50} value of 15 nM comparing well with that of **1**, 5.9 nM, in the biochemical assay.[12] Following up on this promising result, we undertook a synthesis program around the new scaffold that has led to a new class of potent, selective, and orally available JAK2 inhibitors.[6]

One of the most potent inhibitors obtained in the new benzoxazole series was compound **3** bearing a sulfonamide group in para position of the 7-phenyl moiety (12 nM). Looking for additional new inhibitor chemotypes, we were inspired by the concept of C–H···O pseudo hydrogen bond.[13,14] This type of interaction involv-

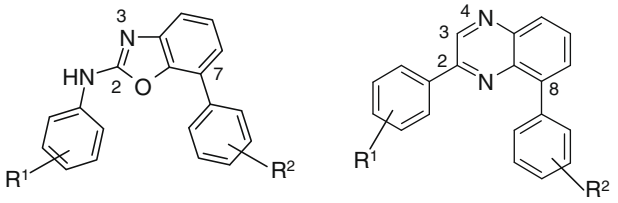

Figure 3. Designed scaffolds.

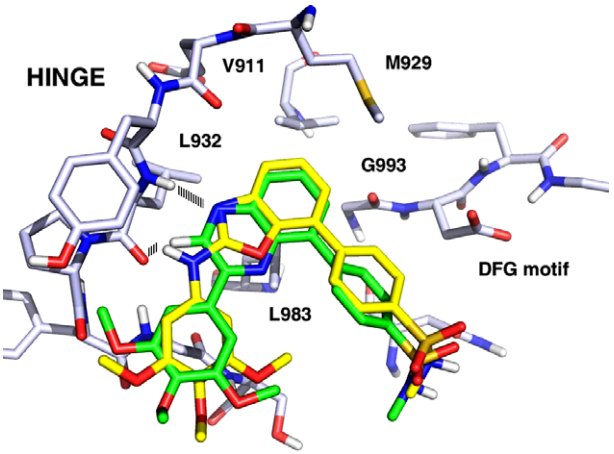

Figure 5. Model of prototype compound **4** (green) docked in the ATP pocket. The mimicked compound **3** appears in yellow. Key hydrogen bonds are represented as dashed lines.

ing an aromatic C–H group of the inhibitor polarized by an adjacent nitrogen atom and the backbone carbonyl function of one of the hinge residues has been observed in crystal structures of kinase-inhibitor complexes.[15] However, it is usually not considered in the design of new inhibitors.

Thus, the 2,8-diaryl-quinoxaline scaffold shown in Figure 3 was designed as a mimic of the benzoxazole one and a prototype, compound **4**, morphing the potent benzoxazole derivative **3** was envisaged for synthesis. As illustrated in Figure 5 with the docking model of **4**, the driving idea here was to mimic the hydrogen bond between the 2-amino substituent of the benzoxazole inhibitor and the backbone carbonyl group of hinge residue L932 by a non conventional pseudo hydrogen bond involving the aromatic C-H group in position 3 of the quinoxaline ring.[16] This implied to attach a trimethoxyphenyl moiety in position 2 of the quinoxaline to match that of the benzoxazole compound. The resulting molecule **4** was able to form the same interactions with the ATP binding site as **3** as can be judged from the excellent overlap of the two molecules displayed in Figure 5.

To our satisfaction, taking the risk of replacing a standard hydrogen bond interaction by a non conventional one paid off. With an IC_{50} value of 42 nM in the biochemical assay, **4** showed potent inhibition of JAK2. Thus, we had access to an additional new

series of potent JAK2 inhibitors that was subsequently optimized towards compounds suitable for in vivo efficacy evaluation.[7]

The two examples presented here illustrate the efficiency of innovative scaffold morphing to generate new useful chemotypes in the very competitive field of kinase inhibitor research. In particular, our work gives support to the notion that a pseudo hydrogen bond formed between an inhibitor aromatic C–H group and one of the backbone amide carbonyl groups of the hinge segment is a favorable interaction to seek in kinase inhibitor design.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.151.

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16. In our model, the designed C–H···O interaction had the attributes of a H-bond (see Ref. 13): a distance between the proton and the acceptor oxygen atom of 2.3 Å which is significantly less than the sum of the van der Waals radii (2.7 Å), an angle C–H···O of 140° approaching the ideal value of 180° (linearity) and an elevation angle of 30° approaching the ideal value of 0° indicating the tendency of the H···O contact to lie in the plane containing the oxygen lone pairs. A crystal structure of compound **4** in complex with the kinase domain of JAK2 was subsequently solved (Ref. 7). It fully confirmed the validity of the design concept. In this structure a C–H···O pseudo hydrogen bond is observed between the C–H group in position 3 of the quinoxaline ring and the backbone carbonyl oxygen atom of residue L932. The geometric parameters of this hydrogen bond are the following: distance proton-oxygen of 2.34 Å, angle C–H···O of 132° and elevation angle of 40.4°.