Chinese Chemical Letters 33 (2022) 2969–2974

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Design, synthesis and SAR study of 2-aminopyridine derivatives as potent and selective JAK2 inhibitors

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ARTICLE INFO

Article history:
Received 27 October 2021
Revised 24 December 2021
Accepted 31 December 2021
Available online 6 January 2022

Keywords:
JAK2
Selectivity
Inhibitors
Cancer
Structure-activity relationships

ABSTRACT

The abnormal activation of JAK2 kinase is closely related to the occurrence and progression of myeloproliferative neoplasms (MPNs). At present, there is still an obvious unmet medical need for selective JAK2 inhibitors in clinic. In this paper, a class of 2-aminopyridine derivatives as potent and selective JAK2 inhibitors was obtained by combining drug design, synthesis and structure-activity relationship studies based on the previously identified lead Crizotinib. Among them, **21b** exhibited high inhibitory activity against JAK2 with an IC_{50} of 9 nmol/L, moreover, it showed 276- and 184-fold selectivity over JAK1 and JAK3, respectively. Besides, **21b** had a significant antiproliferative activity against HEL cells, and also inhibited the phosphorylation of JAK2 and its down-stream signaling pathway. These results indicated that 2-aminopyridine compound **21b** had the potential to be developed as a selective JAK2 inhibitor for further study.

Janus kinases include JAK1, JAK2, JAK3 and TYK2, which belong to the family of nonreceptor tyrosine kinases. The Janus family regulates signal transduction through JAK-STAT (STAT, signal transductions and activators of transcription) signaling pathway, and plays an essential role in innate and adaptive immunity and hematopoiesis [1,2]. A variety of cytokines activates Janus kinases, causing phosphorylation and dimerization of STAT proteins in the cell, and then transfer to the nucleus to regulate gene transcription [3,4]. JAK2 mediates the signal transduction of cytokines such as IL-3, IL-5, granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO) and thrombopoietin (TPO), which are related to the growth and progression of myeloid cells [5–7]. Therefore, the excessive activity of JAK2 causes the JAK2-STAT signaling pathway to be constitutively activated, and leading to a variety of malignant diseases [8].

Myeloproliferative neoplasms (MPNs) include chronic myeloid leukemia (CML), myelofibrosis (MF), essential thrombocythemia (ET), and polycythemia vera (PV), which are a group of heterogeneous hematologic diseases resulting from deregulated proliferation of myeloid cells [9]. JAK2-STAT can be abnormally activated by mutations in JAK2 pseudokinase domain (JAK2 V617F), thrombopoietin receptor (MPL W515l) and calreticulin gene (CALR) exon 9, causing the occurrence and progression of myeloproliferation neoplasms (MPNs) [10,11]. The V617F mutation in JAK2 was found to be carried by approximately 95% of PV patients and approximately 50% of MF and ET patients [12].

Indeed, several pan-JAK inhibitors have been marketed and selective JAK2 inhibitors continue to be discovered (Fig. 1). The pan-JAK inhibitors Ruxolitinib (**1**) and Tofacitinib (**2**) were approved for the treatment of myelofibrosis and rheumatoid arthritis, respectively [13–15]. Fedratinib (**3**) is currently the only approved selective JAK2 inhibitor for the treatment of primary or secondary (intermediate-2 or high-risk) myelofibrosis [16]. Unfortunately, there are several selective JAK2 inhibitors, such as XL019 (**4**) and AZD1480 (**5**), clinical trials of which were suspended due to central or peripheral neurotoxicity and dose-limiting toxicity, respectively [17–19]. These results indicate that the development of selective JAK2 inhibitors over the broader kinase spectrum and other JAK family kinases can reduce off-target side effects and unnecessary immunosuppression [20]. However, the high degree of homology in catalytic domain of the JAK family makes the discovery of selective inhibitors against JAK2 proved to be a huge challenge [21,22].

Our lab has been committed to discovering and developing JAK2 selective inhibitors as anticancer drugs, and found that ALK

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https://doi.org/10.1016/j.cclet.2021.12.099
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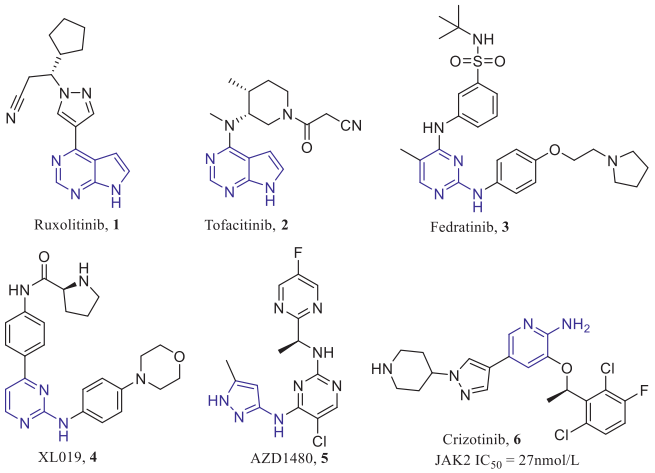


Fig. 1. Structures of representative JAK2 inhibitors.

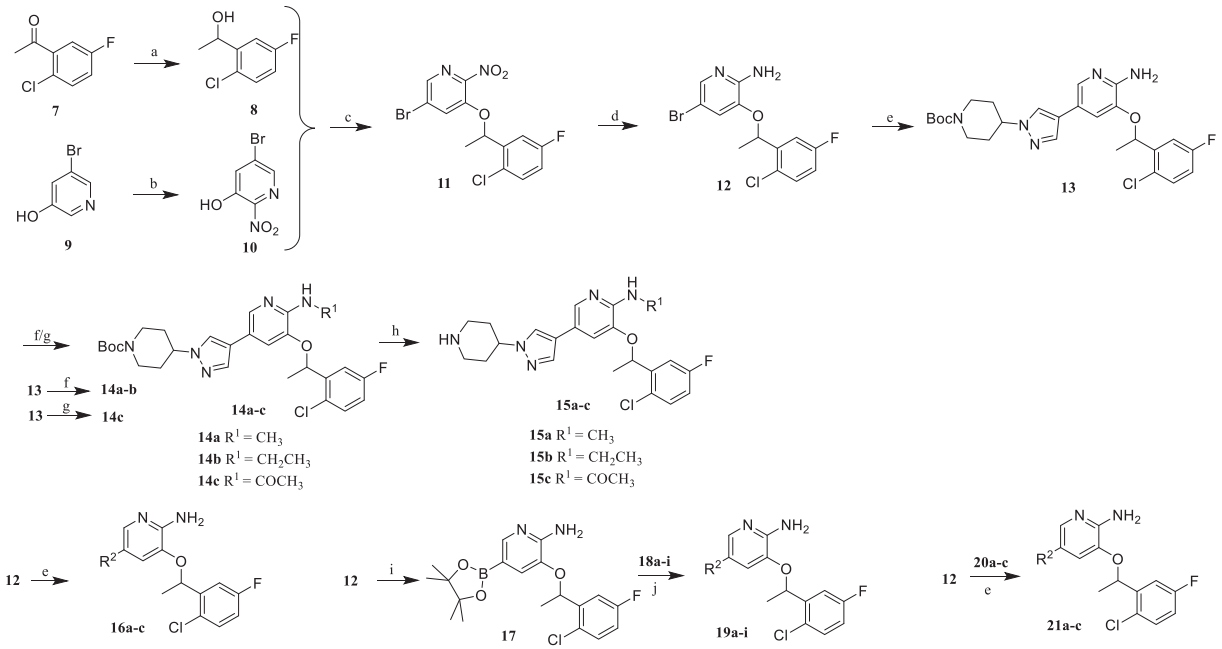
and c-MET inhibitor Crizotinib (Fig. 1) had good inhibitory activity against JAK2 with an IC_{50} value of 27 nmol/L, then, in order to improve the activity and selectivity of JAK2, the benzene ring in the hydrophobic region and the solvent exposed region of Crizotinib were optimized, and some effective compounds were obtained [23–25], however, these compounds have not been further studied due to druggability or toxicity problems.

In this paper, we focused on exploring a wider range of pharmacophore effects on JAK2 activity and selectivity through structure-based drug design. A series of 2-aminopyridine structures derived from Crizotinib were designed and synthesized as JAK2 selective inhibitors. The *in vitro* kinase inhibitory activities and selectivity of compounds were evaluated, and the cell antiproliferative activity and primary mechanism of the most potential compound were analyzed.

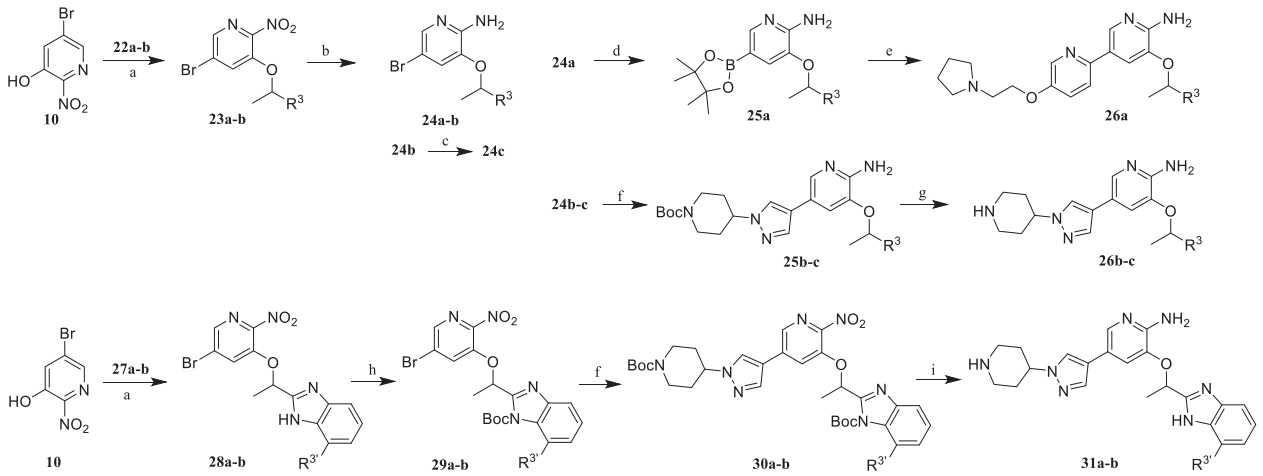
The general synthetic route of compounds **15a-c**, **16a-c**, **19a-i** and **21a-c** was shown in Scheme 1. The commercially available starting material 2–chloro-5-fluoroacetophenone was reduced by $NaBH_4$ to obtain **8**, which was subjected to Mitsunobu reaction with intermediate **10** obtained by nitration of 3–hydroxy-5-bromopyridine to obtain intermediate **11**. The key intermediate **12** was obtained after **11** was reduced by Fe powder, then it was coupled with aryl borate to obtain intermediate **13**, after which a substitution reaction occurred on **13**. Compounds **14a-c** were treated with trifluoroacetic acid to obtain the target products **15a-c**. The target products **16a-c** and **21a-c** were obtained by Suzuki coupling of the key intermediate **12** with different aryl borates. Compound **12** could also be coupled with boric acid ester first, and then coupled with aryl halides to obtain the target products **19a-i**.

Compounds **26a-c**, **31a** and **31b** were synthesized according to Scheme 2. Intermediates **23a** and **23b** were prepared by Mitsunobu reaction with **10** and 1-aryl-1-ethanol, which were reduced by Fe powder to obtain **24a** and **24b**, then cyano group of **24b** was reduced by $NaBH_4$ to obtain the amide derivative **24c**. Intermediate **24a** was coupled with boric acid ester and then coupled with aryl halide to obtain the target product **26a**, while **24b** and **24c** were coupled with aryl borate and treated with trifluoroacetic acid to obtain the target products **26b** and **26c**. The intermediate **28a** and **28b** were obtained by the Mitsunobu reaction of **10** and benzimidazole derivatives. Compounds **28a** and **28b** were protected by Boc group and then coupled with aryl borate to obtain intermediates **30a** and **30b**. Finally, **31a** and **31b** were provided by reducing **30a** and **30b** and removing the Boc group.

The pharmacophore of Crizotinib consist of a hydrophobic 2,6-dichloro-3-fluorophenyl group, a 2-aminopyridine core located in the hinge region and a solvent exposed region. In order to explore SAR, we first introduced some small substituents on the amino group. However, from the enzymatic activity results (Table 1), the activities of compounds **15a** and **15b** were greatly reduced compared to Crizotinib. The results indicated that these substituents may collide with the gatekeeper residue Met929 in the ATP binding pocket of JAK2, thereby affecting the interaction with the hinge region. The potency of **15c** was better than **15a** and **15c**, because the carbonyl oxygen atom on the acetyl group faced to the



Scheme 1. Preparation of **15a-c, 16a-c, 19a-i** and **21a-c**. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 3 h, 96.9%; (b) HNO_3, H_2SO_4, 0 °C, 4 h, 63.0%; (c) DIAD, PPh_3, THF, r.t., 6 h, 89.9%; (d) Fe, AcOH, EtOH, 78 °C, 3 h, 66.9%; (e) Aryl borate, $PdCl_2$(dppf), Cs_2CO_3, MePh, H_2O, 80 °C, 5 h, 21.0%–50.9%; (f) Alkyl iodide, NaH, DMF, 0 °C, 8 h, 40.1%–42.7%; (g) Acetic anhydride, Et_3N, CH_2Cl_2, r.t., 8 h, 51.8%; (h) TFA, CH_2Cl_2, r.t., 1 h, 45.8%–55.7%; (i) 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi(1,3,2-dioxaborolane), AcOK, $PdCl_2$(dppf), dioxide, 100 °C, 8 h; (j) Aryl halide, Cs_2CO_3, $PdCl_2$(dppf), dimethoxyethane, 80 °C, 12 h, two steps 17.7%–40.6%.



Scheme 2. Preparation of **26a-c, 31a** and **31b**. Reagents and conditions: (a) 1-aryl-1-ethanol, DIAD, PPh_3, THF, r.t., 6 h, 38.4%–75.2%; (b) Fe, AcOH, EtOH, 78 °C, 3 h, 16.5%–93.8%; (c) $NaBH_4$, EtOH, 80 °C, 24 h, 71.1%; (d) 4,4,4′,4′,5,5,5′,5′-Octamethyl-2,2′-bi(1,3,2-dioxaborolane), AcOK, $PdCl_2$(dppf), dioxide, 100 °C, 8 h; (e) Aryl halide, Cs_2CO_3, $PdCl_2$(dppf), dimethoxyethane, 80 °C, 12 h, two steps 24.5%; (f) Aryl borate, $PdCl_2$(dppf), Cs_2CO_3, MePh, H_2O, 80 °C, 12 h, 28.6%–72.5%; (g) TFA, CH_2Cl_2, r.t., 3 h, 17.6%–19.4%, (h) $(Boc)_2O$, DMAP, CH_2Cl_2, r.t., 1 h, 79.6%–82.7%; (i) 1) 10% Pd/C, H_2, MeOH, 38 °C, 2 h; 2) TFA, CH_2Cl_2, 0 °C, 1 h, two steps 37.5%–49.9%.

hinge region and probably formed hydrogen bond interaction with Leu932, but the key hydrogen bond interaction between the amino and the hinge region Glu930 disappeared (Fig. 2A).

Subsequently, the efforts were paid to the modification of the solvent exposed region, in which the non-conserved residues are considered to be the main factors for improving selectivity [26]. In our previous work, we mainly explored the influence of six-membered aromatic rings and five-fused-six membered heterocyclic rings on selectivity [25], while in this paper, we focused on the effects of five-membered aromatic rings and longer hydrophilic side chains. In order to explore the influence of the position and number of methyl substitutions on pyrazole, we first designed compounds **16a-c**. The results showed that the **16a** with a methyl group at 1-position of pyrazole had the best inhibitory potency for JAK2 (IC_{50} = 0.024 μmol/L), while the activities of **16b** and **16c** decreased significantly. The possible reason was the introduction of methyl substitutions at both 3-position and 5-position, which destroyed the stability of the ligand planar arrangement. At the same time, compounds **19a** and **19b** were designed to explore the effect of the position and number of nitrogen atoms of five-membered aromatic heterocycles on the activity. Compared to **16a**, when the pyrazole ring was replaced by the imidazole ring, the potency of **19a** against JAK2 was 77-fold lost. The similar tendency was also found between compounds **16a** and **19b**. According to the docking pose of **19a** (Fig. 2B), the carbonyl oxygen atoms of Leu932 and Leu855 faced to the ortho-position of the five-membered heterocycle, therefore, the nitrogen atoms at this position (**19a**, **19b**) may had an unfavorable electrostatic interaction with carbonyl oxygen atoms and reduced the activity.

After the two rounds of optimization described above, compared with Crizotinib, their inhibitory activities against JAK2 were still not significantly improved due to the absence of additional beneficial interactions. Therefore, we hypothesized that the pyrazole of **16a** was replaced with six-membered aromatic ring containing lactam or cyano substituents so that it could interact with the hinge region Tyr931 by hydrogen bonding. Immediately, compounds **19c-e** were designed and synthesized, but their potencies were reduced remarkably compared with **16a**. This result implied that the six-membered aromatic ring plane failed to rotate towards Tyr931, thus the carbonyl or cyano group could not form hydrogen bonds with the hinge region as we expected.

The **19f** obtained by replacing pyrazole with pyridine has better activity, which stimulated us to investigate the active potential

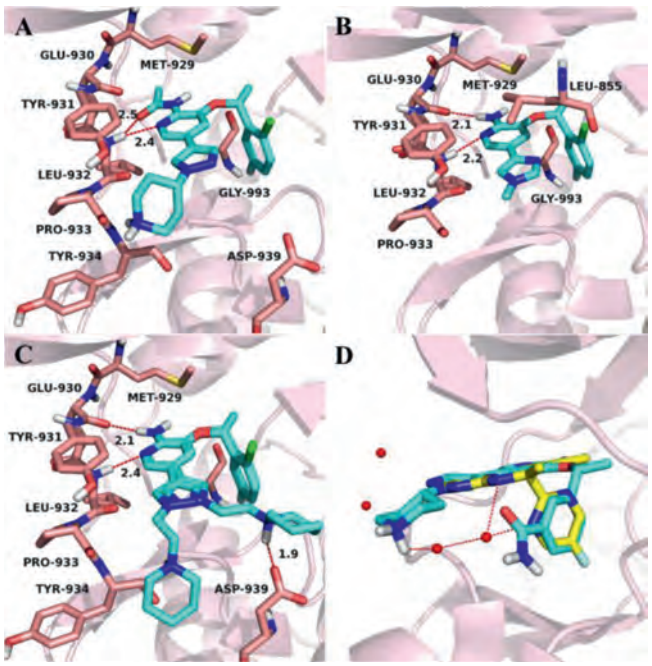
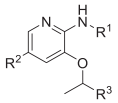
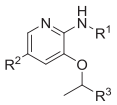
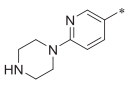
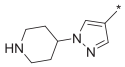
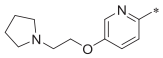
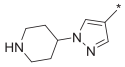
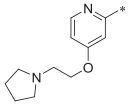
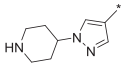
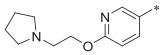
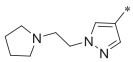
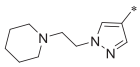
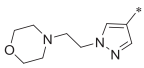
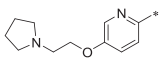
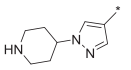
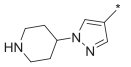


Fig. 2. The docking poses of **15c** (A), **19a** (B), **21b** (C) and **26c** (D) in the JAK2 ATP-binding pocket (PDB: 2XA4). The receptor is shown in pink cartoon, **15c, 19a, 21b** and **26c** are presented as blue stick model. (A) The carbonyl oxygen atom and pyridine nitrogen atom of **15c** formed H-bonds with the hinge residue Leu932. (B) The 2-aminopyridine scaffold of **19a** can form two H-bonds with the hinge residues Glu930 and Leu932. (C) The 2-aminopyridine scaffold of **21b** was firmly bound by two hydrogen bonds with the hinge residues Glu930 and Leu932, while 2-piperidinylethyl could swing to the left and right in the solvent region, forming an additional hydrogen bond with Asp939 when it pointed to the right. (D) Superposition of **26c** and AZD1480 in JAK2 ATP-binding pocket, AZD1480 is shown in yellow stick model.

of pyridine modification. In addition, the substitution modification of pyridine is easier to synthesize than pyrazole, so the influence of hydrophilic side chain of pyridine on the activity was explored next. After comparing among **19g**, **19h** and **19i**, it was concluded that the 3-position (2-pyrrolidine)ethoxy of pyridine was superior to 4-position, and the activity was better when the nitrogen atom of pyridine was adjacent to the scaffold. In general, the activities of compounds **19g-i** were still significantly lower than that of **19f**. The

Table 1
SAR exploration of different substituents in 2-aminopyridine.



Compd.	R^1	R^2	R^3	JAK2 IC_{50} (μmol/L)[a]
15a	CH_3			1.272 ± 0.229
15b	CH_2CH_3			6.705 ± 1.298
15c	$COCH_3$			0.050 ± 0.006
16a	H			0.024 ± 0.002
16b	H			0.844 ± 0.100
16c	H			0.041 ± 0.001
19a	H			1.844 ± 0.025
19b	H			0.086 ± 0.005
19c	H			1.472 ± 0.006
19d	H			4.495 ± 0.083
19e	H			3.012 ± 0.017
19f	H			0.019 ± 0.002
19g	H			0.280 ± 0.009
19h	H			0.366 ± 0.001
19i	H			0.400 ± 0.031
21a	H			0.030 ± 0.002
21b	H			0.009 ± 0.001
21c	H			0.011 ± 0.001
26a	H			6.798 ± 0.005
26b	H			1.472 ± 0.058
26c	H			1.086 ± 0.043
31a	H			>10
31b	H			>10

[a] IC_{50} of the compounds are mean values of at least three independent experiments.

Table 2
Selective test of compounds against JAK1, JAK2 and JAK3.

Compd.	Enzyme inhibitory activity IC_{50} (μmol/L)[a]			Enzyme selectivity (ratio)	
	JAK1	JAK2	JAK3	JAK1/JAK2	JAK3/JAK2
Fedratinib	0.227 ± 0.036	0.003 ± 0.001	0.264 ± 0.045	76	88
Crizotinib[b]	0.563 ± 0.011	0.027 ± 0.002	1.360 ± 0.074	21	50
16a	0.312 ± 0.048	0.024 ± 0.002	1.492 ± 0.116	13	62
16c	0.097 ± 0.003	0.041 ± 0.001	1.067 ± 0.145	2	26
19f	2.389 ± 0.160	0.019 ± 0.002	3.599 ± 0.245	126	189
21a	2.104 ± 0.054	0.030 ± 0.002	1.741 ± 0.102	70	58
21b	2.486 ± 0.441	0.009 ± 0.001	1.659 ± 0.306	276	184
21c	1.270 ± 0.115	0.011 ± 0.001	0.288 ± 0.076	115	26

[a] IC_{50} of the compounds are mean values of at least three independent experiments.
[b] These data were obtained according to the procedure in reference [24].

Table 3
The antiproliferative activity on HEL cells of **21b**.

Compd.	Cellular antiproliferative activity IC_{50} (μmol/L)[a]
Fedratinib	1.340 ± 0.059
Crizotinib[b]	4.725 ± 0.049
21b	6.824 ± 0.449

[a] IC_{50} of the compounds are mean values of at least three independent experiments.
[b] These data were obtained according to the procedure in reference [24].

possible reason was the secondary amine group on the piperazine of **19f** could interact with water molecules in the solvent region, but the side chains of **19g-i** were too large to bind with the target. Hence, we had to reinvestigate the effect of the side chains with moderate length on activity in the presence of the pyrazole group. Surprisingly, compounds **21a-c** showed very good activity, especially **21b**, with an IC_{50} value of 0.009 ± 0.001 μmol/L. In the binding pocket of JAK2 (Fig. 2C), the 2-aminopyridine scaffold of **21b** was firmly bound by two hydrogen bonds with the hinge residues Glu930 and Leu932; the halogen-substituted benzene occupied the hydrophobic cavity; 2-piperidinylethyl could swing to the left and right in the solvent region, forming an additional hydrogen bond with Asp939 when it pointed to the right, which may be the main reason for its increased activity.

Finally, we turned our attention to the benzene ring in the hydrophobic region to study its effect on activity. We designed compound **26a** without the F and Cl substituents on the benzene, in order to change the overall trend of the molecule to make it closer to the hinge region. However, the potency of **26a** was reduced by 24-fold compared to **19g**, indicating that the halogens might play an important role in the binding of the benzene and the hydrophobic region. We analyzed the superposition of JAK2 inhibitor AZD1480 and **26c** in the JAK2 pocket (Fig. 2D), and found that adding a cyano group and an amide group to the 3-position of the benzene as hydrogen bond donors might interact with the water molecule.

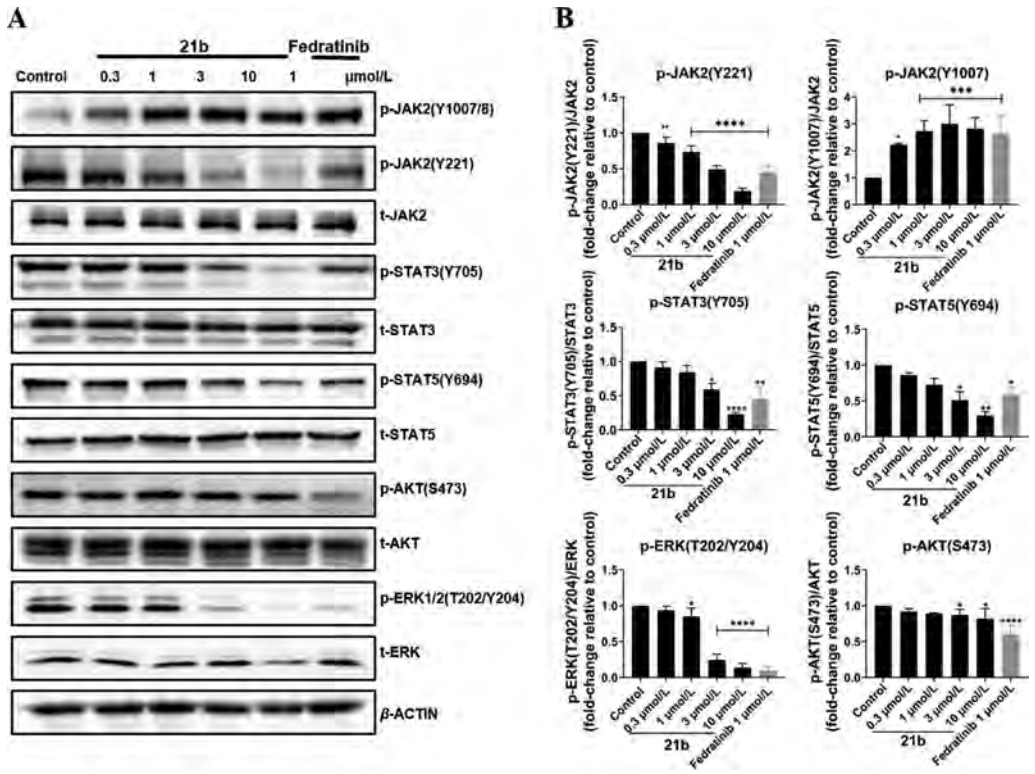


Fig. 3. Compound **21b** effectively blocked the JAK2-STAT signaling pathways in HEL cells. (A) Western blot analysis of phosphorylation of JAK2 (Y1007/8), JAK2 (Y221), STAT3, STAT5, AKT and ERK. (B) The bands intensity was quantitatively analyzed from Western blotting images. Each column represents the means ± SD of 3 independent experiments. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

On the contrary, the activity of **26b** and **26c** did not improve as estimated, it is speculated that the expected hydrogen bond interaction did not occur, and the presence of large groups would also cause desolvation and reduced the activity. We also substituted benzene with benzimidazole and designed compounds **31a** and **31b**, but their activity was completely lost. Although the hydrophobic pocket could accommodate benzimidazole, it formed a torsion angle compared with the benzene (Fig. S1 in Supporting information), which might be the main cause of inactivation.

Subsequently, several compounds (**16a**, **16c**, **19f**, **21a**, **21b** and **21c**) with better JAK2 inhibitory activity were selected for selective testing of JAK1 and JAK3. As indicated in Table 2, these compounds exhibited high JAK2 selectivity over JAK1 and JAK3, among which **21b** was 276- and 184-fold selective over JAK1 and JAK3, respectively. This series of compounds exhibited weak inhibitory activity against JAK3 probably due to the influence of Ala966 in the hydrophobic pocket area, while there is a Gly993 in JAK2. In addition, the piperidine nitrogen atom of **21b** formed a hydrogen bond with the solvent area Asp939 of JAK2, instead of Glu966 in JAK1, which explained its good selectivity. The results also indicated that substituents in the solvent region could significantly affect the selectivity and inhibitory activity of JAK enzyme.

Based on the results of enzyme activity assays, **21b** was further evaluated for its antiproliferative activity against the HEL cells (Table 3), which is known as human erythroleukemia cell line contains JAK2 V617F mutation. The results showed that compound **21b** could significantly inhibit the proliferation of HEL cells with an IC_{50} value of 6.824 μmol/L.

In order to explore the effect of **21b** in the JAK2-STAT signal transduction pathways in HEL cells, Western-blot experiments were performed to assay its effect on the phosphorylation level of JAK2 and its downstream targets. As shown in Fig. 3, compound **21b** dose-dependently increased the phosphorylation of JAK2(Y1007/8), which is consistent with the reported type I JAK2 inhibitors. Moreover, **21b** inhibited JAK2(Y221), STAT3(Y705), STAT5(Y694) and ERK(T202/Y204) phosphorylation in a dose-dependent manner. In addition, **21b** showed weakly inhibition on AKT phosphorylation. In short, these results indicated that **21b** inhibited the activation of the JAK2-STAT signaling pathway by blocking the phosphorylation of JAK2 and its downstream substrates in HEL cells.

In summary, based on the structure of Crizotinib, some potential selective JAK2 inhibitors were designed by optimizing the 2-aminopyridine scaffold, the kinase solvent region and the hydrophobic region, respectively. After structure confirmation and systematic biological activity evaluation, **21b** showed high inhibitory activity against JAK2 with an IC_{50} of 9 nmol/L, moreover, it showed 276- and 184-fold selectivity over JAK1 and JAK3, respectively. **21b** significantly inhibited the proliferation of HEL cells with an IC_{50} of 6.824 μmol/L, and blocked JAK2-STAT signaling pathway in HEL cells. The results indicated that 2-aminopyridine compound **21b** was expected to be developed as a selective JAK2 inhibitor, and the structure-activity analysis process will be beneficial to the development of new selective JAK2 inhibitors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The research is supported in part by the National Key Research and Development Program (No. 2016YFA0502304), the National Natural Science Foundation of China (No. 81825020), the Shanghai Committee of Science and Technology (No. 20S11901000), the Fundamental Research Funds for the Central Universities. Honglin Li is also sponsored by the National Program for Special Supports of Eminent Professionals and the National Program for Support of Top-Notch Young Professionals.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.12.099.

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