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Identification of 4-(2-furanyl) pyrimidin-2-amines as Janus kinase 2 inhibitors

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Footnotes

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Abstract: Janus kinases inhibitor is considered to have therapeutic potential for the treatment of oncology and immune-inflammatory diseases. Two series of 4-(2-benzofuranyl) pyrimidin-2-amine and 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatives have been designed and synthesized. Primary SAR studies resulted in the discovery of a novel class of 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine based JAK2 inhibitors with higher potency (IC_{50} of 0.7 nM) and selectivity (>30 fold) to JAK3 kinase than tofacitinib.

Keywords: JAK2 inhibitor; 4-(2-furanyl) pyrimidin-2-amine; 4,5,6,7-tetrahydro-furo[3,2-*c*]pyridine; kinase selectivity

1. Introduction

Janus kinases (JAKs) are a family of non-receptor tyrosine kinase. They play an important role in hematopoiesis and immune response. Upon stimulation of cytokine signaling, JAKs function as subsequent activation of the downstream signal transducer and activator of transcription (STAT).[1] There are four isoforms identified in human: JAK1, JAK2, JAK3, and TYK2. Among these, JAK3 is expressed mostly in lymphoid cells and binds exclusively to the common γ-chain of the IL-2 family of receptors.[2] A mutation or loss of JAK3 results in severe combined immune deficiency.[3] In contrast, JAK2 is expressed on multiple cell transmitting signals of hormones and growth factors, which is critical for controlling the generation of blood cells from hematopoetic stem cells. JAK2 mutations lead to impaired erythropoiesis.[4] Besides, gene silencing studies showed that loss of JAK1 or TYK2 leads to defective lymphopoiesis.[5] Therefore, JAKs have been regarded as potentially effective targets for the treatment of oncology and immune-inflammatory diseases.

Indeed, several small-molecule JAK inhibitors have been developed for treatment of rheumatoid arthritis (RA), myelofibrosis, psoriasis, leukemia, lymphoma, etc (Fig. 1). Ruxolitinib was the first approved JAK inhibitor by FDA in late 2011 for use in myelofibrosis treatment.[6] Tofacitinib, a pan-JAK inhibitor, was launched for RA one year later.[7] Following that, impressive progress in this field has been made recently (Fig. 1). According to the inhibition of primary isoform, they will be examplified by JAK3 inhibitor (VX-509 [9]), JAK2 inhibitor (CEP-701 [10], SB1518 [11], LY2784544 [12], BMS-911543 [13]), and JAK1 inhibitor (GLPG0634 [14]). In contrast to the current JAK-targeting biological agents, they are featured by the action mechanism and oral availability.

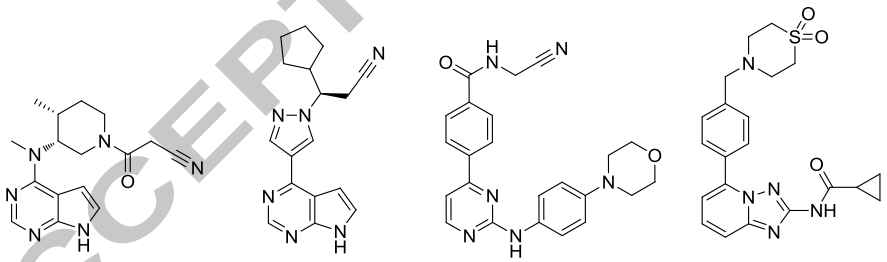


Figure 1. Representative JAK inhibitors.

The molecular structure of the JAK inhibitors is divided into four parts marked as A, B, C and D (Fig. 2). The structural cores of part A varied from pyrrolopyrimidines, pyrrolopyridines, 2-aminopyrimidines, to triazolopyridines. The tail C emerged mainly as amide, sulfonamide, and cyano group. By means of modification in part C, better selectivity could be achieved. For example, replacement of the N-(cyanomethyl) benzamide

moiety (CYT387 [15]) by 2-pyrrolidine carboxamide (XL019 [16]) leads to more than 30-fold JAK2 selectivity enhancement within JAK family. Finally, the linker B could be the key to discover new lead structures. Pyrazole, pyrimidine, and benzene were successfully adopted to replace the tertiary amine linker of tofacitinib. Based on the knowledge of structural and molecular biology, inhibition of JAK2 may be an effective approach for the treatment of myeloproliferative neoplasms (MPNs).[17] During which, primary myelofibrosis (MF) represents a significant unmet clinical need. Structure modification of part B and C offers an opportunity to discover potentially selective JAK2 inhibitors.

The fused-furan was widely existed in the world, such as nature products, agrochemicals, pharmaceutical products, dyes and spices. The two kinds of fused-furan framework, benzofuran and 4,5,6,7-tetra-hydrofuro[3,2-*c*]pyridine moieties, came forth as privileged structures thereof commonly used in medicinal chemistry.

Based on the above considerations, pyrimidine, the core structure of momelotinib, was firstly choosed as our leading core. Based on the linker structure of Ruxolitinib, 4-(2-benzofuranyl)-pyrimidin-2-amine derivatives was designed with the strategy of bioisosterism (a, pyzole to furan) and cyclization (b). With the strategy of cyclization (c), 4-(4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatives was designed from the linker structure of tofacitinib. Herein we describe the synthesis, biochemical and cellular evaluation of the 4-(2-furanyl) pyrimidin-2-amine derivatives as JAK2 inhibitors.

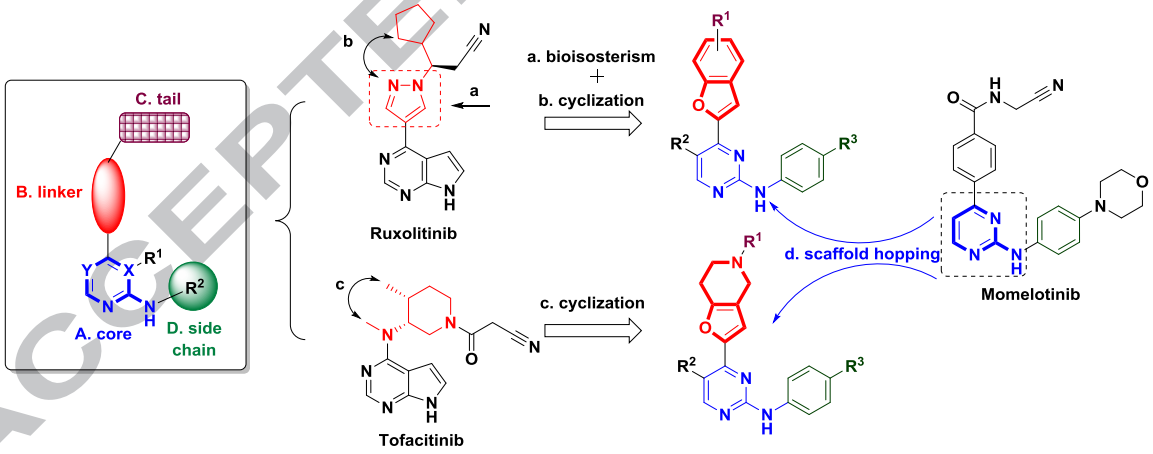


Figure 2. Design of the target compounds

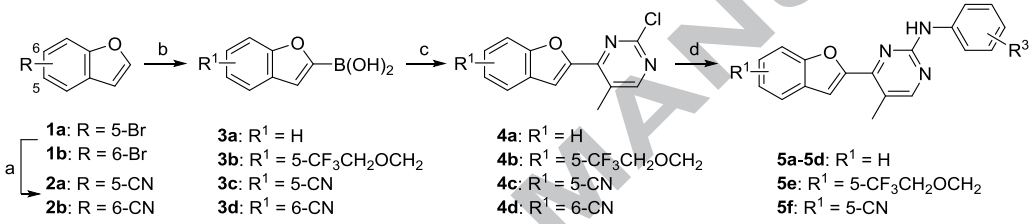
2. Results and discussion

2.1. Chemistry

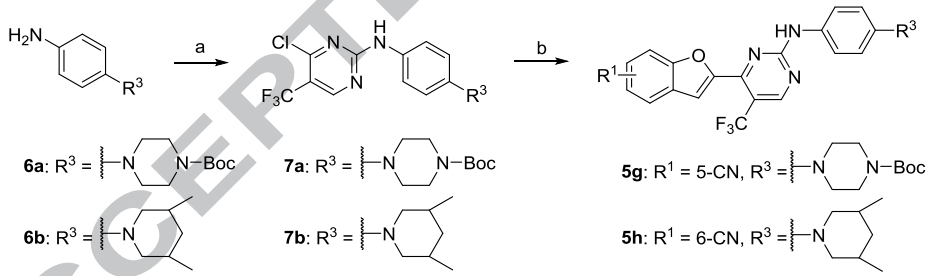
The novel 4-(2-benzofuranyl) pyrimidin-2-amine (**5a**–**5k**) and 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)

pyrimidin-2-amine derivatives (**16a**–**16h**) were prepared as illustrated in Schemes 1–4.

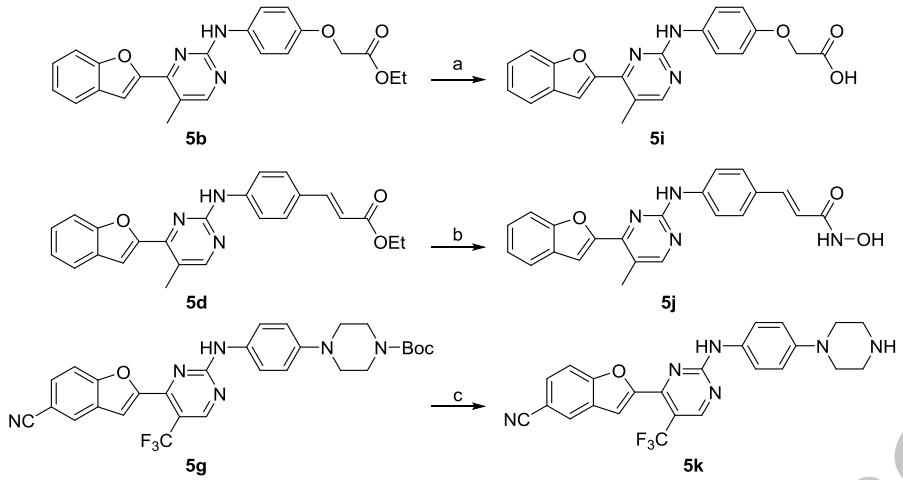
As indicated in Scheme 1-2, our key steps in the synthesis of 4-(2-benzofuranyl) pyrimidin-2-amine derivatives (**5a**–**5h**) involved two palladium-catalyzed cross-coupling reactions. Based on the reactivity difference between two chloride atoms of pyrimidine core, Suzuki coupling of 2,4-dichloro-5-methyl pyrimidine and 2-benzofuranyl boronic acid **3** gave compounds **4a**–**4d**, then Buchwald-Hartwig coupling with various anilines afforded compounds **5a**–**5f** (Scheme 1). When the substitute at the 5-position of pyrimidine was trifluoromethyl, the aniline moieties **6a**–**6b** were first installed selectively to 2-position of 2,4-dichloro-5-trifluoromethyl pyrimidine to generate intermediates **7a**–**7b** mediated by Lewis acid.[18] Then compound **7** was subjected to Suzuki coupling with 2-benzofuranyl boronic acids **3** to produce target compounds **5g**–**5h** (Scheme 2). Compound **5b** was hydrolyzed to generate free acid **5i**. Hydrolysis followed by condensation of ester **5d** produced *α*,*β*-unsaturated hydroximic acid **5j**. Removal Boc of **5g** gave free piperazine **5k** (Scheme 3).



Scheme 1. Reaction conditions and reagents: (a) CuCN, NMP, 200 ºC, 24 h, 45-82%. (b) *n*-BuLi, THF, -78 ºC; then $B(O^iPr)_3$, -78 ºC to rt; then 2 N HCl, 79-87%. (c) 2,4-dichloro-5-methyl pyrimidine, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, 90 ºC, 64-80%. (d) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, dioxane, 90 ºC, 15 h, 62-86%.

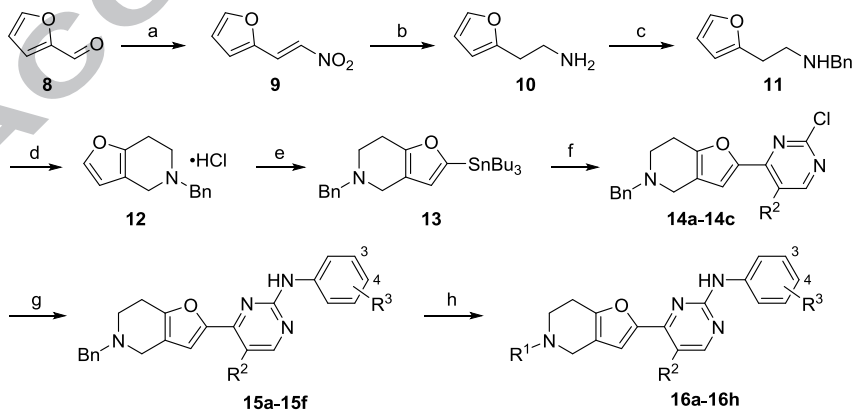


Scheme 2. Reaction conditions and reagents: (a) 2,4-dichloro-5-trifluoromethyl pyrimidine, $ZnCl_2$, NEt_3, *t*-BuOH, CH_2Cl_2, Et_2O, 69-84%. (b) **3c** or **3d**, $Pd(PPh_3)_4$, Na_2CO_3, DMF, microwave, 160 ºC, 56-71%.



Scheme 3. Reaction conditions and reagents: (a) NaOH, MeOH, H_2O, 75%. (b) NaOH, MeOH, H_2O, 42%. then 1,1'-carbonyldiimidazole, $NH_2OH.HCl$, THF, 71%. (c) TFA, CH_2Cl_2, rt, 98%.

As shown in Scheme 4, a similar method was used to construct the 4-(4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatives **16a**–**16h**. The key building block **12** used in this study was prepared from feedstock furfural for the first time, which avoids the need of more expensive 3-furaldehyde.[19] For this route, condensation of nitromethane with furfural, followed by reduction with $LiAlH_4$ in refluxing *tert*-butyl methyl ether to afford amine **10**. Then protection with benzyl and Pictet-Spengler reaction with aqueous formaldehyde gave 5-benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine hydrochloride **12**. Lithiation of **12** followed by quench with chlorotributyltin resulted compound **13**. Then Stille coupling of the tin regent **13** and 2,4-dichloro pyrimidine produced **14a**–**14c** with 71-89% yield. At this point, attempt to perform Suzuki coupling from the corresponding boronic acid failed. Treating compound **14** and aniline with HCl-KI under microwave irradiation, followed by deprotection with 1-chloroethyl chloroformate [20] and subsequently acylation or sulfonylation afforded the desired products **16a**–**16h**.



Scheme 4. Reaction conditions and reagents: (a) CH_3NO_2, NaOH, MeOH, -20~-5 °C, 0.5 h, 49%. (b) $LiAlH_4$, *t*-BuOMe, reflux, 2 h,

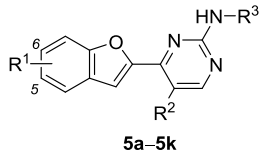
53%. (c) PhCHO, toluene, reflux, 2 h; then $NaBH_4$, MeOH, 0 °C, 1 h, 74%. (d) HCHO (37% aq.), rt, 1 h; then HCl-dioxane, DMF, rt, 95%. (e) K_2CO_3, CH_2Cl_2/H_2O, rt; then *n*-BuLi, *n*-Bu_3SnCl, THF, 0 °C, 2.5 h; (f) R^2 = H, F, CH_3: $Pd(PPh_3)_2Cl_2$, DMF, 90 ºC, 3 h, 71-89%. (g) HCl, KI, CF_3CH_2OH, dioxane, microwave, 150 °C, 34-54%. (h) 1-chloroethyl chloroformate, CH_2Cl_2, MeOH, reflux, 2 h; then $MeSO_2Cl$, NEt_3, CH_2Cl_2, or $NCCH_2COOH$, EDCI, HOBt, NEt_3, CH_2Cl_2, 50-99%.

2.2. In vitro JAK kinase inhibition studies for the new compounds

The newly synthesized 4-(2-benzofuranyl) pyrimidin-2-amine (**5a**–**5k**) and 4-(4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatives (**16a**–**16h**) were evaluated for their enzymatic inhibitory activities of the JAK2 and JAK3. Since tofacitinib is commonly used as a positive control, the data on the new agents was reported in direct comparison to this reference compound. The IC_{50} values in JAK enzyme assays are summarized in Tables 1–2.

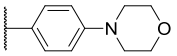
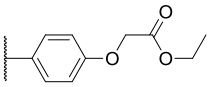
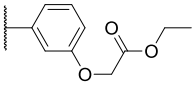
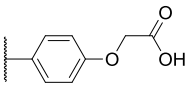
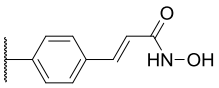
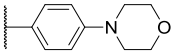
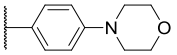
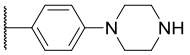
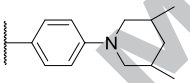
Among the 4-(2-benzofuranyl)-pyrimidin-2-amine series, most of the target compounds exhibited stronger JAK2 inhibitory activity than JAK3 with selectivity varied 1.5 to 35-fold. While substituent variation at R1 position appeared tolerant with less than 3-fold differences on potency (**5a**, **5e**, **5f**), diversification at R3 position could significantly affect the inhibitory activity and JAK2/3 selectivity. 4-Morpholinophenyl (**5a**) was replaced with a 4-ethoxycarbonyl-methoxy phenyl (**5b**) or N-hydroxycinnamamide (**5j**); as a result, a significant decrease in JAK2 inhibitory activity (25.4 to 36.5 fold) and JAK3 inhibitory activity (6.5 to 8.6 fold) was observed. The free acid **5i** showed good JAK2 inhibitory activity with an IC_{50} of 16.6 nM. The bio-isostere of the morpholine ring with piperazine (**5k**) also resulted in a 13 fold decrease in potency and loss of selectivity. The replacement of morpholine ring with piperidine (**5h**) also led to a dramatic loss of potency on JAK2 and JAK3, which demonstrated that the distal heteroatom of aniline played an important role in binding. The optimal R^3 group is 4-morpholinophenyl, which is consistent with the reported SAR of Ruxolitinib. Replacement of the methyl on the 5-position of pyrimidine with trifluoromethyl (**5k**) could not improve the potency. Among this series, compound **5f** (IC_{50} = 10.4 nM) displayed an almost 4-fold reduction in JAK2 potency compared to tofacitinib, along with 35-fold JAK2/3 selectivity.

Table 1. Enzymatic data on 4-(2-benzofuranyl)-pyrimidin-2-amine derivatives



5a–**5k**

Compds	R^1	R^2	R^3	JAK2 IC_{50} (nM) [a]	JAK3 IC_{50} (nM) [a]	fold selectivity [b]

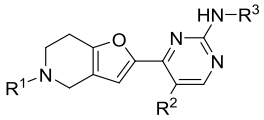
5a	H	CH_3		8.9	183.2	20.6
5b	H	CH_3		324.5	1195.4	3.7
5c	H	CH_3		18.9	87.6	4.6
5i	H	CH_3		16.6	359.4	21.7
5j	H	CH_3		226.1	1580.6	7.0
5e	5-$CF_3CH_2OCH_2$	CH_3		25.7	836.5	32.5
5f	5-CN	CH_3		**10.4**	**364.4**	**35.0**
5k	5-CN	CF_3		136.7	201.8	1.5
5h	6-CN	CF_3		7089.0	5174.0	0.7
tofacitinib				2.8	1.2	

[a] Values are means of three experiments.
[b] IC_{50} (JAK3) / IC_{50} (JAK2)

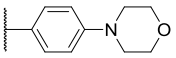
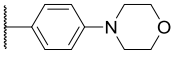
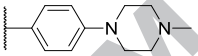
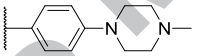
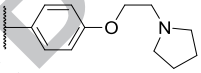
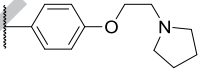
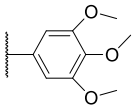
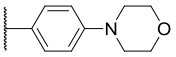
As for 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine series, quite different SAR was concluded at the preliminary stage (Table 2). JAK2 and JAK3 inhibitory activity were tolerant of a variety of aniline substitute ranging from morpholine, N-methylpiperazine to pyrrolidinethyl ether. Cyanoacetamide morpholine aniline analogue **16b** showed IC_{50} values of 13.2 nM against JAK2 and 140.5 nM against JAK3, while methanesulfonamide pyrrolidinethyl ether analogue **16e** exhibited much weaker inhibitory activity. Substitution of fluorine for hydrogen leads to minor steric alterations but major binding affinity and lipophilicity.[21] As we expected, incorporation of a fluorine atom into the 5-pyrimidine (**16f**) led to 3-fold potency increase with selectivity retained. Accordingly, other anilines were introduced to the 5-fluoropyrimidin-2-amine scaffold. For instance, 1,2,3-trimethoxyphenyl analogue **16g** displayed IC_{50} values of 9.4 nM and 178.1 nM against JAK2 and JAK3, respectively. It seems to imply that more steric groups are beneficial for bioactivity. Noticeably, when a methyl was installed to the 5-pyrimidine (**16h**), the JAK2 and JAK3 inhibitory activity were greatly improved, with IC_{50} values of 0.7 nM and 23.2 nM, respectively. Besides, the JAK2/3 selectivity was

remarkablely enhanced to 33.1 fold. In this 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine series, **16h** was found to display better JAK2 inhibitory activities and JAK2/3 selectivity than positive control tofacitinib.[22] Based on the above SAR, we proposed the modification of R^3 group could impove the potency and selectivity of 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatices, while the R^2 group was fixed as methyl or more steric substituents. Subsequent structure optimization is in progress.

Table 2. Enzymatic data on 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amines



16a–16h

Compds	R^1	R^2	R^3	JAK2 IC_{50} (nM) [a]	JAK3 IC_{50} (nM) [a]	fold selectivity [b]
16a	CH_3SO_2	H		42.9	226.1	5.3
16b	NC-CH_2CO	H		13.2	140.5	10.6
16c	CH_3SO_2	H		37.9	204.2	5.4
16d	NC-CH_2CO	H		53.7	136.1	2.5
16e	CH_3SO_2	H		164.0	500.5	3.1
16f	CH_3SO_2	F		55.4	175.8	3.2
16g	CH_3SO_2	F		9.4	178.1	18.9
16h	CH_3SO_2	CH_3		**0.7**	**23.2**	**33.1**
tofacitinib				2.8	1.2	

[a] Values are means of three experiments.

[b] IC_{50} (JAK3) / IC_{50} (JAK2)

2.3. Cellular inhibitory activities for the new compounds

Having identified leading compound **16h** showing excellent in vitro JAK2 inhibitory activity, we carried out an evaluation in cell proliferation (Table 3).[23] All the compounds tested were demonstrated low potency for TF-1 and HT-2 cell lines dependent on the JAK2 and JAK3 signal pathway, respectively, only **16h** displayed comparable inhibitory activity against TF-1 cell line. To our delight, three compounds (**5f**, **16e**, **16h**) displayed higher potency against human erythroblast leukemia (HEL) that are known to harbor JAK2-V617F mutation than

positive control tofacitinib, which was independent of JAK2 in vitro inhibitory activities. Furthermore, in accordance with in vitro inhibitory assay, the most potent **16h** further showed the strongest inhibited proliferation of HEL with IC_{50} value of 1254 nM, which was nearly 4-fold more active than tofacitinib. In combination of weak HT-2 inhibitory activities, **16h** exhibited good selectivity over JAK3. These results indicate that the novel compounds might function under a distinctive mechanism in cells.

Table 3. Cellular inhibitory activities for compound **5** and **16** (IC_{50}, nM)

Compds	TF-1 (JAK2)	HEL (JAK2/V617F)	HT-2 (JAK3)
5f	1052	3088	1724
16b	3125	5521	10078
16d	2338	7443	3325
16e	4311	1258	5357
16h	425.6	1254	848
tofacitinib	275.1	4724	156

3. Conclusion

We described the design, synthesis and biological screening of two novel series of 4-(2-benzofuranyl) pyrimidin-2-amine and 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amine derivatives as JAK2 inhibitors. The preparation of key building block 5-benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine was optimized. Primary SAR studies resulted in the discovery of a novel class of 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine based JAK2 inhibitors with higher potency (IC_{50} of 0.7 nM) and selectivity (>30 fold) to JAK3 kinase than tofacitinib. Our further effort will be devoted on exploiting the comprehensive SARs, design of more highly efficient and selective agents with satisfactory druggability and safety profiles.

4. Experimental

4.1. General methods

All reagents were used as purchased without further purification unless otherwise noted. The solvents (MeOH, EtOAc, EtOH, CH_2Cl_2, THF, etc) were purchased from Nanjing Chemical Co., Ltd. and used without further purification. Microwave reaction was operated on CEM discover sp microwave synthesizer. Concentration and evaporation were carried out on Büchi rotary evaporator. Purification by column chromatography was accomplished using standard silica gel (200-300 mesh, Qingdao Haiyang Chemical Co., Ltd.). Melting points were obtained using a Melt-Temp II apparatus and are uncorrected. MS spectra was obtained on an Agilent 6120 quadrupole LC/MS (ESI). ^{1}H NMR spectra were recorded on a 400 or 500 MHz

NMR spectrometer. The purity of the compounds was detected by the HPLC study using a mixture of solvent methanol/water or acetonitrile/water at the flow rate of 2 mL/min and peak detection at 254 nm under UV. tofacitinib [7], **3** [24], **10** [25] were synthesized according to the reported procedures.

4.2. General procedures for the synthesis of intermediates 4a-4d

To a mixture of compound **3a** (6.40 g, 39.5 mmol) and 2,4-dichloro-5-methyl pyrimidine (6.44 g, 39.5 mmol) in dioxane (50 mL) was added $Pd(PPh_3)_4$ (2.31 g, 2.0 mmol) and K_2CO_3 (16.40 g, 118.5 mmol) under nitrogen. The reaction mixture was stirred at reflux for 12 h before cooling to room temperature and filtered to remove any solid. The filtrate was concentrated and purified by flash chromatography to give the desired products.

4.2.1. 4-(Benzofuran-2-yl)-2-chloro-5-methyl pyrimidine (4a)

White solid, yield 64%;. MS (ESI) *m*/*z* 245.1 $[M+H]^+$.

4.2.2. 2-Chloro-5-methyl-4-(5-((2,2,2-trifluoroethoxy)methyl)benzofuran-2-yl) pyrimidine (4b)

White solid; yield 72%. MS (ESI) *m*/*z* 357.2 $[M+H]^+$.

4.2.3. 2-(2-Chloro-5-methylpyrimidin-4-yl)benzofuran-5-carbonitrile (4c)

White solid, yield 80%. MS (ESI) *m*/*z* 270.1 $[M+H]^+$.

4.2.4. 2-(2-Chloro-5-methylpyrimidin-4-yl)benzofuran-6-carbonitrile (4d)

White solid, yield 74%. MS (ESI) *m*/*z* 270.1 $[M+H]^+$.

4.3. General procedures for the synthesis of targets 5a-5f

To a solution of **4a** (0.757 g, 3.09 mmol), 4-morpholinoaniline (0.500 g, 2.81 mmol), $Pd(OAc)_2$ (0.032 g, 0.14 mmol) and *rac*-BINAP (0.087 g, 0.14 mmol) in dioxane (10 mL) was added Cs_2CO_3 (1.83 g, 5.62 mmol) under nitrogen. The reaction mixture was stirred at 90 ºC overnight, cooled to room temperature and filtered through Celite. The filtrate was concentrated and purified by flash chromatography to give the desired products.

4.3.1. 4-(Benzofuran-2-yl)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-amine (5a)

Light yellow solid, yield 86%. mp 253-255 °C; MS (ESI) m/z 387.1 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.45 (s, 1H), 7.89-7.74 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.46 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.36 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.19 (brs, 1H), 7.18 (s, 1H), 3.85 (s, 4H), 3.22 (s, 4H); HPLC: 98.6%.

4.3.2. 4-(Benzofuran-2-yl)-5-methyl-N-(4-morpholinophenyl)pyrimidin-2-amine (5b)

Yellow solid, yield 85%. mp 198-201 °C; MS (ESI) m/z 404.3 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.66-7.51 (m, 3H), 7.53 (s, 1H), 7.43-7.35 (m, 1H), 7.30 (t, *J* = 11.7 Hz, 1H), 7.10 (s, 1H), 6.99-6.90 (m, 2H), 4.62 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); HPLC: 95.6%.

4.3.3. Ethyl 2-(3-((4-(benzofuran-2-yl)-5-methylpyrimidin-2-yl)amino)phenoxy) acetate (5c)

Yellow solid, yield 62%. mp 231-233 °C; MS (ESI) m/z 404.1 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.77-7.68 (m, 3H), 7.46 (t, *J* = 8.4 Hz, 1H), 7.42-7.34 (m, 2H), 7.20 (t, *J* = 8.2 Hz, 1H), 6.52 (dd, *J* = 8.2, 2.2 Hz, 1H), 4.78 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); HPLC: 95.9%.

4.3.4. 5-Methyl-N-(4-morpholinophenyl)-4-(5-(2,2,2-trifluoroethoxy)benzofuran-2-yl) pyrimidin-2-amine (5e)

Yellow solid, yield 62%. mp 201-202 °C; MS (ESI) m/z 499.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.42 (s, 1H), 7.80 (s, 1H), 7.71 (dd, *J* = 16.8, 8.0 Hz, 4H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.78 (s, 2H), 4.13 (q, *J* = 7.6 Hz, 2H), 3.75 (t, *J* = 4.8 Hz, 4H), 3.05 (t, *J* = 4.8 Hz, 4H), 2.48 (s, 3H); HPLC: 95.3%. HRMS (ESI) m/z calcd for $C_{26}H_{26}F_3N_4O_3$ [M+H]+, 499.1952, found 499.1964.

4.3.5. 2-(5-Methyl-2-((4-morpholinophenyl)amino)pyrimidin-4-yl)benzofuran-5-carbonitrile (5f)

Yellow solid, yield 77%. mp 198-200 °C; MS (ESI) m/z 412.3 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.47 (s, 1H), 8.38 (s, *J* = 1.2 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.74 (s, 1H), 7.69 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 3.76 (t, *J* = 4.8 Hz, 4H), 3.05 (t, *J* = 4.8 Hz, 4H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 159.1, 156.6, 156.2, 146.5, 133.6, 130.0, 128.8, 128.1, 120.4, 119.6, 117.4, 116.2, 113.7, 109.9, 107.4, 107.0, 66.7, 49.9, 16.7; HPLC: 96.7%. HRMS (ESI) m/z calcd for $C_{24}H_{22}N_5O_2$ $[M+H]^+$, 412.1768, found 412.1765.

4.4. General procedures for the synthesis of intermediates 7a-7b

To a solution of aniline **6a** (2.75 g, 9.9 mmol) in Et_2O (6 mL), *t*-BuOH (4 mL) and CH_2Cl_2 (15 mL) in ice bath was added $ZnCl_2$ (2.70 g, 19.8 mmol), 2,4-dichloro-5-trifluoromethyl pyrimidine (2.15 g, 9.9 mmol) and NEt_3 (1.10 g, 10.9 mmol) sequentially. The mixture was stirred for 5 h, quenched with water (30 mL), extracted with CH_2Cl_2 (40 mL x 3), washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography to give the desired products.

4.4.1. Tert-butyl 4-(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)piperazine-1-carboxylate (7a)

Off-white solid, yield 69%. MS (ESI) m/z 458.2 $[M+H]^+$.

4.4.2. 4-Chloro-N-(4-(3,5-dimethylpiperidin-1-yl)phenyl)-5-(trifluoromethyl)pyrimidin-2-amine (7b)

Yellow solid, yield 84%. MS (ESI) m/z 385.2 $[M+H]^+$.

4.5. Synthesis of intermediates 5g and target 5k

4.5.1. Tert-butyl 4-(4-((4-(5-cyanobenzofuran-2-yl)-5-(trifluoromethyl)pyrimidin-2-yl)amino)phenyl)

piperazine-1-carboxylate (5g)

To a 10 mL microwave vessel charged with a solution of **3c** (0.308 g, 1.65 mmol), **7a** (0.500 g, 1.1 mmol) and $Pd(PPh_3)_4$ (0.064 g, 0.055 mmol) in DMF (4 mL) was added Na_2CO_3 (0.233 g, 2.2 mmol). The mixture was stirred at 160 ^oC for 1 h at automatic CEM microwave reactor. The reaction mixture was cooled to room temperature, filtered through Celite, diluted with water (30 mL), extracted with EtOAc (30 mL x 3), washed with brine (50 mL x 2), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography to give compound **5g** as a yellow solid (0.350 g, 56%).

4.5.2. 2-(2-((4-(Piperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)benzofuran-5-carbonitrile (5k)

To a solution of **5g** (0.200 g, 0.35 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred for 30 min, diluted with water (3 mL), basified with saturated aq. $NaHCO_3$ to pH 8-9, extracted with CH_2Cl_2 (15 mL x 3), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography to give compound **5k** as a yellow solid (0.158 g, 98%). mp 345-346 °C; MS (ESI) m/z 465.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.10 (s, 1H), 7.72 (s, 2H), 7.70 (s, 1H), 7.58-7.50 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.23-3.17 (m, 4H), 3.14-3.08 (m, 4H); HPLC: 95.8%.

4.6. 2-(2-((4-(3,5-Dimethylpiperidin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)benzofuran-6-carbonitrile (5h)

Compound **5h** was prepared by a similar procedure of **5g** as a yellow solid (139 mg, 71%). mp 275-278 °C; MS (ESI) m/z 492.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.82 (s, 1H), 7.70 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.56-7.45 (m, 4H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.66-3.58 (m, 2H), 2.25 (t, *J* = 11.2 Hz, 2H), 1.93-1.77 (m, 4H), 0.97 (d, *J* = 6.4 Hz, 6H); HPLC: 96.0%.

4.7. 2-(4-((4-(Benzofuran-2-yl)-5-methylpyrimidin-2-yl)amino)phenoxy)acetic acid (5i)

To a solution of **5b** (0.271 g, 0.67 mmol) in MeOH (2.0 mL) and water (2.0 mL) was added NaOH (0.107 g, 2.68 mmol). The reaction mixture was stirred for 5 h, acidified with 1 N HCl to pH 2, diluted with water, extracted with EtOAc (20 mL x 3), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography to give **5i** as a light yellow solid (0.189 g, 75%). mp 300-302 °C; MS (ESI) m/z 376.2 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ 12.89 (s, 1H), 9.45 (s, 1H), 8.43 (s, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.76-7.69 (m, 3H), 7.67 (s, 1H), 7.45 (t, *J* = 5.7 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 4.62 (s, 2H), 2.50 (s, 3H); HPLC: 97.3%.

4.8. *(E)*-3-(4-((4-(benzofuran-2-yl)-5-methylpyrimidin-2-yl)amino)phenyl)-N-hydroxyacrylamide (5j)

Compound **5d** was prepared by a similar procedure of **5a** as a yellow solid (0.325 g, 68%). To a solution of **5d** (0.268 g, 0.67 mmol) in MeOH (2.0 mL) and water (2.0 mL) was added NaOH (0.107 g, 2.68 mmol). The reaction mixture was stirred for 5 h, acidified with 1 N HCl to pH 2, diluted with water, extracted with EtOAc (20 mL x 3), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography to give the acid as a yellow solid (0.105 g, 42%). A solution of the acid above (0.105 g, 0.28 mmol) and 1,1'-carbonyldiimidazole (0.045 g, 0.28 mmol) in THF (2.0 mL) was stirred for 1.5 h before addition of hydroxylamine hydrochloride (0.039 g, 0.56 mmol). The reaction mixture was stirred overnight, diluted with water (10 mL), extracted with EtOAc (20 mL x 3), dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography to give compound **5j** as a yellow solid (0.077 g, 71%). mp 267-269 °C; MS (ESI) m/z 387.1 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.54 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.73 (s, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 15.9 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 2.49 (s, 3H); HPLC: 96.6%.

4.9. 5-Benzyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine hydrochloride (12)

To a solution of **10** (24.5 g, 0.22 mol) in toluene (50 mL) was added benzaldehyde (23.3 g, 0.22 mol) dropwise. The resulting mixture was refluxed for 2 h under dehydrating conditions in a Dean-Stark trap. The reaction mixture was concentrated to driness to give the imine (43.8 g, 100%). MS (ESI) m/z 200.2 $[M+H]^+$. To a solution of the imine above (246.5 g, 1.24 mol) in methanol (500 mL) in ice bath was added $NaBH_4$ (28.83 g, 0.76 mol) portionwise over 0.5 h. The reaction mixture was stirred for 0.5 h, quenched with water (20 mL), concentrated, extracted with EtOAc (300 mL x 3), washed with brine, and acidified with conc. HCl (100 mL). The suspension was filtered, and the filter cake was dissolved in a solution of NaOH (52.0 g) in water (200 mL), extracted with CH_2Cl_2 (300 mL x 3), dried (Na_2SO_4), filtered, concentrated to give the desired product **11** (185.7 g, 74%). Formalin (37% aq.) was added dropwise to **11** (40.2 g, 0.2 mol). The mixture was stirred for 1 h at rt, extracted with Et_2O (100 mL x 3), washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. DMF (60 mL) and HCl saturated dioxane (40 mL) was added to the above oil. The mixture was stirred overnight at room temperature. The solid separated out after filtration and dry in vacuo at 50 ºC to give compound **12** as a white solid (47.6 g, 95%). MS (ESI) m/z 214.1 $[M+H]^+$; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.57-7.47 (m, 6H), 6.36 (s, 1H), 4.49 (s, 2H), 4.19 (s, 2H), 3.55-3.49 (m, 2H), 3.09-3.01 (m, 2H).

4.10. 5-Benzyl-2-(tributylstannyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (13)

To a solution of K_2CO_3 (10.86 g, 78.7 mmol) in CH_2Cl_2 (200 mL) and water (100 mL) was added **12** (13.11 g, 52.5 mmol). The aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried

(Na_2SO_4), filtered, concentrated to give the free base. To a solution of this free base in anhydrous THF (150 mL) in ice bath was added dropwise *n*-BuLi (21.0 mL, 52.5 mmol) over 40 minutes and n-Bu_3SnCl (20.8 g, 63.9 mmol) over 20 minutes sequentially under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2.5 h, quenched with water (100 mL), extracted with EtOAc (500 mL x 3), washed with brine (500 mL), dried (Na_2SO_4), filtered, and concentrated to give compound **13** as a light yellow liquid, which was used in the next step without further purification.

4.11. General procedures for the synthesis of intermediates 14a-14c

A solution of compounds **13** (5.07 g, 10.1 mmol), 2,4-dichloropyrimidine (1.0 g, 6.7 mmol), and $Pd(PPh_3)_2Cl_2$ (0.238 g, 0.34 mmol) in DMF (20 mL) was stirred at 90 °C for 3 h. The mixture was concentrated under high vacuum and purified by flash chromatography to give the desired products.

4.11.1. 5-Benzyl-2-(2-chloropyrimidin-4-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (14a)

White solid, yield 77%. MS (ESI) m/z 326.1 $[M+H]^+$.

4.11.2. 5-Benzyl-2-(2-chloro-5-fluoropyrimidin-4-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (14b)

White solid, yield 71%. MS (ESI) m/z 344.2 $[M+H]^+$.

4.11.3. 5-Benzyl-2-(2-chloro-5-methylpyrimidin-4-yl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (14c)

White solid, yield 89%. MS (ESI) m/z 340.2 $[M+H]^+$.

4.12. General procedures for the synthesis of targets 16a-16h

To a 10 mL microwave vessel charged with a solution of **14a** (0.500 g, 1.53 mmol), 4-morpholinoaniline (0.300 g, 1.68 mmol) in 2,2,2-trifluoroethanol (5 mL) was added KI (0.101 g, 0.61 mmol) and dioxane (saturated with HCl gas, 6.6 M, 0.67 mL). The mixture was stirred at 150 ^oC for 2 h at automatic CEM microwave reactor. The reaction mixture was cooled to room temperature, diluted with water (20 mL), neutralized with saturated aq. $NaHCO_3$, extracted with CH_2Cl_2 (20 mL x 3), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography to give compound **15a** as a yellow solid (0.415 g, 58%). To a solution of compound **15a** (1.0 g, 2.1 mmol) in CH_2Cl_2 (8 mL) was added 1-chloroethyl chloroformate (0.45 g, 3.2 mmol) slowly. The reaction mixture was stirred for 1 h, concentrated under high vacuum to driness. The residue was dissolved in MeOH (8 mL) and refluxed for 2 h before cooling to room temperature. The precipitated solid was collected and basified with K_2CO_3 to give the debenzylative product as a yellow solid (0.30 g, 38%). MS m/z 378.2 $[M+H]^+$. To a solution of the debenzylative compound above (0.10 g, 0.265 mmol) and triethyl amine (0.03 g, 0.30 mmol) in CH_2Cl_2 (5 mL) was added methyl sulfuryl chloride (0.045 g, 0.39 mmol). The reaction mixture was stirred overnight, concentrated and purified by flash chromatography to give compound **16a** as a yellow solid (0.080 g,

67%).

4.12.1. 4-(5-(Methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)-N-(4-morpholinophenyl)pyrimidin-2-amine (16a)

MS (ESI) m/z 456.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.6 Hz, 1H), 7.56 (d, *J* = 9.2 Hz, 2H), 7.24 (s, 1H), 7.09 (s, 1H), 7.04-6.93 (m, 3H), 4.38 (s, 2H), 3.91 (t, *J* = 4.8 Hz, 4H), 3.74 (t, *J* = 4.8 Hz, 2H), 3.17 (t, *J* = 4.8 Hz, 4H), 2.97 (t, *J* = 5.6 Hz, 2H), 2.90 (s, 3H); HPLC: 95.5%.

4.12.2. 3-(2-(2-((4-Morpholinophenyl)amino)pyrimidin-4-yl)-6,7-dihydrofuro[3,2-*c*]pyridin-5(4H)-yl)-3-oxopropanenitrile (16b)

Yellow solid, 82% yield. MS (ESI) m/z 445.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.17 (s, 1H), 7.07 (s, 1H), 7.03-6.91 (m, 3H), 4.52 (s, 1H), 4.48 (s, 1H), 4.02 (t, *J* = 5.6 Hz, 1H), 3.97-3.86 (m, 4H), 3.82 (t, *J* = 5.6 Hz, 1H), 3.62 (d, *J* = 7.2 Hz, 2H), 3.25-3.08 (m, 4H), 3.02 (t, 1H), 2.90 (t, *J* = 5.6 Hz, 1H); HPLC: 97.7%.

4.12.3. N-(4-(4-methylpiperazin-1-yl)phenyl)-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)pyrimidin-2-amine (16c)

Yellow solid, 60% yield. MS (ESI) m/z 469.2 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.2 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.98 (d, *J* = 6.0 Hz, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.37 (s, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 3.23 (t, *J* = 4.8 Hz, 4H), 2.97 (t, *J* = 5.6 Hz, 2H), 2.90 (s, 3H), 2.66 (t, *J* = 4.8 Hz, 4H), 2.41 (s, 3H); HPLC: 96.1%.

4.12.4. 3-(2-(2-((4-(4-Methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-6,7-dihydrofuro[3,2-*c*]pyridin-5(4H)-yl)-3-oxopropanenitrile (16d)

Yellow solid, 50% yield. MS (ESI) m/z 458.4 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 9.2, 6.0 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.06 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 5.6 Hz, 1H), 4.02 (t, *J* = 6.0 Hz, 1H), 3.82 (t, *J* = 5.6 Hz, 1H), 3.62 (d, *J* = 6.4 Hz, 2H), 3.23 (t, *J* = 4.8 Hz, 4H), 3.02 (t, *J* = 6.0 Hz, 1H), 2.90 (t, *J* = 5.6 Hz, 1H), 2.66 (t, *J* = 4.8 Hz, 4H), 2.42 (s, 3H); HPLC: 98.1%.

4.12.5. 4-(5-(Methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)-N-(4-(2-(pyrrolidin-1-yl)ethoxy) phenyl)pyrimidin-2-amine (16e)

Yellow solid, 51% yield. MS (ESI) m/z 484.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.2 Hz, 1H), 7.54 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.06 (s, 1H), 7.05 (s, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 6.95 (dd, *J* = 6.8, 2.0 Hz, 2H), 4.37 (s, 2H), 4.18 (t, *J* = 6.0 Hz, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 3.05-2.93 (m, 4H), 2.90 (s, 3H), 2.74 (s, 4H), 1.92-1.85 (m, 4H); HPLC: 95.5%.

4.12.6. 5-Fluoro-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)-N-(4-(2-(pyrrolidin-1-yl) ethoxy)phenyl)pyrimidin-2-amine (16f)

Yellow solid, 99% yield. MS (ESI) m/z 501.9 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 3.2 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 2.8 Hz, 1H), 7.09 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.39 (d, *J* = 1.6 Hz, 2H), 4.19 (t, *J* = 5.6 Hz, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 3.08-2.97 (m, 4H), 2.91 (s, 3H), 2.76 (s, 4H), 1.89 (t, 4H); HPLC: 95.5%.

4.12.7. 5-Fluoro-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)-N-(3,4,5-trimethoxy-phenyl) pyrimidin-2-amine (16g)

Yellow solid, 60% yield. MS (ESI) m/z 479.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.57 (s, 1H),7.39 (s, 2H), 7.28 (s, 1H), 4.28 (s, 2H), 3.81 (s, 6H), 3.62 (s, 3H), 3.60 (s, 3H), 2.98 (s, 2H), 2.89 (s, 2H); HPLC: 95.8%.

4.12.8. 5-Methyl-4-(5-(methylsulfonyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl)-N-(4-morpholinophenyl) pyrimidin-2-amine (16h)

Yellow solid, 87% yield. MS (ESI) m/z 470.1 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.29 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 6.90 (s, 2H), 4.29 (s, 2H), 3.78-3.70 (m, 4H), 3.59 (t, *J* = 5.5 Hz, 2H), 3.09-3.00 (m, 4H), 2.97 (s, 3H), 2.94-2.88 (m, 2H), 2.34 (s, 3H); HPLC: 98.8%.

4.13. JAK enzymatic inhibition assay

IC_{50} determinations for JAK2 and JAK3 (Invitrogen) were performed with the HTRF (Homogenous Time-Resolved Fluorescence) KinEASE-TK assay from Cisbio according to the manufacturer's instructions. A typical enzyme reaction contains 0.3 ng/μL JAK2 or 0.25 ng/μL JAK3, 0.1 μM TK-subtrate-biotin, 4 μM ATP, 1 mM DTT, and 5 mM $MgCl_2$. Compounds were screened at serial diluted concentration in the presence of 2% DMSO with a 5 min pre-incubation of kinase and compounds. All reactions were started by the addition of ATP and TK-subtrate-biotin, incubated at 30 ºC for 30 min and quenched with the stop buffer containing 25 nM Strep-XL665 and TK Ab-Cryptate. The plates were incubated for 1 h before being read on PHERAStar FS Microplate Reader (BMG LABTECH) using standard HTRF settings. And IC_{50} values were determined using the GraphPad Prism 5.0 software.

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Graphical Abstract

Identification of 4-(2-furanyl) pyrimidin-2-amines as Janus kinase 2 inhibitors

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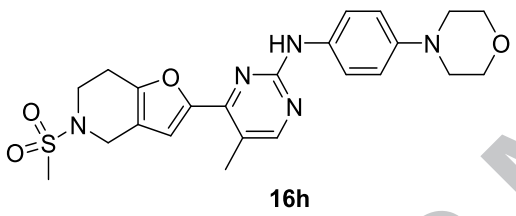

16h

	JAK2 IC_{50}	JAK3 IC_{50}
16h	0.7 nM	23.2 nM
tofacitinib	2.8 nM	1.2 nM

Highlights:

Identification of 4-(2-furanyl) pyrimidin-2-amines as Janus kinase 2 inhibitors

- Novel 4-(2-furanyl)-pyrimidin-2-amine derivatives were designed, synthesized and evaluated as JAK2 inhibitors.
- Some compounds exhibited superior inhibitory activity and JAK2/3 selectivity compared with tofacitinib.
- 4,5,6,7-Tetrahydrofuro[3,2-*c*]pyridine moiety is identified as a promising scaffold for further exploration as JAK inhibitors.