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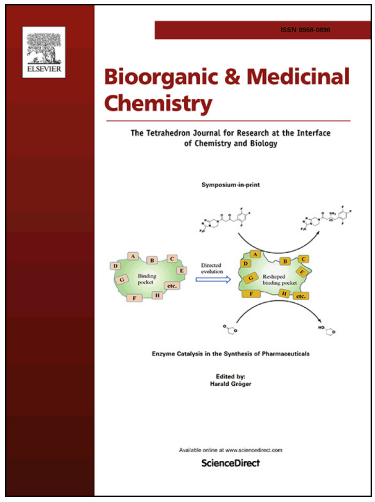

Novel 7-Formyl-naphthyridyl-ureas Derivatives as Potential Selective FGFR4 Inhibitors: Design, Synthesis, and Biological Activity Studies

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Novel 7-Formyl-naphthyridyl-ureas Derivatives as Potential Selective FGFR4 Inhibitors: Design, Synthesis, and Biological Activity Studies

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Key words: FGFR4; selectivity; antitumor; pharmacokinetic profile

Abstract Total twenty-five 7-formyl-naphthyridyl-urea derivatives were designed, synthesized and evaluated for their inhibition of FGFR4 kinase and antitumor activity. The pharmacological data indicated that most of the tested compounds showed high selectivity towards FGFR4 kinase and could significantly inhibit FGFR4 and the tumor cells lines with the high expression of FGFR4. In particular, compounds **6f**, **6g**, **6h**, **6l**, **6m** and **6s** showed a good performance in pharmacokinetic tests. When tested in mice, the representative compound **6f** was found to have good pharmacokinetic parameters, low toxicity, and better tumor inhibiting activity in vivo.

1. Introduction

The biological action of fibroblast growth factors (FGFs) is mediated by specific cell surface receptors belonging to the Receptor Protein Tyrosine Kinase (RPTK) family. These proteins consist of an extracellular ligand binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain which undergoes phosphorylation upon binding of FGF. Four fibroblast growth factor receptors (FGFRs) have been identified to date: FGFR1, FGFR2, FGFR3, and FGFR4. FGFR signaling is involved in the control of multiple developmental and physiological processes, as well as being implicated as a driver in certain forms of cancers such as primary breast cancer,[1] gastric cancer,[2] uterine cervical cancer,[3] colorectal cancer,[4] prostate cancer,[5] pancreatic cancer,[6] hepatocarcinoma,[7] and non-small-cell lung cancer[8] *et al*.

A number of pan-FGFR inhibitors, which target the ATP binding site within the kinase domain of the receptor, have been described and are characterized as being either: biased towards FGFR 1-3 inhibition, with >10-fold lower

FGFR4 potency; or equipotent versus all four family members.[9,10] However, for all of these agents the robust inhibition of FGFR4 often leads to extensive inhibition of the other three isoforms, and as a result will be associated with the side effects resulting from FGFR 1-3 inhibition.[11] Therefore, the opportunity to identify selective inhibitors of FGFR4 was investigated with the anticipation that it would provide better tolerated treatments, and enable more robust inhibition of the target to be explored.

To explore this possibility, scientists have conducted a series of studies in the past years and a number of inhibitors have reported. PD166866 with a structure of quinazoline [12] and compound **1** with a structural of imidazolopyridine are reported to achieve FGFR4 selectivity.[13] Furthermore, the P-loop cysteine in the FGFR family has been targeted for pan-FGFR inhibition in an irreversible-covalent manner with the acrylamide containing inhibitors FIN-1[14] and PRN1371[15], and in a reversible-covalent manner with the structurally-related cyano-acrylamides, as exemplified by **2**.[16] In 2015, Hagel, et. al reported the first selective FGFR4 inhibitor BLU9931 [17], via adding an acrylamide moiety to provide a selectivity of less than 10 nM activity against FGFR4 and larger than 100-fold over FGFR1. They also indicated that the structure-based design of this molecule involved the covalent targeting of a unique Cysteine 552 (Cys552) residue in the hinge region of the receptor. Based on the structure of BLU9931, several similar compounds such as BLU554[18], H2B6527[19], **3**[20], **4**[21], **5**[22] were reported (**Figure 1**).

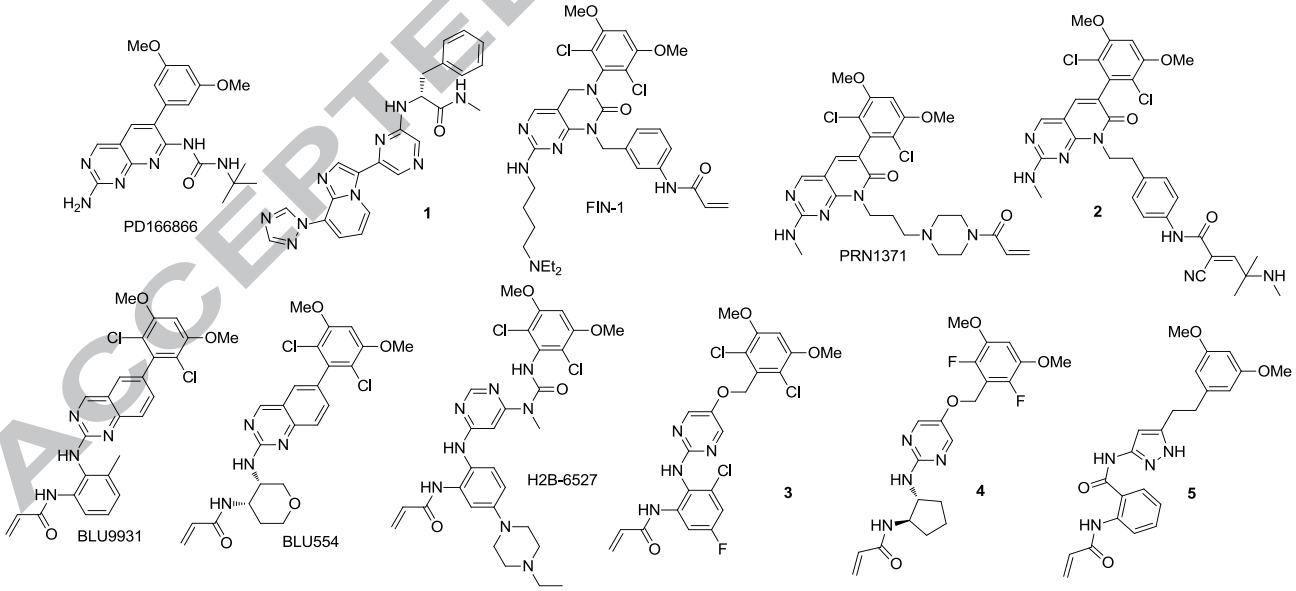


Figure 1. Structures of representative FGFR inhibitors.

Recently, Novartis report a new compound FGF401, a highly-selective inhibitor of FGFR4 which is currently undergoing clinical evaluation for the treatment of FGFR4 and β-klotho positive solid tumors.[23-25] Further research

indicated that 7-formylpyridine ureas (7-FPUs) improved potency and physicochemical properties compared to 7-formylquinoline amide, and revealed that the reversible-covalent mechanism of inhibition the 7-FPUs exhibited slowed binding kinetics. Moreover, the aldehyde, as the putative electrophile, was demonstrated to be a key structural element for activity. The cyano group in the 5-position was also of particular interest based upon the low lipophilicity.[26] In an ongoing effort to discover novel FGFR4 inhibitors and build diversification of chemical library, we continued to develop structurally relevant compounds **6** with diverse substituent on naphthyridine and pyridine. Herein, we reported the synthesis and the biological characterizations of a new class of 7-FPUs derivatives with convenient raw materials availability and industrial manufacture (**Figure 2**).

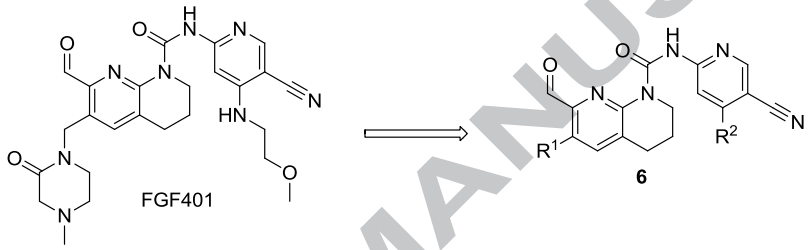
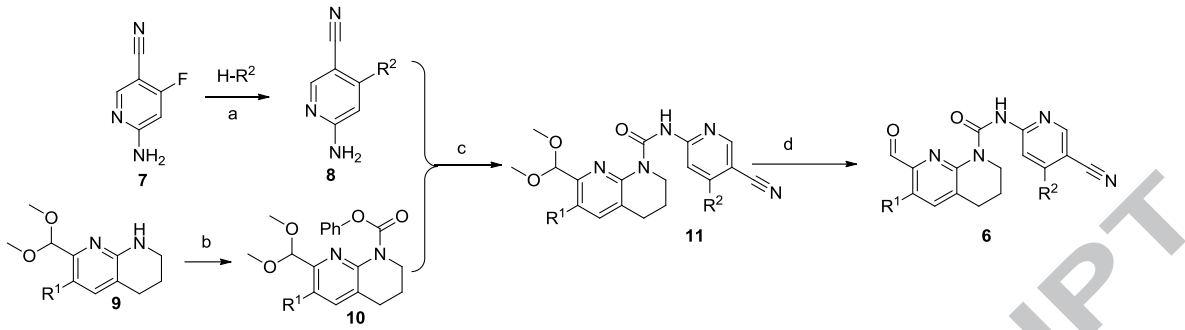


Figure 2. Core modifications lead to the 7-FPUs derivatives

2. Results and discussion

Chemistry The designed inhibitors were readily prepared by using a condensation reaction as the key step (Scheme 1).[27] Briefly, commercially available 6-amino-4-fluoronicotinonitrile **7** was treated with different substituted H-R^2 giving the corresponding intermediates **8** through a nucleophilic substitution reaction. Different 6-position substituted 7-(dimethoxymethyl)-1,2,3,4-tetrahydro-1,8-naphthyridine compounds **9** were treated with diphenyl carbonate under the presence of LiHMDS to afford the phenoxycarbonyl protected products **10**. After a nucleophilic substitution reaction of compounds **8** and **10,** compounds **11** were reacted with HCl to produce the designed molecules **6a-6y**.



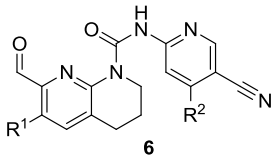
Scheme 1 Synthetic Route of Optically Active Compounds 6: Reagents and conditions: a) compound **7**, H-R^2, DIPEA, DMF, 60 °C; b) compound **9**, diphenyl carbonate, THF, LiHMDS, rt; c) compound **8**, **10**, THF, LiHMDS, rt; d) compound **11**, HCl, THF/H_2O = 11/4, rt, 2h.

Kinase and cell inhibition activity The obtained compounds were examined for their ability to inhibit FGFR 1 and 4 using an enzyme assay, and furthermore a cellular assay was performed to determine the inhibition activity of 7-FPUs derivatives against Hep 3B and HuH-7 with the high expression of FGFR4 as well as SK-HEP-1 cells without FGFR4 gene amplification[28,29] (**Table 1-3**). All of the compounds showed significant kinase inhibition activity against FGFR4 while little activity against FGFR1. Some compounds showed the FGFR4 selectivity >1000 *vs* FGFR1. The reason is probably that, similar to the previous study of FGF401, the aldehyde was demonstrated to be a key structural element for activity. Besides, the 7-formyl-naphthyridyl-ureas scaffold was also involved the covalent targeting of a unique Cysteine 552 (Cys552) residue in the hinge region of the receptor. In the cellular assay the target compounds showed significant inhibition to the cell lines with the high expression of FGFR4 including cell lines Hep 3B and HuH-7. In contrast, the compounds showed little activity against cell line SK-HEP-1 without FGFR4 gene amplification. So it is clear that the 7-FPUs derivatives had high selectivity to FGFR4 kinase.

For initial structure-activity relationship exploration, a series of compounds with a ring substituent of R^1 and an open chain substituent of R^2 were studied. Compound **6a** was served as a benchmark to analyze both enzymatic and cellular potency contributions from different substitution patterns. Similar to the positive control **FGF401,** compound **6a** showed significant kinase inhibition to FGFR4 with IC_{50} of 1.6 nM and showed significant inhibition to both cell lines Hep 3B (8.9 nM) and HuH-7 (16.3 nM). As for the R^2 substituent, it was found that changing the NH group in **6a** to S atom in **6b** or O atom in **6c** led to a little loss of potency; further introduction of an α-methyl into **6c** afforded **6d**, which demonstrated an enhancement of cellular potency compared to **6c**. Increasing the ring size of R^1 from 2-oxo-morpholin to the 7-membered analogues 2-oxo-oxazepan (e.g. **6e)** retained a similar level of

activity as compared with **6d**. Interestingly, when *R*-1-methoxy-*N*-methylpropan-2-amine was introduced into R^2 group, the resulting compound **6f** was more potent than the other compounds with IC_{50} of 1.5 nM against FGFR4 and IC_{50} of 1.1 nM and 2.5 nM against Hep 3B and HuH-7 respectively. Furthermore, reducing the ring size to the 5-membered analogues, the resulting compounds **6g** and **6h** demonstrated a further enhancement of kinase inhibition activity and cellular potency as compared with **6a**. However, less active was observed in compound **6i** case which containing *S*-1-methoxy-*N*-methylpropan-2-amine as R^2 group.

Table 1 Activity of 7-FPUs derivatives with a ring substituent of R^1 and an open chain substituent of R^2



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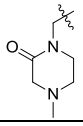
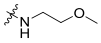
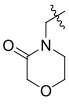
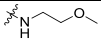
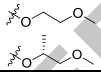
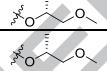
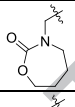
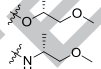
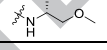
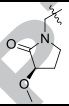
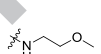
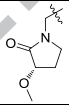
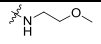
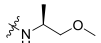
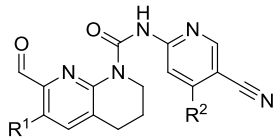
Entry	Compounds	Structure		Enzyme IC_{50} ± SEM (nM)		Cell IC_{50} ± SEM（nM）		
		R^1	R^2	FGFR1	FGFR4	Hep 3B	HuH-7	SK-HEP-1
1	**FGF401**			>10000	1.9±0.3	8.8±0.8	16.3±0.5	ND[a]
2	**6a**			>10000	1.6±0.2	8.9±0. 7	17.3±0. 7	>10000[b]
3	**6b**			>10000	4.6±0. 1	20.8±2. 4	32.2±0. 8	>10000
4	**6c**			>10000	4.5±0. 03	27.7±1. 8	51.8±2. 5	>10000
5	**6d**			>10000	1.3±0. 1	2.9±0. 3	7.8±0. 5	>10000
6	**6e**			>10000	2.1±0. 1	2.2±0. 3	4.6±0. 1	>10000
7	**6f**			>10000	1.5±0. 2	1.1±0. 1	2.5±0. 2	>10000
8	**6g**			>10000	1.2±0. 1	1.9±0. 05	8.3±0. 3	>10000
9	**6h**			>10000	1.7±0. 02	2.3±0. 2	9.0±0. 1	>10000
10	**6i**			>10000	5.0±0. 1	13.6±0. 05	40.5±0. 6	>10000

[a] "ND" means "not determined". [b] ">10000" means that the corresponding compound did not show any activity at the concentration over 10000 nM.

In order to further investigate the influence of R^2 substituent on the activity of the target compounds, compounds **6j-6r** with a ring substituent of R^1 and a ß-ring substituent of R^2 were designed and prepared. Investigation suggested that the aryl substitution in compounds **6j** and **6k** showed a significant loss of kinase activity and cell line inhibition because the aryl substituents had a planar structure while other substituents had a three-dimensional structure. The *S*-tetrahydrofuran-3-thiol and *R*- tetrahydrofuran-3-thiol substituted compounds **6l** and **6m** exhibited a moderate FGFR4 inhibitory potency while compound with the substitution of (1*R*,2*R*)-2-methoxycyclopentanamine (**6n**) or

(3S,4S)-3,4-dimethoxytetrahydro-2H-pyran (**6o**) showed excellent activity in both enzyme and cellular tests, suggesting that the R^2 group size had a great influence on the inhibitory potency. When the tetrahydrofuran-3-amine group was introduced to the R^2, increasing the ring size of R^1 to the 7-membered analogues or reducing the ring size to the 5-membered analogues resulted in molecules **6p**, **6q** and **6r** which all demonstrated excellent inhibitory activity of kinase activity and cell line inhibition, respectively.

Table 2 Activity of 7-FPUs derivatives with a ring substituent of R^1 and an ß-ring substituent of R^2



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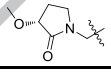
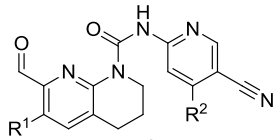
Entry	Compounds	Structure		Enzyme IC_{50} ± SEM (nM)		Cell IC_{50} ± SEM（nM）		
		R^1	R^2	FGFR1	FGFR4	Hep 3B	HuH-7	SK-HEP-1
1	**6j**			>10000	71±1	46±4	69±2	>10000
2	**6k**			>10000	38±0. 03	69±2. 7	20.7±0. 01	>10000
3	**6l**			>10000	5.3±0. 02	14.5±0. 3	36.1±0. 2	>10000
4	**6m**			>10000	7.5±0. 2	22.7±0. 2	50.1±0. 3	>10000
5	**6n**			>10000	1.0±0. 01	1.0±0. 1	2.7±0. 04	>10000
6	**6o**			>10000	2.7±0. 04	10.9±1. 7	40.8±0. 2	>10000
7	**6p**			>10000	1.4±0. 2	3.7±0. 01	7.2±0. 02	>10000
8	**6q**			>10000	1.3±0. 1	2.3±0. 1	4.9±0. 01	>10000
9	**6r**			>10000	1.0±0. 1	1.8±0. 2	5.4±0. 3	>10000

Finally, systematic structural optimization of 7-FPUs derivatives of both ring substituents in R^1 and R^2 revealed that the substituents dramatically impacted FGFR4 inhibition. As summarized in **Table 3**, the compound **6s** with the structure of 2-oxo-morpholin of R^1 and (*S*)-3-methoxypyrrolidine of R^2 showed a good enzymatic potency against FGFR4 with IC_{50} of 3.5 nM and inhibition of Hep 3B cell line (24.5 nM) and HuH-7 cell line (24.7 nM). The relatively low potency of **6t** and **6u** indicated that the larger substitution of R^2 such as (*S*)-2-(methoxymethyl)pyrrolidine or *N*,*N*-dimethylpyrrolidin-3-amine were less tolerable. Our investigation also

suggested that *R*-isomer in 2'-position of the R^2 substitution showed a better activity than the *S*-isomer by comparing the compounds **6v** vs **6w** and **6x** vs **6y**.

Table 3 Activity of 7-FPUs derivatives with a ring substituent in R^1 and a ring substituent in R^2



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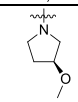
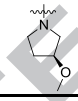
Entry	compounds	Structure		Enzyme IC_{50} ± SEM (nM)		Cell IC_{50} ± SEM（nM）		
		R^1	R^2	FGFR1	FGFR4	Hep 3B	HuH-7	SK-HEP-1
1	**6s**			>10000	3.5±0. 01	24.9±1. 8	27.5±0. 1	>10000
2	**6t**			>10000	9.1±0. 3	22.9±3. 5	65.3±2. 9	>10000
3	**6u**			>10000	9.4±0. 7	93.8±11. 5	297±0. 6	>10000
4	**6v**			>10000	9.5±0. 01	38.7±3. 4	29.6±0. 9	>10000
5	**6w**			>10000	4.7±0. 3	9.9±0. 01	10.2±0. 3	>10000
6	**6x**			>10000	4.6±0. 3	13.3±3. 2	11.8±0. 8	>10000
7	**6y**			>10000	11.1±0. 2	39.3±1. 0	34.6±1. 3	>10000

Pharmacokinetic study With the excellent in vitro enzyme and cell potencies, the pharmacokinetic properties of **6f**, **6g**, **6h**, **6l**, **6m** and **6s** were also evaluated in vivo, and the results were summarized in Table 4. Selected compounds were administrated to male Sprague-Dawley (SD) rats: orally by gavage at a 5 mg/kg dose. The result suggested that designed 7-formylpyridine urea derivatives showed a good performance in the pharmacokinetic study. Compounds **6f**, **6g**, **6h** and **6s** demonstrated higher plasma concentration than compounds **6l** and **6m,** however, longer residence time was observed by **6l** and **6m.**

Table 4 Pharmacokinetic profile of various 7-formyl-naphthyridyl-ureas derivatives

Compound	6f	6g	6h	6l	6m	6s
Dose (mg/kg)	5mg/kg					
Cmax (ng/mL)	3377	3762	3287	2335	1640	3356
AUC (ng/mL*h)	9464	12280	11327	1954	6780	14659
$t_{1/2}$ (h)	1.27	1.1	1.0	0.79	0.96	1.2
MRT (h)	2.48	3.2	2.9	3.5	3.65	2.6

Kinases Screening Due to the excellent biological activity and good performance in the pharmacokinetic study, 7-formylpyridine urea derivatives **6f** was further evaluated for the inhibitory activities against other 36 kinase in vitro (Table 5). It was found that compound **6f** showed excellent inhibition against FGFR4 kinase (IC_{50} 1.5 nM, Table 1 entry 7). In contrast, compound **6f** showed little activity against the other 36 species of kinase. It is clear that the 7-formylpyridine urea derivative, **6f**, inhibited FGFR4 kinase activity with high selectivity and specificity.

Table 5 Activity of 6f against different kinases

Kinase Name	IC_{50}(nM)	Kinase Name	IC_{50}(nM)
KDR	>10000	MAPKAPK3	>10000
ROS	>10000	MET	>10000
PDGFRa	>10000	RET	>10000
PDGFRb	>10000	ZAP70	>10000
EGFR	>10000	TIE2	>10000
MUSK	>10000	FAK	>10000
JAK2	>10000	TRK-A	>10000
JAK3	>10000	AXL	>10000
EphA1	>10000	RON	>10000
EphB1	>10000	ALK	>10000
HER4	>10000	CKIT	>10000
INSR	>10000	IGF1R	>10000
HER2	>10000	FLT1	>10000
SYK	>10000	FLT4	>10000
LTK	>10000	MAPKAPK2	>10000
FLT3	>10000	FGFR1	>10000
TYK2	>10000	FGFR2	>10000
JAK1	>10000	FGFR3	>10000

In vivo antitumor activity Two different human tumor cell lines (HuH7 and Hep 3B) were used to study the in vivo efficacy of compound **6f** and positive control **FGF401** in tumor xenograft nude mouse model (**Figures** 3 and **4**). At all of the test dosages (10, 30, and 100 mg/kg), **6f** significantly inhibited the tumor (HuH7) growth in nude mice and the inhibitory rates were 28.1%, 62.7%, and 70.8%, respectively. In contrast, the inhibition rate of **FGF401**

(30 mg/kg) was 52.5%, which is lower than **6f** at the same dosage. For the inhibition of Hep 3B tumor growth, compound **6f** showed even better activity. The inhibition rates of **6f** (3, 10, and 30 mg/kg) reached 69.8%, 126.5%, and 164.6%, respectively, while **FGF401** (10 mg/kg) showed the worse inhibitory effect (85.9%) at the same dosage. The results clearly indicated that **6f** had a better inhibiting activity than positive control **FGF401** in a dose-dependent manner.

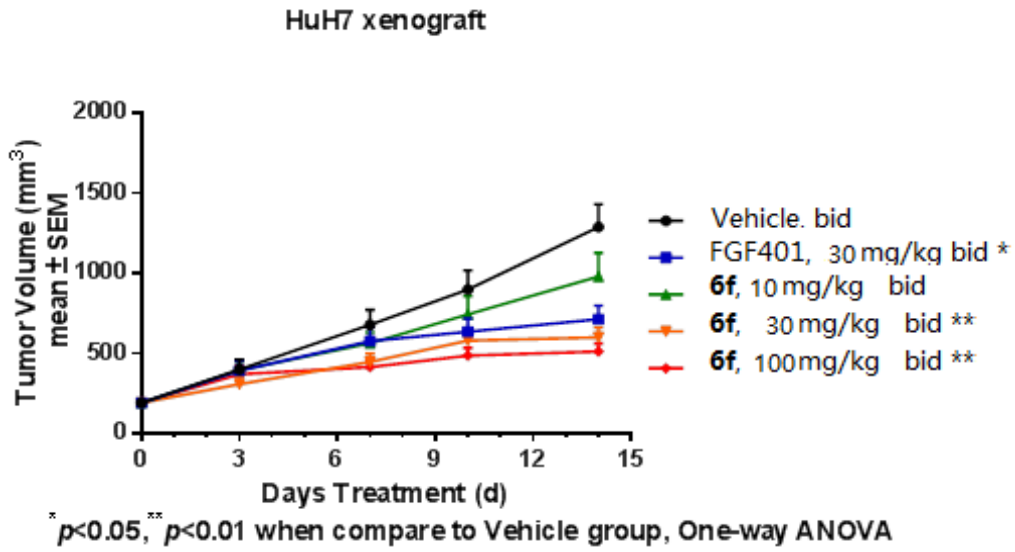


Figure 3. Efficacy of **6f** and **FGF401** on resistant human hepatocarcinoma HuH7 tumor xenograft in nude mouse (n=5).

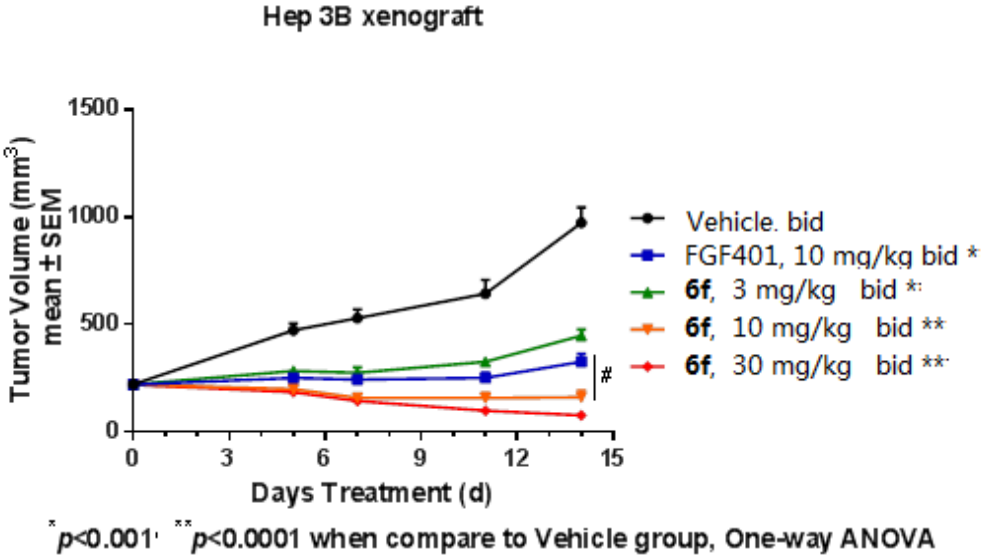


Figure 4. Efficacy of **6f** and **FGF401** on resistant human hepatocarcinoma Hep 3B tumor xenograft in nude mouse (n=5).

Toxicity studies in mice Long-term toxicity studies were performed in male and female SD mice to determine potential adverse effects and maximum tolerated dose (MTD) for **6f**. Both male and female SD mice were treated for 28 days with compound **6f** at 50, 150, or 450 (mg/kg)/day and then rehabilitate for another 28 days. The body weights of all treated mice remained normal during the study when compared to the vehicle-treated controls. In the 450 mg/kg dose group, the test substance-related death was observed, but no toxicity was observed in the male animals. Under the conditions of this experiment, no significant toxicity dose (NOAEL) was found for the dosage of 450 mg/kg in male animals; no significant toxicity dose (NOAEL) was found for the dosage of 150 mg/kg in female animals. Acute toxicity studies were performed in male and female SD mice for once with compound **6f** at 200, 600 or 2000 (mg/kg). No biologically significant changes in clinical pathology were observed. The NOAEL in mice acute toxicity studies was estimated to be 2000 (mg/kg)/day.

3. Conclusion

A series of 7-formylpyridine urea derivatives **6** were designed and synthesized. The synthesized compounds were evaluated for their potential as selective FGFR4 Inhibitors. It was found that most of the target compounds showed potent inhibitory activity to FGFR4 kinase and FGFR4 high-expressing tumor cells, and possessed high selectivity towards FGFR4 over other kinases. In particular, compounds **6f**, **6g**, **6h**, **6l**, **6m** and **6s** showed a good performance in pharmacokinetic tests. Moreover, the representative compound **6f** also showed a better antitumor activity than **FGF401** in a dose-dependent manner in vivo, and an excellent and a higher level of NOAEL in mice toxicity. Altogether, the target compounds showed promising exploration values as selective FGFR4 inhibitors for the treatment of tumor.[30] Further studies on structural optimization and biological activities about these derivatives are still underway in our laboratory and will be reported in the future.

4. Experimental section

Chemistry All chemicals were obtained from commercial purchase and solvents were purified and dried by standard procedures. Flash chromatography (FC): silica gel (SiO_2; 40 mm, 200~300 mesh). Melting points were uncorrected and were determined using a capillary apparatus (RDCSY-I). ^{1}H NMR and ^{13}C NMR Spectra: Bruker AVANCE-400 Digital NMR Spectrometer, ESI-MS: Thermo Finnigan LCQ advantage MAX. Elemental analysis was performed on a Vario EL III apparatus.

***N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6a).**

Typical procedure:

A mixture of 6-amino-4-fluoronicotinonitrile **7** (4.11 g, 30 mmol), 2-methoxyethanamine (4.5 g, 60 mmol), and DIPEA (1.16 g, 90 mmol) in DMF (120 mL) was stirred at 60ºC until the reaction was completed by TLC. After quenched with water, the reaction solution was extracted with CH_2Cl_2 (3×100 mL), washed with sequentially with satd $NaHCO_3$ (aq) and brine and then dried over anhydrous Na_2SO_4. Filtration, evaporation, and chromatography on silica gel afforded the product **8** (3.84g, 67%). MS m/z (ESI): 193.1 $[M+H]^+$

A solution of 4-((2-(dimethoxymethyl)-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methyl)morpholin-3-one **9** (642mg, 2 mmol) and dimethyl carbonate (643mg, 3 mmol) in THF was cooled down to -78ºC under N_2 atmosphere, then a solution of LiHMDS in THF (4mL, 4mmol) was dropped, and warmed to rt, stirring until the reaction was completed by TLC. The reaction mixture was quenched with an aqueous solution of saturated NH_4Cl (100 mL) and extracted with EA (2×50 mL).The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Filtration, evaporation, and chromatography on silica gel afforded the product **10** (400mg, 45%). MS m/z (ESI): 442.1 $[M+H]^+$

A solution of 6-amino-4-((2-methoxyethyl)amino)nicotinonitrile **8** (20 mg, 0.09 mmol) and phenyl 7-(dimethoxymethyl)-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate **10** (38 mg, 0.09 mmol) in THF (2 mL) was cooled down to -78ºC under N_2 atmosphere, then a solution of LiHMDS in THF (0.2 mL, 0.2mmol) was dropped, and warmed to rt, stirring until the reaction was completed by TLC. The reaction mixture was quenched with an aqueous solution of saturated NH_4Cl (20 mL) and extracted with EA (2×30 mL).The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Filtration, evaporation, and chromatography on silica gel afforded the product **11** (23 mg, 46%). MS m/z (ESI): 580.2 $[M+H]^+$

To the solution of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-(dimethoxymethyl)-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide **11** (23 mg, 0.04mmol) in THF/water (2/1, 1.5 mL) was added concentrated hydrochloric acid (0.15 mL, 1.8 mmol), the combined solution was stirred for 2 hour. The reaction mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (20 mL) and extracted with EA (2×30 mL).The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Filtration, evaporation, and chromatography on silica gel afforded the product **6a** (15 mg, 70%). ^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.57 (s, 1 H), 10.24 (s, 1 H), 8.18 (s, 1 H), 7.67 (s, 1 H), 7.58 (s, 1 H), 5.34 (s, 1 H), 5.11 (s, 2 H), 4.25 (s, 2 H), 4.07-4.10 (t, *J*=5.60 Hz, 2 H), 3.87-3.90 (m, 2 H), 3.63-3.65 (t, *J*=5.20 Hz, 2 H), 3.49-3.51 (t, *J*=5.20

Hz, 2 H), 3.42 (s, 3 H), 3.40-3.42 (m, 2 H), 2.92-2.95 (m, 2 H), 2.05-2.06 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ 193.6, 167.5, 155.7, 155.1, 152.6, 152.3, 151.1, 144.2, 140.7, 128.2, 128.0, 116.5, 93.2, 89.9, 69.9, 68.3, 63.9, 59.0, 46.9, 43.9, 43.8, 42.5, 28.4, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{24}H_{28}N_7O_5$ Exact Mass: 493.2146 found 494.2130. HPLC purity: 99.1%.

***N*-(5-cyano-4-((2-methoxyethyl)thio)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6b).**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ 13.86 (s, 1 H), 10.23 (s, 1 H), 8.35 (s, 1 H), 8.27 (s, 1 H), 7.69 (s, 1 H), 5.11 (s, 2 H), 4.26 (s, 2 H), 4.08-4.11 (m, 2 H), 3.88-3.91 (m, t, *J*=5.20 Hz, 2 H), 3.75-3.78 (t, *J*=6.00 Hz, 2 H), 3.47 (s, 3 H), 3.41-3.43 (m, 2 H), 3.32-3.36 (m, 2 H), 2.94-2.97 (m, 2 H), 2.06-2.08 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ 193.3, 167.5, 155.3, 154.7, 152.6, 152.3, 150.1, 144.1, 140.8, 128.3, 128.2, 115.6, 107.9, 102.4, 69.8, 68.3, 63.9, 59.9, 47.0, 44.0, 43.9, 31.2, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{24}H_{27}N_6O_5S$ Exact Mass: 511.1764 found 511.1741. HPLC purity: 98.1%.

***N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6c)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ 13.86 (s, 1 H), 10.24 (s, 1 H), 8.36 (s, 1 H), 7.97 (s, 1 H), 7.68 (s, 1 H), 5.11 (s, 2 H), 4.34-4.35 (m, 2 H), 4.26 (s, 2 H), 4.09 (m, 2 H), 3.89 (m, 2 H), 3.83 (m, 2 H), 3.47 (s, 3 H), 3.42 (m, 2 H), 2.95 (m, 2 H), 2.06 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ 193.3, 167.5, 167.4, 157.1, 153.2, 152.6, 151.0, 144.1, 140.8, 128.3, 128.2, 114.9, 96.5, 95.2, 70.2, 69.0, 68.3, 64.0, 59.6, 44.0, 43.9, 29.7, 22.7, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{24}H_{27}N_6O_6$ Exact Mass: 495.1992 found 495.1970. HPLC purity: 98.1%.

(*R*)-*N*-(5-cyano-4-((1-methoxypropan-2-yl)oxy)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide (6d)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ 13.81 (s, 1 H), 10.24 (s, 1 H), 8.35 (s, 1 H), 8.00 (s, 1 H), 7.68 (s, 1 H), 5.11 (s, 2 H), 4.86-4.87 (m, 1 H), 4.26 (s, 2 H), 4.08-4.11 (t, *J*=5.60 Hz, 2 H), 3.88-3.91 (t, *J*=5.20 Hz, 2 H), 3.56-3.67 (m, 2 H), 3.43 (s, 3 H), 3.41-3.42 (m, 2 H), 2.93-2.96 (m, 2 H), 2.04-2.07 (m, 2 H), 1.41-1.43 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ 193.4, 167.5, 167.0, 157.0, 153.4, 152.6, 151.1, 144.1, 140.8, 128.3, 128.2, 115.1, 97.2, 95.7, 68.3, 63.9, 59.6, 46.9, 43.9, 43.8, 31.9, 29.7, 28.4, 22.7, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{29}N_6O_6$ Exact Mass: 509.2149 found 509.2128. HPLC purity: 97.8%.

(*R*)-*N*-(5-cyano-4-((1-methoxypropan-2-yl)oxy)pyridin-2-yl)-7-formyl-6-((2-oxo-1,3-oxazepan-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6e)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.83 (s, 1 H), 10.24 (s, 1 H), 8.35 (s, 1 H), 8.01 (s, 1 H), 7.73 (s, 1 H), 4.95 (s, 2 H), 4.86-4.88 (m, 1 H), 4.14-4.16 (m, 2 H), 4.08-4.10 (m, 2 H), 3.56-3.69 (m, 2 H), 3.43 (s, 3 H), 3.30-3.33 (m, 2 H), 2.93-2.96 (m, 2 H), 2.04-2.06 (m, 2 H), 1.87-1.91 (m, 2 H), 1.73-1.74 (m, 2 H), 1.41-1.42 (d, *J*=6.00Hz, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ 193.3, 167.1, 160.9, 156.9, 153.2, 152.6, 150.9, 143.9, 140.4, 129.2, 128.1, 115.1, 97.2, 95.7, 75.3, 75.2, 70.5, 59.6, 49.6, 48.7, 43.8, 28.8, 28.4, 26.0, 20.9, 16.3; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{31}N_6O_6$ Exact Mass: 523.2305 found 523.2293. HPLC purity: 98.8%.

(*R*)-*N*-(5-cyano-4-((1-methoxypropan-2-yl)amino)pyridin-2-yl)-7-formyl-6-((2-oxo-1,3-oxazepan-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6f)

^{1}HNMR (400MHz, DMSO-d6, ppm) δ13.50 (s, 1 H), 10.06 (s, 1 H), 8.27 (s, 1 H), 7.71 (s, 1 H), 7.56 (s, 1 H), 6.61-6.62 (d, 1 H), 4.79 (s, 2 H), 4.08-4.10 (m, 2 H), 3.97-3.99 (m, 2 H), 3.83-3.88 (m, 1 H), 3.47-3.51 (m, 1 H), 3.38-3.41 (m, 1 H), 3.32 (s, 3 H), 3.26-3.28 (m, 2 H), 2.96 (t, 2 H), 1.93-1.95 (m, 2 H), 1.76-1.79 (m, 2 H), 1.60-1.62 (m, 2 H), 1.20-1.21 (d, 3 H). ^{13}CNMR (100MHz, DMSO-d6, ppm) δ192.6, 160.3, 155.8, 155.4, 154.3, 152.5, 150.7, 143.7, 139.4, 129.8, 129.1, 117.5, 93.2, 88.9, 75.1, 70.2, 58.8, 49.3, 49.1, 47.9, 43.9, 28.9, 28.0, 26.0, 20.8, 17.3; HRMS calcd for $[M+K]^+$ Chemical Formula: $C_{26}H_{31}N_7O_5K$ Exact Mass: 560.2024 found 560.1992. HPLC purity 99.9%.

(*R*)-*N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-methoxy-2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6g)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.57 (s, 1 H), 10.23 (s, 1 H), 8.18 (s, 1 H), 7.63 (s, 1 H), 7.58 (s, 1 H), 5.34 (s, 1 H), 4.88-4.99 (dd, *J*=15.20 Hz, 28.00 Hz, 2 H), 4.06-4.09 (m, 2 H), 3.98-4.01 (m, 1 H), 3.63-3.65 (m, 2 H), 3.59 (s, 3 H), 3.47-3.51 (m, 2 H), 3.41 (s, 3 H), 3.39-3.40 (m, 1 H), 3.29 (m, 1 H), 2.90-2.93 (m, 2 H), 2.39 (m, 1 H), 1.85-2.04 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.4, 173.0, 155.7, 155.2, 152.6, 152.4, 151.1, 144.1, 140.9, 128.2, 127.8, 116.3, 93.2, 89.9, 77.9, 69.9, 59.0, 58.1, 44.3, 43.8, 42.5, 40.7, 28.4, 26.2, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{30}N_7O_5$ Exact Mass: 508.2308 found 508.2286. HPLC purity: 95.5%.

(*S*)-*N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-methoxy-2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6h)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.57 (s, 1 H), 10.23 (s, 1 H), 8.18 (s, 1 H), 7.63 (s, 1 H), 7.58 (s, 1 H), 5.34 (s, 1 H), 4.87-4.99 (dd, *J*=15.20 Hz, 28.00 Hz, 2 H), 3.98-4.09 (m, 3 H), 3.63-3.65 (m, 2 H), 3.58 (s, 3 H), 3.50-3.51 (m, 2 H), 3.48 (s, 3 H), 3.37-3.47 (m, 1 H), 3.27-3.29 (m, 1 H), 2.90-2.93 (m, 2 H), 2.36 (m, 1 H), 2.01-2.05 (m, 2 H), 1.94-1.98 (m, 1 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.4, 173.0, 155.7, 154.6, 152.6, 152.4, 151.1, 144.1,

140.1, 128.2, 127.8, 116.3, 93.2, 89.9, 77.9, 69.9, 59.0, 58.1, 44.3, 43.8, 42.5, 40.7, 28.3, 26.2, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{30}N_7O_5$ Exact Mass: 508.2308 found 508.2285. HPLC purity: 97.5%.

_N_-(5-cyano-4-(((S)-1-methoxypropan-2-yl)amino)pyridin-2-yl)-7-formyl-6-(((S)-3-methoxy-2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2_H_)-carboxamide (6i)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.54 (s, 1 H), 10.23 (s, 1 H), 8.17 (s, 1 H), 7.63 (s, 1 H), 7.61 (s, 1 H), 5.18-5.20 (d, *J*=7.6Hz, 1 H), 4.88-4.99 (dd, *J*=15.60 Hz, 28.00 Hz, 2 H), 4.06-4.09 (m, 2 H), 3.98-4.00 (m, 2 H), 3.58 (s, 3 H), 3.38-3.49 (m, 6 H), 3.29 (m, 1 H), 2.90-2.93 (m, 2 H), 2.40 (m, 1 H), 1.92-2.06 (m, 3 H), 1.31-1.32 (d, *J*=6.40 Hz, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.4, 173.0, 155.6, 155.0, 152.6, 152.4, 151.1, 144.0, 140.9, 128.2, 127.7, 116.5, 93.4, 89.9, 77.9, 75.1, 59.3, 58.1, 48.0, 44.3, 43.8, 40.8, 28.4, 26.2, 20.9, 17.3; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{32}N_7O_5$ Exact Mass: 522.2465 found 522.2443. HPLC purity: 97.1%.

_N_-(5-cyano-4-(2-methoxyphenoxy)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2_H_)-carboxamide (6j)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.78 (s, 1 H), 10.23 (s, 1 H), 8.45 (s, 1 H), 7.65 (s, 1 H), 7.52 (s, 1 H), 7.28-7.32 (m, 1 H), 7.17-7.19 (m, 1 H), 7.02-7.08 (m, 2 H), 5.10 (s, 2 H), 4.24 (s, 2 H), 3.97-3.99 (m, 2 H), 3.87-3.90 (m, 2 H), 3.80 (s, 3 H), 3.39-3.42 (m, 2 H), 2.88-2.91 (m, 2 H), 1.97-2.04 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.3, 167.7, 167.5, 156.8, 153.0, 152.2, 151.3, 151.0, 144.1, 141.3, 140.8, 128.2, 128.1, 127.7, 122.6, 121.5, 114.7, 113.5, 98.5, 95.0, 68.3, 64.0, 56.0, 46.9, 43.9, 43.7, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{28}H_{27}N_6O_6$ Exact Mass: 543.1992 found 543.1974. HPLC purity: 99.0%.

_N_-(5-cyano-4-((4-methoxypyridin-3-yl)amino)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2_H_)-carboxamide (6k)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.63 (s, 1 H), 10.22 (s, 1 H), 8.65 (s, 1 H), 8.41-8.42 (d, *J*=5.20 Hz, 1 H), 8.32 (s, 1 H), 7.92 (s, 1 H), 7.65 (s, 1 H), 6.94-6.95 (d, *J*=5.60 Hz, 1 H), 6.61 (s, 1 H), 5.10 (s, 2 H), 4.25 (s, 2 H), 4.00-4.03 (m, 2 H), 3.96 (s, 3 H), 3.87-3.90 (m, 2 H), 3.39-3.42 (m, 2 H), 2.90-2.93 (m, 2 H), 1.99-2.02 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 167.5, 158.2, 156.2, 153.3, 153.0, 152.3, 151.1, 148.2, 144.2, 144.1, 140.6, 128.3, 127.9, 124.4, 116.1, 106.9, 95.6, 91.4, 68.3, 63.9, 55.9, 46.9, 43.9, 43.7, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{27}H_{27}N_8O_5$ Exact Mass: 543.2104 found 543.2082. HPLC purity: 100.0%.

(_S_)-_N_-(5-cyano-4-((tetrahydrofuran-3-yl)thio)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2_H_)-carboxamide (6l)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.89 (s, 1 H), 10.23 (s, 1 H), 8.37 (s, 1 H), 8.28 (s, 1 H), 7.69 (s, 1 H), 5.11 (s, 2 H), 4.35-4.40 (m, 1 H), 4.26 (s, 2 H), 4.00-4.11 (m, 3 H), 3.88-3.99 (m, 4 H), 3.79-3.82 (m, 1 H), 3.41-3.43 (m, 2 H), 2.94-2.97 (m, 2 H), 2.57-2.60 (m, 1 H), 2.03-2.09 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.2, 167.5, 154.9, 154.7, 152.6, 152.4, 151.0, 144.1, 140.1, 128.4, 128.3, 115.5, 108.6, 102.1,73.1, 68.3, 67.6, 63.9, 47.0, 44.0, 42.3, 32.9, 29.7, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{27}N_6O_5S$ Exact Mass: 523.1764 found 523.1743. HPLC purity: 97.6%.

(*R*)-*N*-(5-cyano-4-((tetrahydrofuran-3-yl)thio)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6m)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.91 (s, 1 H), 10.24 (s, 1 H), 8.37 (s, 1 H), 8.29 (s, 1 H), 7.69 (s, 1 H), 5.11 (s, 2 H), 4.36-4.40 (m, 1 H), 4.26 (s, 2 H), 3.94-4.11 (m, 3 H), 3.88-3.91 (m, 4 H), 3.79-3.82 (m, 1 H), 3.41-3.44 (m, 2 H), 2.94-2.97 (m, 2 H), 2.59-2.60 (m, 1 H), 2.03-2.08 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.2, 167.5, 155.0, 154.7, 152.6, 152.2, 151.0, 144.1, 140.1, 128.4, 128.3, 115.4, 108.6, 102.1,73.1, 68.3, 67.6, 63.9, 47.0, 44.0, 42.3, 32.9, 29.7, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{27}N_6O_5S$ Exact Mass: 523.1764 found 523.1749. HPLC purity: 97.4%.

***N*-(5-cyano-4-(((1R,2R)-2-methoxycyclopentyl)amino)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6n)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.54 (s, 1 H), 10.23 (s, 1 H), 8.17 (s, 1 H), 7.74 (s, 1 H), 7.66 (s, 1 H), 5.11 (s, 2 H), 4.87-4.89 (d, *J*=6.00 Hz, 1 H), 4.25 (s, 2 H), 4.08-4.11 (m, 2 H), 3.87-3.93 (m, 3 H), 3.68-3.69 (m, 1 H), 3.42 (s, 3 H), 3.39 (m, 2 H), 2.91-2.95 (m, 2 H), 2.32 (m, 1 H), 1.75-2.05 (m, 6 H), 1.52-1.54 (m, 1 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.6, 167.5, 155.8, 155.3, 152.5, 151.2, 144.2, 140.6, 128.2, 127.9, 116.6, 94.0, 89.7, 86.9, 77.2, 68.3, 63.9, 59.2, 57.2, 46.9, 43.9, 43.7, 31.0, 29.8, 28.5, 21.5, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{27}H_{32}N_7O_5$ Exact Mass: 534.2465 found 534.2446. HPLC purity: 97.4%.

***N*-(5-cyano-4-(((3S,4S)-4-methoxytetrahydro-2H-pyran-3-yl)oxy)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6o)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.82 (s, 1 H), 10.24 (s, 1 H), 8.36 (s, 1 H), 8.07 (s, 1 H), 7.69 (s, 1 H), 5.11 (s, 2 H), 4.53-4.54 (m, 1 H), 4.26 (s, 2 H), 4.07-4.12 (m, 3 H), 3.88-3.96 (m, 3 H), 3.61 (m, 1 H), 3.58-3.59 (m, 2H), 3.55 (s, 3 H), 3.40-3.54 (m, 2 H), 2.93-2.96 (m, 2 H), 2.19-2.22 (m, 1 H), 2.04-2.07 (m, 2 H), 1.71-1.74 (m, 1 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.3, 167.5, 166.9, 157.0, 153.1, 152.5, 151.0, 144.1, 140.8, 128.3, 128.2, 114.8,

97.3, 95.7, 78.2, 77.2, 68.3, 66.4, 65.3, 63.9, 57.7, 46.9, 43.9, 43.8, 29.6, 28.4, 20.8; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{27}H_{31}N_6O_7$ Exact Mass: 551.2254 found 551.2237. HPLC purity: 98.8%.

(*S*)-*N*-(5-cyano-4-((tetrahydrofuran-3-yl)amino)pyridin-2-yl)-7-formyl-6-((2-oxo-1,3-oxazepan-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6p)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.64 (s, 1 H), 10.24 (s, 1 H), 8.20 (s, 1 H), 7.72 (s, 1 H), 7.62 (s, 1 H), 5.07-5.08 (d, *J*=6.40 Hz, 1 H), 4.95 (s, 2 H), 4.33 (m, 1 H), 4.01-4.16 (m, 6 H), 3.87-3.90 (m, 1 H), 3.78-3.81 (m, 1 H), 3.32 (m, 2 H), 2.92-2.96 (m, 2 H), 2.45 (m, 1 H), 1.88-2.06 (m, 5 H), 1.72-1.74 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 160.1, 155.6, 154.8, 152.7, 152.5, 150.9, 144.0, 140.3, 129.1, 128.0, 116.2, 93.7, 90.0, 70.4, 67.0, 53.3, 49.6, 43.8, 33.2, 31.9, 29.3, 28.8, 26.0, 22.7, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2291. HPLC purity: 97.0%.

(*R*)-*N*-(5-cyano-4-((tetrahydrofuran-3-yl)amino)pyridin-2-yl)-7-formyl-6-((2-oxo-1,3-oxazepan-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6q)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.57 (s, 1 H), 10.17 (s, 1 H), 8.13 (s, 1 H), 7.65 (s, 1 H), 7.55 (s, 1 H), 5.01-5.02 (d, *J*=6.40 Hz, 1 H), 4.88 (s, 2 H), 4.25 (m, 1 H), 3.94-4.09 (m, 6 H), 3.71-3.82 (m, 2 H), 3.23-3.25 (m, 2 H), 2.85-2.89 (m, 2 H), 2.37 (m, 1 H), 1.81-1.99 (m, 5 H), 1.65-1.67 (m, 2 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 160.9, 155.6, 154.8, 152.7, 152.5, 150.9, 144.0, 140.3, 129.1, 128.0, 116.2, 93.7, 90.0, 70.4, 67.0, 53.3, 49.6, 43.8, 33.2, 31.9, 29.3, 28.8, 26.0, 22.7, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2287. HPLC purity: 96.9%.

***N*-(5-cyano-4-(((R)-tetrahydrofuran-3-yl)amino)pyridin-2-yl)-7-formyl-6-(((R)-3-methoxy-2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6r)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.55 (s, 1 H), 10.16 (s, 1 H), 8.12 (s, 1 H), 7.56 (s, 1 H), 7.54 (s, 1 H), 5.01-5.02 (d, *J*=6.40 Hz, 1 H), 4.80-4.92 (dd, *J*=15.60 Hz, 30.00 Hz, 2 H), 4.06 (m, 1 H), 3.90-4.02 (m, 5 H), 3.80-3.82 (m, 1 H), 3.71-3.74 (m, 1 H), 3.51 (s, 3 H), 3.32-3.33 (m, 1 H), 3.20-3.22 (m, 1 H), 2.84-2.87 (m, 2 H), 2.33 (m, 2 H), 1.86-1.98 (m, 4 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.3, 173.0, 155.6, 154.8, 152.6, 152.4, 151.1, 144.0, 140.9, 128.2, 127.9, 116.2, 93.7, 90.0, 77.9, 73.1, 67.0, 58.1, 53.3, 44.3, 43.8, 40.8, 33.2, 28.3, 26.2, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2281. HPLC purity: 96.7%.

(*S*)-*N*-(5-cyano-4-(3-methoxypyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6s)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.48 (s, 1 H), 10.24 (s, 1 H), 8.20 (s, 1 H), 7.67 (s, 1 H), 7.48 (s, 1 H), 5.11 (s, 2 H), 4.25 (s, 2 H), 4.06-4.09 (m, 3 H), 3.79-3.89 (m, 6 H), 3.39-3.42 (m, 2 H), 3.37 (s, 3 H), 2.91-2.95 (m, 2 H), 2.20-2.22 (m, 1 H), 2.05-2.07 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.6, 167.5, 155.2, 154.5, 154.2, 152.6, 151.1, 144.2, 140.7, 128.1, 127.9, 119.9, 96.2, 88.3, 79.1, 68.3, 63.9, 56.6, 54.4, 47.4, 46.9, 43.8, 43.7, 30.4, 28.4, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2290. HPLC purity: 97.3%.

(*S*)-*N*-(5-cyano-4-(2-(methoxymethyl)pyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6t)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ 13.46 (s, 1 H), 10.24 (s, 1 H), 8.21 (s, 1 H), 7.66 (s, 1 H), 7.60 (s, 1 H), 5.11(s, 2 H), 4.56 (m, 1 H), 4.25 (s, 2 H), 4.07-4.10 (m, 2 H), 3.87-3.90 (m, 3 H), 3.56-3.65 (m, 2 H), 3.45-3.49 (m, 1 H), 3.40-3.42 (m, 2 H), 3.38 (s, 3 H), 2.91-2.95 (m, 2 H), 1.97-2.14 (m, 6 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.6, 167.5, 155.8, 154.7, 153.6, 152.6, 151.2, 144.2, 140.7, 128.1, 127.9, 120.2, 96.8, 88.6, 72.3, 68.3, 63.9, 59.4,58.4, 50.3, 46.9, 43.8, 43.7, 28.5, 28.4, 23.2, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{27}H_{31}N_7O_5$ Exact Mass: 534.2465 found 534.2447. HPLC purity: 98.0%.

***N*-(5-cyano-4-(3-(dimethylamino)pyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6u)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.50 (s, 1 H), 10.23 (s, 1 H), 8.20 (s, 1 H), 7.66 (s, 1 H), 7.45 (s, 1 H), 5.11 (s, 2 H), 4.25 (s, 2 H), 4.07-4.09 (m, 2 H), 3.87-3.92 (m, 4 H), 3.72-3.74 (m, 1 H), 3.58 (m, 1 H), 3.39-3.42 (m, 2 H), 2.86-2.98 (m, 3 H), 2.35 (s, 6 H), 2.22 (m, 1 H), 2.03 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.6, 167.5, 155.6, 154.8, 153.9, 152.7, 151.2, 144.2, 140.7, 128.2, 127.9, 120.0, 95.8, 88.1, 68.3, 65.1, 63.9, 53.3, 48.6, 46.9, 44.2, 43.8, 43.7, 29.8, 29.7, 28.5, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{27}H_{33}N_8O_4$ Exact Mass: 533.2625 found 533.2603. HPLC purity: 98.5%.

(*S*)-*N*-(5-cyano-4-(3-methoxypyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-((2-oxooxazolidin-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6v)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.47 (s, 1 H), 10.23 (s, 1 H), 8.20 (s, 1 H), 7.75 (s, 1 H), 7.48 (s, 1 H), 4.88 (s, 2 H), 4.31-4.35 (t, *J*=8.00 Hz, 2 H), 4.06-4.10 (m, 3 H), 3.78-3.82 (m, 4 H), 3.57-3.61 (m, 2 H), 3.37 (s, 3 H), 2.93-2.96 (m, 2 H), 2.20 (m, 1 H), 2.01-2.06 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 158.9, 155.2, 154.5, 154.2, 152.6, 151.4,144.1, 141.5, 128.2, 127.3, 119.9, 96.2, 88.3, 79.1, 62.2, 56.6, 54.4, 47.4, 45.0, 43.8, 42.2, 30.4,

28.4, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{28}N_7O_5$ Exact Mass: 506.2152 found 506.2131. HPLC purity: 95.9%.

(*R*)-*N*-(5-cyano-4-(3-methoxypyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-((2-oxooxazolidin-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6w)

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.47 (s, 1 H), 10.24 (s, 1 H), 8.20 (s, 1 H), 7.75 (s, 1 H), 7.49 (s, 1 H), 4.88 (s, 2 H), 4.31-4.35 (t, *J*=8.00 Hz, 2 H), 4.07-4.09 (m, 3 H), 3.79-3.82 (m, 4 H), 3.57-3.61 (m, 2 H), 3.37 (s, 3 H), 2.93-2.96 (m, 2 H), 2.22 (m, 1 H), 2.02-2.07 (m, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 158.9, 155.2, 154.5, 154.2, 152.6, 151.4,144.1, 141.5, 128.2, 127.3, 119.9, 96.2, 88.3, 79.1, 62.2, 56.6, 54.4, 47.4, 45.0, 43.8, 42.2, 30.4, 28.4, 20.9; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{25}H_{28}N_7O_5$ Exact Mass: 506.2152 found 506.2132. HPLC purity: 96.5%.

***N*-(5-cyano-4-((*R*)-3-methoxypyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-(((*S*)-4-methyl-2-oxooxazolidin-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6x)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.48 (s, 1 H), 10.24 (s, 1 H), 8.20 (s, 1 H), 7.76 (s, 1 H), 7.48 (s, 1 H), 5.03-5.07 (d, *J*=16.40 Hz, 1 H), 4.76-4.81 (d, *J*=16.40 Hz, 1 H), 4.39-4.44 (t, *J*=8.00 Hz, 2 H), 4.06-4.09 (m, 3 H), 3.78-3.93 (m, 6 H), 3.37 (s, 3 H), 2.92-2.95 (m, 2 H), 2.20-2.24 (m, 1 H), 2.02-2.05 (m, 3 H), 1.28-1.29(d, *J*=4.00 Hz, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 158.8, 155.2, 154.5, 154.2, 152.6, 151.2, 143.6, 140.8, 128.4, 128.1, 119.9, 96.1, 88.3, 79.1, 69.3, 56.6, 54.4, 51.8, 47.4, 43.8, 39.7, 30.4, 28.4, 20.9, 18.5; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2292. HPLC purity: 100.0%.

***N*-(5-cyano-4-((*S*)-3-methoxypyrrolidin-1-yl)pyridin-2-yl)-7-formyl-6-(((*S*)-4-methyl-2-oxooxazolidin-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide (6y)**

^{1}HNMR (400MHz, $CDCl_3$, ppm) δ13.48 (s, 1 H), 10.24 (s, 1 H), 8.20 (s, 1 H), 7.76 (s, 1 H), 7.48 (s, 1 H), 5.03-5.07 (d, *J*=16.00 Hz, 1 H), 4.76-4.81 (d, *J*=16.00 Hz, 1 H), 4.40-4.44 (t, *J*=8.00 Hz, 2 H), 4.06-4.09 (m, 3 H), 3.79-3.93 (m, 6 H), 3.37 (s, 3 H), 2.92-2.95 (m, 2 H), 2.21-2.24 (m, 1 H), 2.02-2.05 (m, 3 H), 1.29-1.30 (d, *J*=4.00 Hz, 3 H). ^{13}CNMR (100MHz, $CDCl_3$, ppm) δ193.5, 158.8, 155.2, 154.5, 154.2, 152.6, 151.2, 143.6, 140.8, 128.4, 128.1, 119.9, 96.1, 88.3, 79.1, 69.3, 56.6, 54.4, 51.8, 47.4, 43.8, 39.7, 30.4, 28.4, 20.9, 18.5; HRMS calcd for $[M+1]^+$ Chemical Formula: $C_{26}H_{30}N_7O_5$ Exact Mass: 520.2308 found 520.2292. HPLC purity: 99.2%.

In-vitro biochemical kinase assays All assays were performed in 384 well microtiter plates. Each assay contained 8-point serial dilutions for 40 test compounds, as well as four 8-point serial dilutions of staurosporine as reference compound, plus 16 high and 16 low controls.

Liquid handling and incubation steps were done on an innovadyne Nanodrop express equipped with a robotic arm (Thermo CatX, Caliper Twister II) and an incubator (Liconic STX40, Thermo Cytomat 2C450). The assay plates were prepared by addition of 50 nl per well of compound solution in 90% DMSO. The kinase reactions were started by stepwise addition of 4.5 ul per well of peptide/ATP-solution and 4.5 uL per well of enzyme solution. Kinase reactions were incubated at 30 ºC for 60 minutes and subsequently terminated by addition of 16 ul per well of stop solution. Plates with terminated kinase reaction were transferred to the Caliper LC3000 workstations for reading. Phosphorylated and unphosphorylated peptides were separated using the Caliper microfluidic mobility shift technology. Samples from terminated kinase reactions were applied to the chip. Analytes are transported through the chip by constant buffer flow and migration of the substrate peptide is monitored by the fluorescence signal of its label. Phosphorylated peptide and unphosphorylated peptides are separated in an electric field by their charge/mass ratio. Kinase activities were calculated from the amounts of formed phosphor-peptide. IC_{50} values were determined from percent inhibition values at different compound concentrations by non-linear regression analysis.

In-vitro cellular assays Hep 3B, HuH-7, and SK-HEP-1 cell lines were used for the cell proliferation assays. In this experiment, the inhibitory effect of the compound on the proliferation of experimental cells was tested by CellTiter-Glo method, and the IC_{50} of the compound inhibiting cell proliferation activity was obtained: Inoculate 50-100 uL of experimental cell suspension in a 96-well cell culture plate at a density of $1\text{-}5\times10^4$ cells/mL, and place the plate in an incubator for 16-24 h (37 °C, 5% CO_2). Then add a gradient dilution of the solution of the compound to be tested to the culture plate, and incubate the plate for 72 h (37 °C, 5% CO_2) in the incubator. Add 50-100uL CellTiter-Glo reagent to each well, shake at room temperature or let stand for 5-30 min. Determination of the chemiluminescence signal value of each plate by a microplate reader, then calculate the inhibition rate by the value of the chemiluminescence signal and the IC_{50} of the compound is obtained by curve fitting according to the inhibition rates of different concentrations.

Pharmacokinetic Assay Rates, half male and half female for 6~7 weeks, are purchased from Shanghai SLAC Laboratory Animal CO. LTD; feed the mice under grade SPF. Rats were intragastrically administered, fasted for not less than 12 hours before administration, free to drink water, and fed for 4 hours after administration. Blood samples were taken from the posterior ocular veins before administration and 5 min, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 10 and 24 h after administration. Determination of **6f** concentration in rat plasma by LC-MS and the pharmacokinetic parameters of rats were calculated using the non-compartmental model of Phoenix WinNonlin 6.4 software (Pharsight, USA).

In Vivo Efficacy Study BALB/c nude mice were subcutaneously inoculated with 0.1 ml of experimental cell suspension (7×10^7/ml) to establish a subcutaneous xenograft model. When the tumors were grown to an average volume of 200-250 mm^3, they were randomly divided into 5 groups (each group 5 animals) and administered according to tumor size and mouse body weight. Tumor volume was measured twice a week, and the weight of tumor-bearing mice was weighed twice a day, and data were recorded. After 14 days of administration, the tumor tissue was taken and weighed, and photographed at the same time. The T/C values were calculated according to the National Cancer Institute (NCI) standardized transplant tumor evaluation method.

Long-term Toxicity Studies in Mice BALB/c small nude mice, half male and half female for 6~7 weeks, are purchased from Shanghai SLAC Laboratory Animal CO. LTD; feed the mice under grade SPF. Successively dose the mice by intragastric administration with dosage of 50 mg/kg, 150 mg/kg and 450 mg/kg once a day for 4 weeks; feed the mice for 4 weeks to recovery after dosage; weigh the mice of the same group at the start of the test, after administration and after the recovery time. Dissect the mice after bloodletting to die, weigh the corresponding visceral organs, observe and check the tissue.

Acute Toxicity Studies in Mice BALB/c small nude mice, half male and half female for 6~7 weeks, are purchased from Shanghai SLAC Laboratory Animal CO. LTD; feed the mice under grade SPF. Dose the mice by intragastric administration with dosage of 200 mg/kg, 400 mg/kg or 2000 mg/kg by single-dose; observe the mice for 14 days after administration; weigh the mice of the same group at the start of the test and after the observing time. Dissect the mice after bloodletting to die, weigh the corresponding visceral organs, observe and check the tissue.

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REFERENCES

(1) Wei, W.; You, Z.; Sun, S.; Wang, Y.; Zhang, X.; Pang, D.; Jiang, Y. *Mol. Carcinog.,* **2018**. *57*. 988-996.

(2) Chen, H.; Shen, D.; Zhang, Z.; Liu, J.; Shen, Y.; Ni, X. *World J Gastroenterol,* **2015**. *21*. 1838-1844.

(3) Chen, T.-H.; Yang, S.-F.; Liu, Y.-F.; Lin, W.-L.; Han, C.-P.; Wang, P.-H. *Reprod. Sci.,* **2017**. *36*. 86-93.

(4) Ahmed, M. A.; Selzer, E.; Dörr, W.; Jomrich, G.; Harpain, F.; Silberhumer, G. R.; Müllauer, L.; Holzmann, K.; Grasl-Kraupp, B.; Grusch, M.;Berger, W.; Marian, B. *Oncotarget,* **2016**. *7*. 69976-69990.

(5) Chen, L.; Lei, Z.; Ma, X.; Huang, Q.; Zhang, X.; Zhang, Y.; Hao, P.; Yang, M.; Zhao, X.; Chen, J.; Liu, G.; Zhenga, T. *Sci. Rep.,* **2016**. *6*. 2045-2322.

(6) Ishiwata, T.; Yoshimura, H.; Matsuda, Y.; *AACR 107th Annual Meeting on Bioinformatics and Systems Biology*., Meeting address: New Orleans. APR 16-20, **2016**.

(7) Sheu, M.-J.; Hsieh, M.-J.; Chiang, W.-L.; Yang, S.-F.; Lee, H.-L.; Lee, L.-M.; Yeh, C.-B. *Plos One,* **2015** *10*.

(8) Huang, H.-P.; Feng, H.; Qiao, H.-B.; Ren, Z.-X.; Zhu, G.-D. *Onco. Targets Ther.*, **2017**. *8*. 1157-1164.

(9) Lemieux, S.; Hadden, M. K. *Anti-Cancer Agents Med. Chem*., **2013**, *13*, 748-761.

(10) Yan, W.; Wang, X.; Dai, Y.; Zhao, B.; Yang, X.; Fan, J.; Gao, Y.; Meng, F.; Wang, Y.; Luo, C.; Ai, J; Geng, M.-Y.; Duan, W. *J. Med. Chem.*, **2016**, *59*, 6690–6708.

(11) Dienstmann, R.; Rodon, J.; Prat, A.; Perez-Garcia, J.; Adamo, B.; Felip, E.; Cortes, J.; Iafrate, A. J.; Nuciforo, P.; Tabernero, J. *Ann. Oncol*., **2014**, *25*, 552–563.

(12) Connolly, J. C.; Hamby, J. M.; Schroeder, M. C.; Barvian, M.; Lu, G. H.; Panek, R. L.; Amar, A.; Shen, C.; Kraker, A. J.; Fry, D. W.; Klohs, W. D. Doherty, A. M. *Bioorg. Med. Chem. Lett*., **1997**, *7*, 2415–2420.

(13) Pike, K. G.; Buttar, D.; Tucker, J.; Jones, C.; Presented at the 23rd Int. Symp. Med. Chem., Lisbon, Sep. 7-11, 2014, European Federation for edicinal Chemistry, LE098.

(14) Zhou, W.; Hur, W.; McDermott, U.; Dutt, A.; Xian, W.; Ficarro, S. B.; Zhang, J.; Sharma, S. V.; Brugge, J.; Meyerson, M.; Settleman J.; Gray, N. S. *Chem. Biol.*, 2010, 17, 285–295.

(15) Brameld, K. A. Presented at the 253rd National Meeting, San Francisco, April 5th, **2017**, American Chemical Society, MEDI 352.

(16) Bradshaw, J. M.; McFarland, J. M.; Paavilainen, V. O.; Bisconte, A.; Tam, D.; Phan, V. T.; Romanov, S.; Finkle, D.; Shu, J.; Patel, V.; Ton, T.; Li, X.; Loughhead, D. G.; Nunn, P. A.; Karr, D. E.; Gerristen, M. E.; Funk, J.

O.; Owens, T. D.; Verner, E.; Brameld, K. A.; Hill, R. J.; Goldstein, D. M.; Taunton, J. *Nat. Chem. Biol*., **2015**, *11*, 525–531.

(17) Hagel, M.; Miduturu, C.; Sheets, M.; Rubin, N.; Weng, W.; Stransky, N.; Bifulco, N.; Kim, J. L.; Hodous, B.; Brooijmans, N.; Shutes, A.; Winter, C.; Lengauer, C.; Kohl, N. E.; Guzi, T. *Cancer Disc*. **2015**, *5*, 424-437.

(18) Hao, M.-H.; Wang, J.; Prajapati, S.; Satoh, T.; Selvaraj, A. PCT Int. Appl. **2016**, WO 2016164703-A1.

(19) Selvaraj, A.; Corcoran, E.; Coffey, H.; Prajapati, S.; Hao, M.-H.; Larsen, N.; Tsai, J.; Satoh, T.; Ichikawa, K.; Joshi, J. J.; Hurley, R.; Wu, J.; Huang, C.-L.; Bailey, S.; Karr, C.; Kumar, P.; Rimkunas, V.; Mackenzie, C.; Rioux, N.; Kim, A.; Akare, S.; Lai, G.; Yu, L.; Fekkes, P.; Wang, J.; Warmuth, M.; Smith, P.; Reynolds, D. Presented at the AACR Annual Meeting, Washington, April 1-5, **2017**, American Association for Cancer Research, abstract 3126.

(20) Mo, C.; Zhang, Z.; Guise, C. P.; Li, X.; Luo, J.; Tu, Z.; Xu, Y.; Patterson, A. V.; Smaill, J. B.; Ren, X.; Lu, X.; Ding, K. *ACS Med. Chem. Lett*., **2017**, *8*, 543–548.

(21) Wang, Y.; Chen, Z.; Dai, M.; Sun, P.; Wang, C.; Gao, Y.; Zhao, H.; Zeng, W.; Shen, L.; Mao, W.; Wang, T.; Hu, G.; Li, J.; Chen, S.; Long, C.; Chen, X.; Liu, J.; Zhang, Y. *Bioorg. Med. Chem. Lett.*, **2017**, *27*, 2420-2423.

(22) Robin, A. F.; Thomas, K.; Catherine, L.; Nicole, B.; Christoph, G.; Jutta, B.; Inga, G.; Jörg, T.; Chao, Z.; Johannes, V.; Christine, G.; Peggy, B.-L.; Francis, B.; Diana, G.-P.; Pascal, F. *Medchem. Comm*. **2017**, *8*, 1604-1613 .

(23) Fairhurst, R. A.; Knoepfel, T.; Furet, P.; Buschmann, N.; Leblanc, C.; Mah, R.; Kiffe, M.; raus-Porta, D.; Weiss, A.; Kinyamu-Akunda, J.; Wartmann, M.; Trappe, J.; Gabriel, T.; Hofmann F.; Sellers, W. R. Presented at the 253rd National Meeting, San Francisco, April 5th, 2017, American Chemical Society, MEDI 353.

(24) Graus-Porta, D.; Weiss, A.; Stamm, C.; Fairhurst, R. A.; Wartmann, M.; Knoepfel, T.; Leblanc, C.; Buschmann, N.; Blank, J.; Furet, P.; Galuba, I.; Trappe, J.; Mignault, A.; Ramkumar, T.; Kauffmann, A.; Engelman, J. A.; Hofmann, F.; Sellers, W. R. Presented at the AACR Annual Meeting, Washington, April 1–5, 2017, American Association for Cancer Research, abstract 2098.

(25) Weiss, A.; Graus-Porta, D.; Reimann, F.; Buhles, A.; Stamm, C.; Fairhurst, R. A.; Kinyamu-Akunda, J.; Sterker, D.; Kiffe, M.; Murakami, M.; Wartmann, M.; Wang, Y.; Engelman, J. A.; Hofmann, F.; Sellers, W. R. Presented at the AACR Annual Meeting, Washington, April 1-5, 2017, American Association for Cancer Research, abstract 2103.

(26) Thomas, K.; Pascal, F.; Robert, M.; Nicole, B.; Catherine, L.; Sebastien, R.; Diana, G.-P.; Markus, W.; Inga, G.; Robin, A. F. *ACS Med. Chem. Lett.*, **2018**, *9*, 215-220.

(27) Nicole, B.; Fairhurst, R. A.; Pascal, F. et al., PCT Int. Appl. **2015**, WO 2015/151500-A1.

(28) Gauglhofer, C.; Sagmeister, S.; Schrottmaier, W.; Fischer, C.; Rodgarkia-Dara, C.; Mohr, T.; Stättner, S.; Bichler, C.; Kandioler, D.; Wrba, F.; Schulte-Hermann, R.; Holzmann, K.; Grusch, M.; Marian, B.; Berger, W.; Grasl-Kraupp, B. *Hepatology*, **2011**, *53*, 854-864.

(29) Saraswathi, V.; Perriotte-Olson, C.; Ganesan, M.; Desouza, C. V.; Alnouti, Y.; Duryee, M. J.; Thiele, G. M.; Nordgren, T. M.; Clemens, D. L. *J Nutr. Biochem.*, **2017**, *42*, 149-159.

(30) Gao, P.; Xiu, W. H.; Wang, S. B.; Liu, L.; Bao, R. D. PCT Int. Appl. **2017**, WO 2017/198149-A1.

Novel 7-Formyl-naphthyridyl-ureas Derivatives as Potential Selective FGFR4 Inhibitors: Design, Synthesis, and Biological Activity Studies

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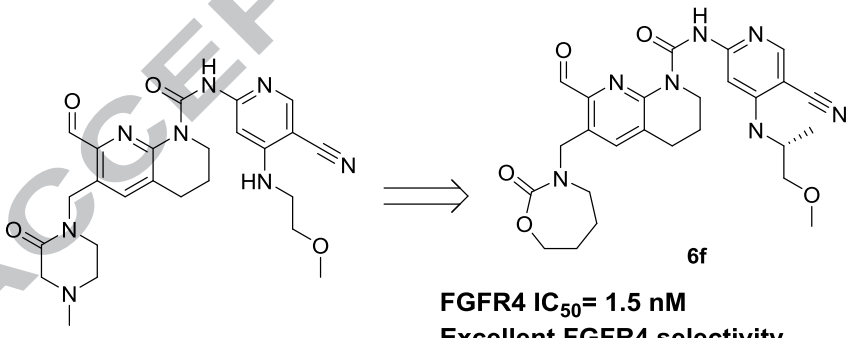

FGFR4 IC_{50}= 1.5 nM
Excellent FGFR4 selectivity
Potent antiproliferative activity
Better antitumor activity and pharmacokinetic properties in vivo