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Synthesis of Antitumor 3,4,6,7-Tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine Derivatives via Reductive Dearomatization-Initiated Intramolecular Cyclization

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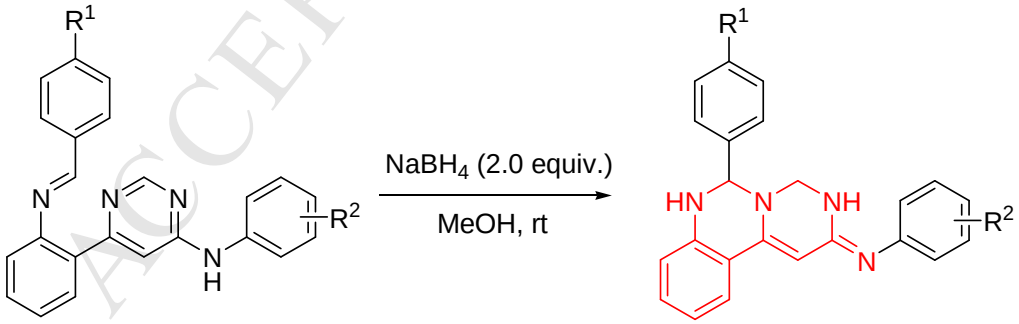

12 examples, up to 80% yield

8f: R^1 = *tert*-butyl, R^2 = 3-OCH_2CH_2O-4

human breast cancer cell line ZR-75-30, IC_{50}= 0.71 ± 0.3 μM

multi-targeted kinases (FLT3, INSR and VEGFR-2) inhibitor

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ABSTRACT: In light of the importance of *N*-fused heterocycles in pharmaceuticals, there is continuing interest in research on *N*-fused heterocycles and their preparation. A new and efficient reductive dearomatization-initiated intramolecular cyclization reaction with a broad scope has been developed, affording 3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine derivatives.

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Notably, this type of compound showed good inhibitory activity against specific kinases and human cancer cell lines. These results might mean a new molecular scaffold for the development of new antitumor agents.

Keywords: 3,4,6,7-Tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine; N-fused heterocycles; cyclization reaction; antitumor agents; kinase inhibitors

1. Introduction

Nitrogen heterocycles are particularly well represented among natural products and biologically active structures.[1] They are also among the most significant structural components of pharmaceuticals,[2-5] present in 59% of all small-molecule drugs[5] and 100% of novel small-molecule kinase inhibitors approved by the U.S. FDA.[6,7] Among them, *N*-fused heterocycles are a special and important type and have been shown to possess a wide range of pharmacological activities. Many types of important drugs contain these scaffolds, such as antibiotics of the penicillin class and cephalosporin class, anxiolytics of the benzodiazepine class, sedative-hypnotics of pyrazolopyrimidine class, antitumor agents among the vinca alkaloid analogues and camptothecin analogues,[3,5] and novel small-molecule kinase inhibitors of the imidazopyridazin class (representative drugs shown in Figure 1).[6,7] In addition, the cephem of cephalosporins and the penam of penicillins are the fourth and eighth most commonly used nitrogen heterocycles in pharmaceuticals, respectively.[5,8,9] In light of the importance of these compound classes, there is continuing interest in research on new *N*-fused heterocycles and their preparation.[10-17] Despite the numerous achievements that have been reported in this field,[10-17] the method for the synthesis of 3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine derivatives remain undeveloped.

Meanwhile, studies on their biological activities are still in the blank fields. Thus, the construction of such a molecular skeleton is not only a challenge in synthetic chemistry, but also interesting in medicinal chemistry. Herein, we wish to report our recent observation on the synthesis of 3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine derivatives as well as their antitumor activities.

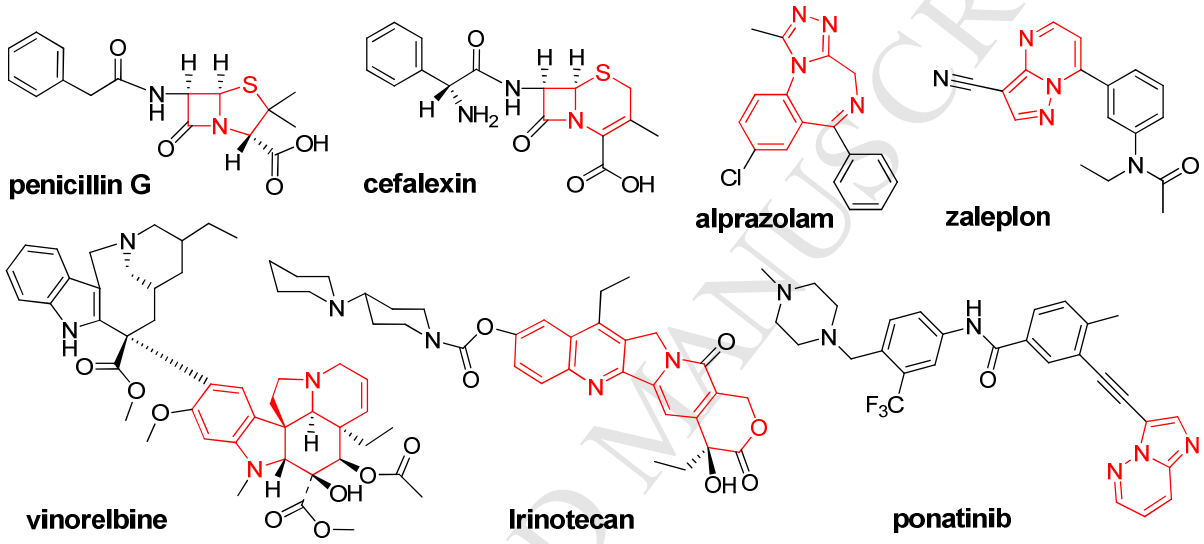


Figure 1. Representative drugs containing *N*-fused heterocycles.

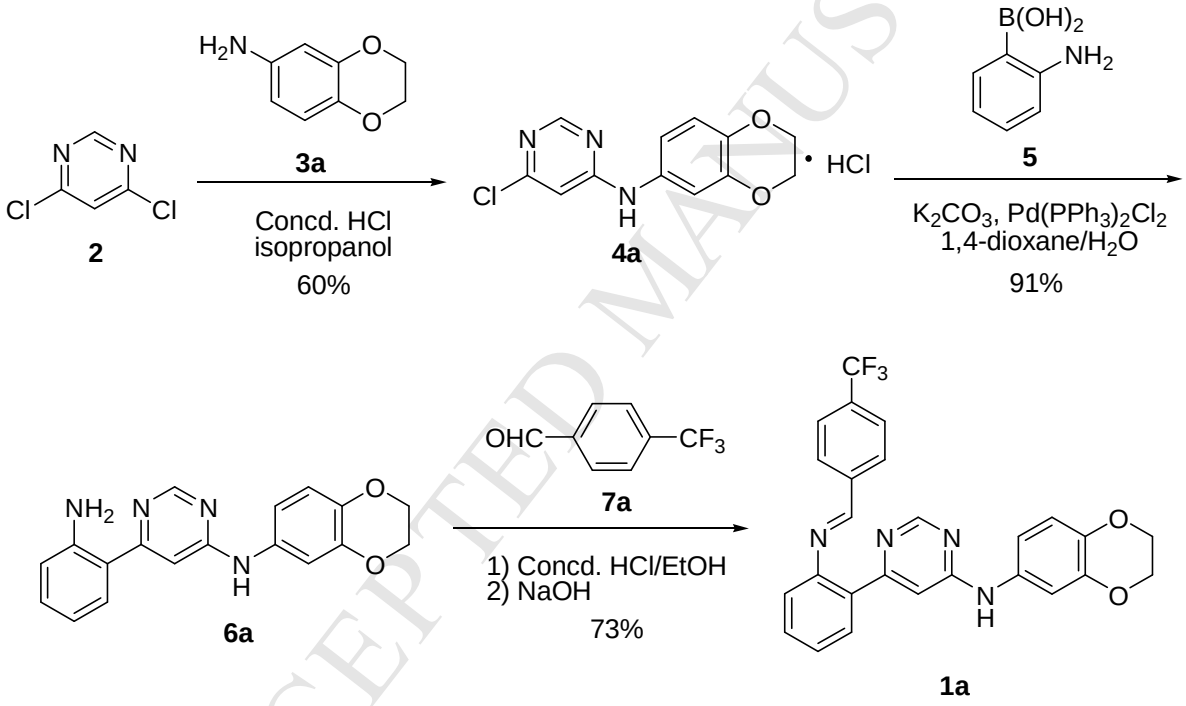
2. Results and discussion

2.1. Chemistry

At the beginning of our studies, the model reactant *N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(2-(4-(trifluoromethyl)benzylideneamino)phenyl)pyrimidin-4-amine (**1a**) was obtained by a simple three-step synthesis route (Scheme 1). In the presence of concentrated HCl, the 4,6-dichloropyrimidine (**2**) reacted with 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**3a**) in isopropanol

affording **4a** in a 60% yield.[18] The following Suzuki-Miyaura cross-coupling reaction of **4a** and 2-aminophenyl boronic acid (**5**) under the catalysis of $Pd(PPh_3)_2Cl_2$ in 1,4-dioxane/H_2O yielded **6a** in a 91% yield. Finally, condensation of **6a** with 4-trifluoromethyl benzaldehyde (**7a**) produced the desired product **1a** in a 73% yield.

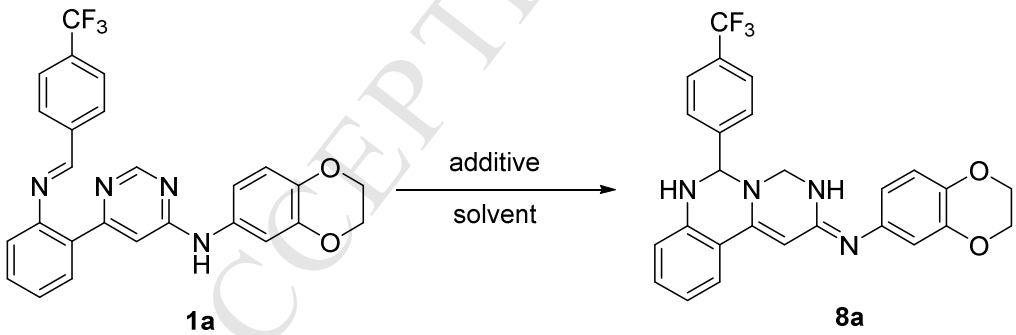
Scheme 1. The synthesis of **1a**



The initial attempt was carried out employing **1a** treated by 2 euqiv. of $NaBH_4$ in EtOH at rt. To our delight, the desired product *N*-(6-(4-(trifluoromethyl)phenyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-ylidene)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (**8a**) was obtained in a 51% NMR yield (entry 1, Table 1). Then we further optimized the reaction

conditions (Table 1). Some commonly used solvents were tested. The results indicated that this cyclization reaction proceeded smoothly in all the tested solvents. The highest yield was observed in MeOH (entry 5, Table 1). We tried to improve the amount of $NaBH_4$, however, the yield decreased dramatically (entry 6, Table 1). Then we tried to reduce the amount of $NaBH_4$, dissappointingly, the yield was even lower (entry 7, Table 1). Next, the reaction was carried out under reflux, which resulted in a 58% isolated yield (entry 7, Table 1). Given that the reductive aminations are often conducted by *in situ* generation of the iminium ion in the presence of a mild acid, an acidic condition with reducing reagents of good acid-tolerance might improve the *N*-fused heterocycle formation. Based on this consideration, some acid-mediated reductive aminations[19-21] were carried out. However, no better results were observed (entries 9-11, Table 1). Thus, Condition A (**1**, $NaBH_4$ (2 equiv.), MeOH, and rt) was applied for further studies.

Table 1. Optimization of the Reaction Conditions[a]



1a **8a**

Entry	Additive (equiv.)	Solvent	Temperature	Time (h)	NMR Yield[b] (%)
1	$NaBH_4$ (2)	EtOH	rt	46	51
2	$NaBH_4$ (2)	DCE	rt	46	59
3	$NaBH_4$ (2)	DMSO	rt	46	41

4	$NaBH_4$ (2)	acetone	rt	46	27
5	$NaBH_4$ (2)	MeOH	rt	46	70
6	$NaBH_4$ (3)	MeOH	rt	46	37
7	$NaBH_4$ (1.2)	MeOH	rt	46	21
8	$NaBH_4$ (2)	MeOH	reflux	46	58
9[c]	$HCOONH_4$ (5)	MeOH	70 °C	7	18
10	$HCOONH_4$ (12)	HCOOH	160 °C	4	21
11	$HCOONH_4$ (1)	Toluene	reflux	12	NR

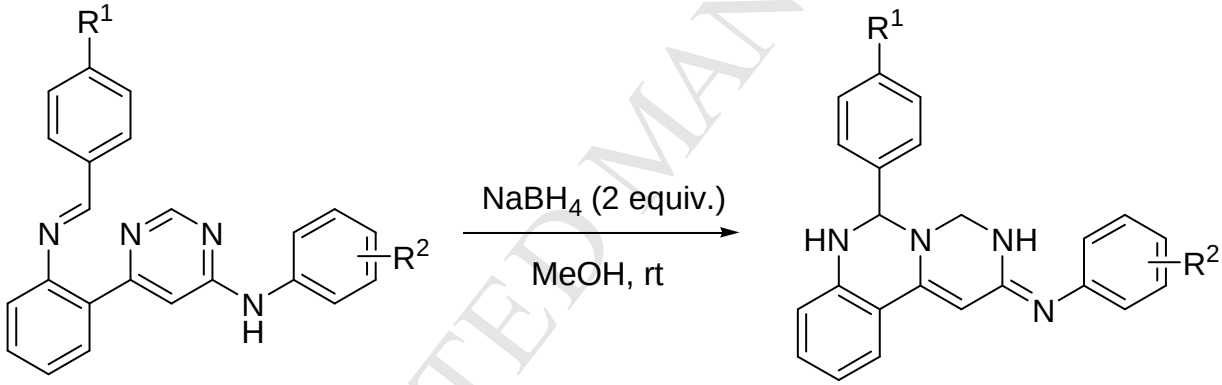
[a] Reaction conditions: **1** (0.1 mmol), additive, and solvent. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture using trifluoromethylbenzene as an internal standard. [c] 0.5 mol% of $[RhCp^*Cl_2]_2$ was applied.

With the optimal conditions in hand, the substrate scope of this cyclization reaction was examined by applying a series of structurally diverse substrates (Table 2). Firstly, strong electron-withdrawing groups (entries 1 and 2, Table 2), weak electron-withdrawing group (entry 3, Table 2), hydrogen (entry 4, Table 2), weak electron-donating groups (entries 5 and 6, Table 2), and strong electron-donating group (entry 7, Table 2) were introduced into the 4-position of the aryl ring in the imide moiety of **1**. The corresponding products were formed in moderate to good yields. No clear electron effect was observed. Secondly, electron effect of the aryl ring in the amine moiety of **1** was explored similarly (entries 8-12, Table 2). No clear electron effect was observed, either. These results indicated that this protocol might serve as the general method for the synthesis of 3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine derivatives.

Based on the above results, two possible reaction pathways for this cyclization were proposed as shown in Scheme 2. In pathway A, the initial 1,3-H transfer of **1** resulted in its tautomer **9** which was easier to be partially reduced by $NaBH_4$. Then, the hydrogen anion from $NaBH_4$ attacked at

the 2-position of the pyrimidine ring to form the nitrogen anion species **10**. The subsequent intramolecular nucleophilic attack resulted in the cyclized nitrogen anion intermediate **11**, which gave the final product **8** after alcoholysis. In pathway B, direct reductive dearomatization of the pyrimidine ring by $NaBH_4$ started the whole process. The following intramolecular nucleophilic addition and alcoholysis afforded intermediate **14**. The final product **8** was produced by isomerization via 1,3-H transfer, which led to a more stabled large conjugated π-system.

Table 2. Substrate Scope of the Cyclization Reaction[a]



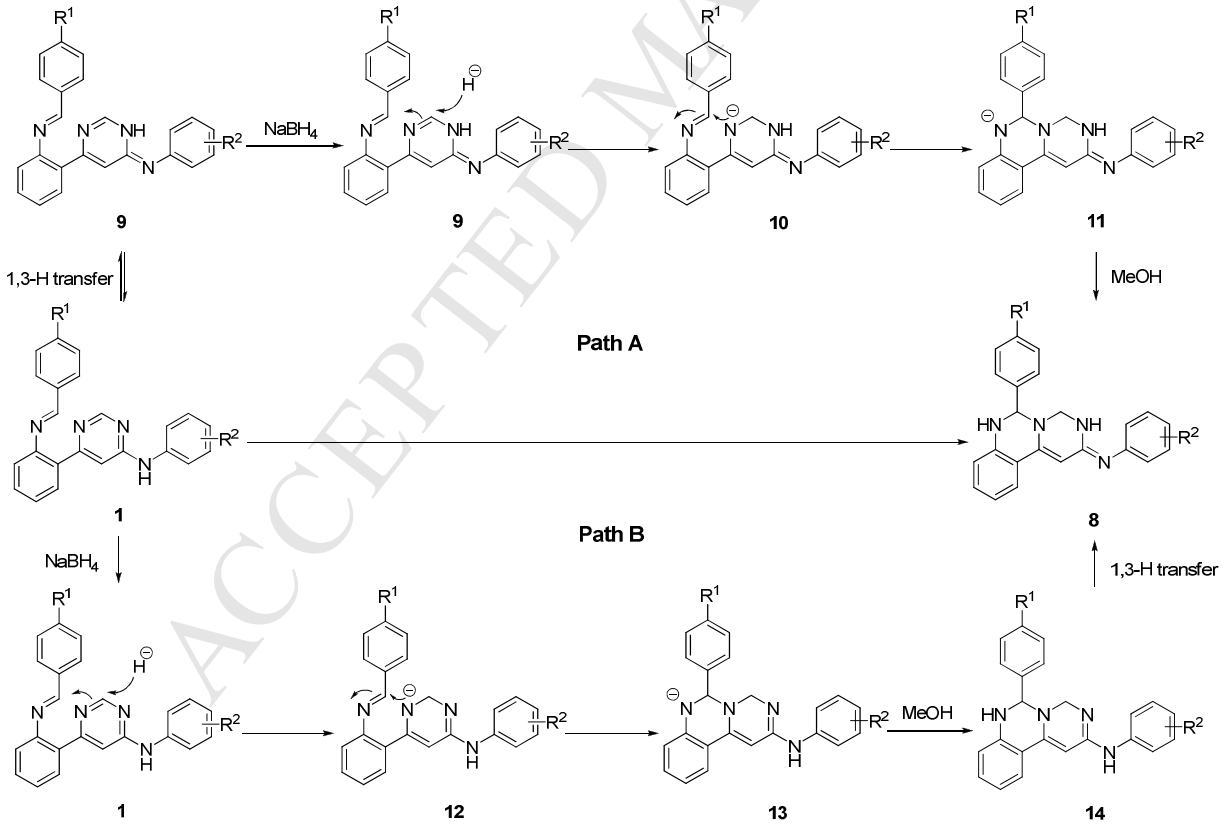
1 **8**

Entry	**1**	R^1	R^2	**8**	Time (h)	Isolated Yield (%)
1	**1a**	CF_3	3-OCH_2CH_2O-4	**8a**	53	70
2	**1b**	COOMe	3-OCH_2CH_2O-4	**8b**	55	54
3	**1c**	Br	3-OCH_2CH_2O-4	**8c**	73	72
4	**1d**	H	3-OCH_2CH_2O-4	**8d**	25	79
5	**1e**	Me	3-OCH_2CH_2O-4	**8e**	74	52
6	**1f**	*tert*-butyl	3-OCH_2CH_2O-4	**8f**	77	52

7	**1g**	OMe	3-OCH_2CH_2O-4	**8g**	76	57
8	**1h**	H	4-CF_3	**8h**	28	58
9	**1i**	H	4-Br	**8i**	31	71
10	**1j**	H	4-H	**8j**	53	71
11	**1k**	H	4-Me	**8k**	60	66
12	**1l**	H	4-OMe	**8l**	60	80

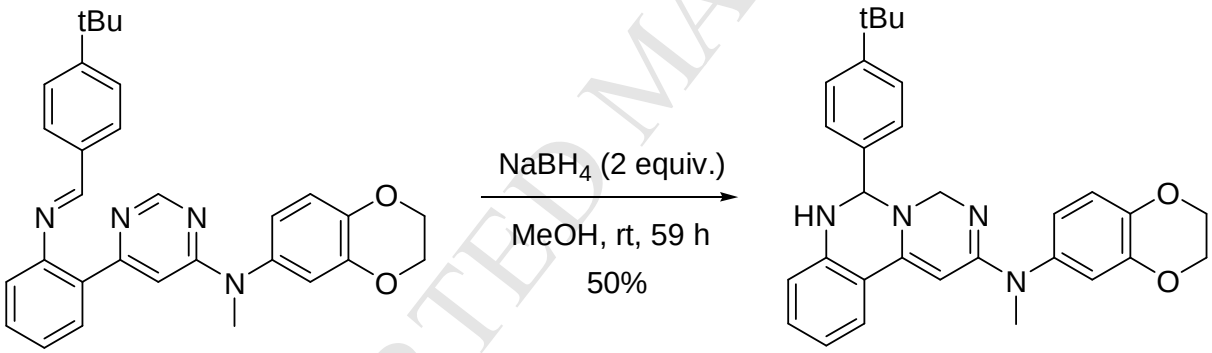
[a] Reaction conditions: **1** (0.2 mmol), $NaBH_4$ (0.4 mmol), MeOH (6 mL), rt.

Scheme 2. Proposed Mechanism for the Cyclization Reaction



To gain more information about the mechanism, an analogue of compound **1** with a methyl group substituted on the amine nitrogen atom (compound **15**, Scheme 3) was prepared and applied in this reaction. If this reaction was initiated via 1,3-H transfer as proposed in pathway A, no reaction would take place, since this key step should be totally inhibited. On the other hand, if this reaction underwent via pathway B, the cyclization would proceed. However, the final isomerization via 1,3-H transfer should be totally inhibited. The result indicated that a cyclized product **16** was afforded, which clearly supported pathway B as the mechanism.

Scheme 3. The reaction of **15** under Condition A



15 **16**

2.2. Biology

In light of the importance of *N*-fused heterocycles in pharmaceuticals,[5] the antitumor activities of two representative target compounds, **8a** and **8f**, were screened. Their inhibitory activities against three common human cancer cell-lines, ZR-75-30 (breast cancer), HCT116 (colon cancer), and A549 (lung cancer), were evaluated by the MTT assay (Table 3). According to the results, these compounds showed obvious inhibitory activity against all of the cancer cell lines.

In particular, compound **8f** showed good activity against the ZR-75-30 cancer cell line, with an IC_{50} value lower than 1 μM. ZR-75-30 is a cell line derived from human estrogen receptor-negative (ER^-) breast cancer, which is a difficult-to-treat type in clinical practice.[22,23] Therefore, compound **8f** could serve as a good lead compound for the further development of new drugs to treat this type of cancer. Furthermore, the possible mechanisms of this compound were explored. Considering all of the approved kinase inhibitors containing nitrogen heterocycles,[6,7] the inhibitory activity of compound **8f** against common kinases was screened. Similar to most of the approved kinase inhibitors, it was multi-targeted.[24,25] As shown in Table 3, it exhibited middling inhibitory activity against FLT3, INSR and VEGFR-2, with an IC_{50} value of approximately 1 μM in all cases. These protein tyrosine kinases are all known to play significant roles in the development and progression of many cancers,[25-27] and INSR and VEGFR-2 are particularly closely associated with breast cancer.[27,28]

Table 3. The Biological Activity of 3,4,6,7-Tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine Derivatives

Compounds	IC_{50} (μM) against human cancer cell lines			IC_{50} (μM) against kinases		
	ZR-75-30	HCT-116	A549	FLT3	INSR	VEGFR-2
8a	2.4	2.9	7.4	/	/	/
8f	0.71	1.1	2.2	0.94	0.86	1.0

3. Conclusion

In summary, a novel and efficient reductive dearomatization-initiated intramolecular cyclization reaction has been developed to construct a valuable *N*-fused heterocycle, 3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine derivatives. The scope was carefully studied. Moreover, this type of compound showed multi-targeted inhibitory activity against several cancer-associated kinases and good activity against the human ER^- breast cancer cell line. Therefore, these compounds might provide a new molecular scaffold for the development of new antitumor agents. Further exploration in this field is underway in our laboratories.

4. Experimental

4.1. Chemistry

Melting points were determined on a WRS-2 apparatus. ^1H (300, 400 or 600 MHz), ^{13}C (75, 100, 150 MHz), and ^{19}F (376 MHz) of samples were recorded on a Bruker AC-300P, AVANCE II600 or an AVANCE III400 spectrometer, using TMS as an internal standard and $CDCl_3$, CD_3OD or DMSO-d_6 as solvents. HRMS (ESI) determinations were carried out on a Bruker Daltonics micrOTOF Ⅱ spectrometer. Compounds **3a** and **7a** were commercial available. Compounds **4a**[18] and **5**[29] were prepared by the known procedures.

Synthesis of 6-(2-aminophenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (compound **6a**). (2-aminophenyl)boronic acid (**5**) (1.9 g, 14 mmol), compound **4a** (3.0 g, 10mmol), K_2CO_3 (4.14 g, 30 mmol) and $Pd(PPh)_3Cl_2$ (0.35 g, 5 mol%) were suspended in a mixture of 1,4-dioxane (30 mL) and H_2O (15mL). After refluxing for 2.5 h under N_2, 15 mL water was added to the whole, and then extracted three times with EtOAc. The combined organic

layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by Silica gel column chromatography with EtOAc/PE (1:2) as the eluent to afford the product **6a** as yellow solid (2.9 g, yield 91%). Mp = 192 - 196 □. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.61 (d, *J* = 1.1 Hz, 1H), 7.41 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.31 (d, *J* = 2.5 Hz, 1H), 7.12 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.95 (d, *J* = 1.1 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.75 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.61 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 6.56 (s, 2H), 4.26 – 4.20 (m, 4H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.8, 160.8, 157.0, 148.3, 143.0, 139.0, 133.3, 130.6, 128.5, 118.4, 116.9, 116.7, 115.8, 113.5, 109.4, 101.9, 64.2, 63.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{18}H_{16}N_4O_2$: 321.1346, Found: 321.1348.

Synthesis of *N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(2-((4-(trifluoromethyl)benzylidene)amino)phenyl)pyrimidin-4-amine (compound **1a**). The compound **6a** (250 mg, 0.78 mmol) and 4-(trifluoromethyl)benzaldehyde (**7a**) (0.19 g, 1.09 mmol) were suspended in the EtOH (5 mL). To the stirring mixture was added dropwise concentrated HCl (0.5 mL), followed by stirring overnight at room temperature. the precipitate was filtrated and washed with a small volume of EtOH. After that, the suspension of the resulting precipitate in MeOH was made alkaline to colourless with NaOH, and then filtered and washed with MeOH to give compound **1a**: white powder, Mp = 218 - 221℃. 294.9 mg, 79.3% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.38 (s, 1H), 8.74 (s, 1H), 8.63 (d, *J* = 0.8 Hz, 1H), 8.08 (d, *J* = 8 Hz, 2H), 7.91 (dd, *J* = 8, 1.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.53 (td, *J* = 7.6, 1.6 Hz, 1H), 7.41 (td, *J* = 7.6, 1.6 Hz, 1H), 7.24 (dd, *J* = 8, 0.8 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 1.2 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 1H), 6.58 (d, *J* = 8.4, 1H), 4.17 – 4.15 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.9, 160.2, 157.9, 149.3, 143.1, 139.5, 139.3, 132.9, 131.9, 131.3, 131.0, 131.0, 129.9, 129.5, 126.4,

125.8, 125.7, 119.4, 116.8, 114.3, 110.2, 106.7, 64.1, 63.9. HRMS (ESI) calcd for $[M+1]^+$ $C_{26}H_{19}F_3N_4O_2$: 477.1533; Found: 477.1539. ^{19}F NMR (376 MHz, DMSO-d_6) -61.3 (s, 3F).

The following compounds were prepared according to the same procedure of compound **1a**.

Methyl-4-(((2-(6-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)amino)pyrimidin-4-yl)phenyl)imino)methyl)benzoate (**1b**): white powder, Mp = 176 - 180℃. 207 mg, 47.4% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.70 (s, 1H), 8.63 (d, *J* = 0.8 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.93 (dd, *J* = 8, 1.6 Hz, 1H), 7.52 (td, *J* = 7.6, 1.2 Hz, 1H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.22(d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 0.8 Hz, 1H), 7.08 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 4.20 – 4.15 (m, 4H), 3.90(s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 160.8, 160.4, 160.2, 157.8, 149.5, 143.1, 139.8, 139.3, 132.8, 131.8, 131.7, 130.5, 129.8, 129.5, 129.0, 126.2, 119.3, 116.7, 114.2, 110.2, 106.4, 64.1, 63.8, 52.3. HRMS (ESI) calcd for $[M+1]^+$: $C_{27}H_{22}N_4O_4$: 467.1714; Found: 467.1713.

6-(2-((4-Bromobenzylidene)amino)phenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (**1c**): white powder, Mp = 182 - 182.5℃. 304.9 mg, 80.2% yield. ^1H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.49 (m, 1H), 7.38 (t, *J* = 8 Hz, 1H), 7.19 (d, *J* = 8 Hz, 1H), 7.09 (s, 1H), 7.07 (s, 1H), 6.85 (d, *J* = 10 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.20 – 4.17 (m, 4H); ^{13}C NMR (101MHz, DMSO-d_6) δ 161.0, 160.2, 157.9, 149.6, 143.1, 139.3, 135.1, 132.8, 131.9, 131.7, 130.7, 130.6, 129.8, 126.1, 125.3, 119.4, 116.8, 114.3, 110.2, 106.5, 64.2, 63.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{25}H_{19}BrN_4O_2$: 487.0764; Found: 487.0769.

6-(2-(Benzylideneamino)phenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (**1d**): white powder, Mp = 174 - 175℃. 206.5 mg, 64.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.62 (d, *J* = 1.2 Hz, 1H), 8.59 (s, 1H), 7.89 – 7.87 (m, 3H), 7.57 – 7.48 (m, 4H), 7.39 – 7.35 (m, 1H), 7.18 (dd, *J* = 8, 0.8 Hz, 1H), 7.14 (d, *J* = 1.2 Hz, 1H), 7.10 (s, 1H), 6.85 (dd, *J* =8.8, 2.4 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 4.19 – 4.16 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 161.1, 160.2, 157.9, 150.0, 143.1, 139.3, 136.0, 132.9, 131.7, 131.6, 130.6, 129.8, 128.9, 128.8, 125.8, 119.4, 116.8, 114.1, 110.1, 107.0, 64.2, 63.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{25}H_{20}N_4O_2$: 409.1659; Found: 409.1658.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(2-((4-methylbenzylidene)amino)phenyl)pyrimidin-4-amine (**1e**): white powder, Mp = 190 - 191℃. 220.4 mg, 55.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.61 (d, *J* = 1.2 Hz, 1H), 8.53 (s, 1H), 7.88 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.49 (td, *J* = 7.6, 1.6 Hz, 1H), 7.37 – 7.29 (m, 3H), 7.16 – 7.14 (m, 2H), 7.10 (s, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H) , 4.19 – 4.16 (m, 4H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 161.1, 160.2, 157.9, 150.1, 143.1, 141.7, 139.3, 133.5, 133.0, 131.6, 130.6, 129.8, 129.4, 128.9, 125.6, 119.4, 116.8, 114.1, 110.1, 106.6, 64.2, 63.9, 21.2. HRMS (ESI) calcd for $[M+1]^+$: $C_{26}H_{22}N_4O_2$: 423.1816; Found: 423.1819.

6-(2-((4-(*Tert*-butyl)benzylidene)amino)phenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)pyrimidin-4-amine (**1f**): white powder, Mp = 242 - 244℃. 261.8 mg, 72.3% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1H), 8.20 (d, *J* = 0.8 Hz, 1H), 8.55 (s, 1H), 7.88 (dd, *J* = 8, 1.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.35 (td, *J* = 8, 1.6 Hz, 1H), 7.16 – 7.10 (m, 3H), 6.86 (dd, *J* = 8.8, 2 Hz, 1H), 6.54 (d, *J* = 8.8Hz, 1H), 4.19 – 4.16 (m, 4H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 161.0, 160.1, 157.9, 154.7, 150.1, 143.1, 139.3, 133.5,

132.9, 131.6, 130.6, 129.8, 128.8, 125.6, 119.4, 116.8, 114.1, 110.1, 106.5, 64.2, 63.9, 34.7, 30.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{29}H_{28}N_4O_2$: 465.2285; Found: 465.2288.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(2-((4-methoxybenzylidene)amino)phenyl)pyrimidin-4-amine (**1g**): white powder, Mp = 215 - 216℃. 322.4 mg, 94.2% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.63 (d, *J* = 1.2 Hz, 1H), 8.49 (s, 1H), 7.89 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.48 (td, *J* = 7.6, 1.6 Hz, 1H), 7.33 (td, *J* = 7.6, 2.4 Hz, 1H), 7.20 (s, 1H), 7.20 – 7.14 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.20 – 4.17 (m, 4H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.0, 161.1, 160.4, 160.1, 157.8, 150.2, 143.1, 139.2, 132.9, 131.4, 130.7, 130.5, 129.7, 128.9, 125.3, 119.4, 116.7, 114.2, 114.1, 110.1, 106.4, 64.1, 63.9, 55.4. HRMS (ESI) calcd for $[M+1]^+$: $C_{26}H_{22}N_4O_3$: 439.1765; Found: 439.1769.

6-(2-(Benzylideneamino)phenyl)-*N*-(4-(trifluoromethyl)phenyl)pyrimidin-4-amine (**1h**): white powder, Mp = 218 - 221℃. 375 mg, 97.9% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.03 (s, 1H), 8.80 (s, 1H), 8.65 (s, 1H), 7.95 – 7.82 (m, 5H), 7.54 – 7.48 (m, 6H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.33 (s, 1H), 7.21 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8, 161.5, 159.5, 157.7, 149.9, 143.5, 136.0, 131.6, 131.5, 130.8, 129.9, 129.0, 128.8, 125.9, 125.9, 125.8, 123.1, 122.1, 121.8, 119.4, 119.2, 108.3. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{17}F_3N_4$: 419.1478; Found: 419.1478. ^{19}F NMR (376 MHz, DMSO-d_6) -60.1 (s, 3F).

6-(2-(Benzylideneamino)phenyl)-*N*-(4-bromophenyl)pyrimidin-4-amine (**1i**): white powder, Mp = 209 - 211℃. 213.9 mg, 56.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.72 (d, *J* = 0.8 Hz, 1H), 8.63(s, 1H), 7.93 – 7.91 (m, 3H), 7.56 – 7.48 (m, 6H), 7.40 – 7.31 (m, 3H), 7.24 (d, *J* = 0.8 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 159.6,

157.7, 149.9, 139.1, 136.0, 131.6, 131.5, 131.4, 130.7, 130.0, 129.0, 128.8, 125.8, 121.9, 119.4, 113.9, 107.5. HRMS (ESI) calcd for $[M+1]^+$: $C_{23}H_{17}BrN_4$: 429.0709; Found: 429.0708.

6-(2-(Benzylideneamino)phenyl)-*N*-phenylpyrimidin-4-amine (**1j**): white powder, Mp = 170 - 172℃. 270 mg, 80.9% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 7.92 – 7.89 (m, 3H), 7.55 – 7.49 (m, 6H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.22 – 7.14 (m, 4H), 6.97 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.4, 161.3, 159.9, 157.8, 149.9, 139.5, 136.0, 131.6, 131.6, 130.6, 129.8, 128.9, 128.8, 128.6, 125.8, 122.6, 120.3, 119.4, 107.0. HRMS (ESI) calcd for $[M+1]^+$: $C_{23}H_{18}N_4$: 351.1604; Found: 351.1609.

6-(2-(Benzylideneamino)phenyl)-*N*-(p-tolyl)pyrimidin-4-amine (**1k**): white powder, Mp = 182 - 184℃. 219 mg, 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.66 (s, 1H), 8.59 (s, 1H), 7.92 – 7.88 (m, 3H), 7.55 – 7.48 (m, 4H), 7.38 – 7.34 (m, 3H), 7.18 – 7.15 (m, 2H), 6.93 (d, *J* = 8Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 161.1, 160.1, 157.9, 149.9, 136.7, 136.0, 131.8, 131.6, 131.6, 130.5, 129.8, 129.1, 128.9, 128.8, 125.8, 120.7, 119.4, 106.6, 20.4. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{20}N_4$: 365.1761; Found: 365.1768.

6-(2-(Benzylideneamino)phenyl)-*N*-(4-methoxyphenyl)pyrimidin-4-amine (**1l**): white powder, Mp = 174 - 176℃. 315 mg, 96.8% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.63 (s, 1H), 8.59 (s, 1H), 7.91 – 7.88 (m, 3H), 7.56 – 7.49 (m, 4H), 7.36 – 7.30 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.64 (d, *J* = 8 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 161.0, 160.3, 158.0, 155.3, 149.9, 136.0, 132.0, 131.7, 131.6, 130.5, 129.8, 128.9, 128.8, 125.8, 122.8, 119.4, 113.9, 105.9, 55.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{20}N_4O$: 381.1710; Found: 381.1719.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-methyl-6-(2-((4-(trifluoromethyl)benzylidene)amino)phenyl)pyrimidin-4-amine (**15**): white powder, Mp = 168 - 170℃. 303 mg, 70.5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, *J* = 1.2 Hz, 1H), 8.4 (s, 1H), 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (td, *J* = 7.2, 1.2 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 0.8 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.39 (d, *J* = 8.4 Hz,1H), 4.16 (s, 4H), 3.34 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3, 161.0, 160.3, 157.7, 154.6, 154.2, 150.0, 143.8, 142.0, 136.8, 133.3, 131.4, 130.5, 129.7, 128.6, 125.6, 119.6, 119.4, 117.6, 115.3, 105.4, 64.0, 63.9, 37.9, 34.8, 30.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{30}H_{30}N_4O_2$: 479.2442, Found: 479.2444.

Synthesis of

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(4-trifluoromethyl)phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8a**). To a 25 mL Schlenck tube were added **1a** (48 mg, 0.1 mmol) and $NaBH_4$ (8 mg, 0.2 mmol) under air. The mixture was then evacuated and backfilled with Ar (3 times). anhydrous MeOH (3 mL) was added subsequently. The tube was screw capped, then stirred at room temperature for 46 hr. After stirring, H_2O was added to the solution, and extracted with dichloromethane, dried over Na_2SO_4. After evaporation of solvent, the residue was purified by the alumina column chromatography with CH_2Cl_2/MeOH (v:v = 100:0 → 100:15) as the eluent to obtain compound **8a**: yellow oil. 67 mg, 70% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8 Hz, 1H),7.31 (t, *J* = 7.7Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.83 – 6.81 (m, 3H), 6.74 (dd, *J* =8.5, 2.3 Hz, 1H), 5.93 (s, 1H), 4.66 – 4.64 (m, 2H), 4.25 (s, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 153.8, 143.9, 143.6, 142.7, 142.4, 134.5, 131.1, 130.8, 129.1, 127.0, 125.8, 125.8, 125.0, 122.3, 119.3, 118.2, 117.8,

116.8, 112.8, 68.5, 64.3, 64.2, 57.5. HRMS (ESI) calcd for $[M+1]^+$: $C_{26}H_{21}F_3N_4O_2$: 479.1689; Found: 479.1686. ^{19}F NMR (376 MHz, CD_3OD) -62.7 (s, 3F). The scaffold of 3,4,6,7-tetrahydropyrimido[1,6-*c*]quinazolin-2-imine was completely confirmed by the multi-dimensional NMR spectrum of compound **8d**.

The following compounds were prepared according to the same procedure of compound **8a**.

Methyl-4-(2-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)imino)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*] quinazolin-6-yl)benzoate (**8b**): yellow oil. 50 mg, 54% yield. ^1H NMR (400 MHz, CD_3OD) δ 7.96 (d, *J* = 8 Hz, 2H), 7.56 – 7.54 (m, 3H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.82 – 6.77 (m, 5H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.71 (s, 1H), 4.49 (s, 2H), 4.20 (s, 4H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 166.3, 158.1, 153.7, 143.8, 143.7, 143.1, 142.5, 134.3, 130.6, 130.0, 129.2, 126.7, 125.7, 119.1, 118.1, 117.7, 116.7, 114.0, 112.6, 77.2, 68.7, 64.2, 64.2, 57.3, 52.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{27}H_{24}N_4O_4$: 469.1870; Found: 469.1878.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(4-bromo)phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8c**): yellow oil. 70 mg, 72% yield. ^1H NMR (400 MHz, CD_3OD) δ 7.60 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.85 – 6.75 (m, 4H), 5.89 (s, 1H), 4.70 – 4.58 (m, 2H), 4.05 (s, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 158.8, 155.7, 145.8, 145.7, 144.4, 139.4, 135.6, 133.1, 129.8, 129.8, 126.9, 124.3, 120.2, 119.2, 118.7, 117.2, 114.7, 113.6, 70.1, 65.7, 65.6, 57.8.. HRMS (ESI) calcd for $[M+1]^+$: $C_{25}H_{21}BrN_4O_2$: 491.0901; Found: 491.0910.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8d**): yellow oil. 65 mg, 79% yield. ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.45 (m, 2H), 7.38 – 7.37 (m, 3H), 7.30 – 7.29 (m, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.5

Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.76 (t, *J* = 7.9 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.76 (s, 1H), 5.62 (s, 1H), 5.49 (s, 1H), 4.44 (d, *J* = 9.9 Hz, 1H), 4.35 (d, *J* = 9.9 Hz, 1H), 4.26 (s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 155.0, 144.7, 144.3, 143.2, 136.9, 134.6, 130.6, 129.8, 129.5, 127.8, 126.3, 120.1, 119.1, 118.2, 116.7, 116.6, 115.1, 113.5, 78.6, 70.9, 64.7, 64.7, 56.6. HRMS (ESI) calcd for $[M+1]^+$: $C_{25}H_{22}N_4O_2$: 411.1816; Found: 411.1822. Its multi-dimensional NMR spectrum attached behind.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(4-methyl)phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8e**): yellow oil. 44 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.70 – 6.67 (m, 2H), 5.61 (s, 1H), 5.53 (s, 1H), 4.43 (d, *J* =9.9 Hz, 1H), 4.37 (d, *J* = 9.9 Hz, 1H), 4.22 (s, 4H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 154.5, 144.4, 143.8, 142.5, 139.9, 134.1, 133.7, 129.8, 129.8, 129.2, 127.2, 127.1, 125.7, 119.2, 118.4, 117.6, 116.2, 114.3, 112.8, 77.2, 70.0, 64.2, 64.2, 56.2, 21.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{26}H_{24}N_4O_2$: 425.1972; Found: 425.1983.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(*tert*-butyl)phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8f**): yellow oil. 48 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 4H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.85 – 6.81 (m, 2H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.06 (s, 1H), 5.64 (s, 1H), 5.53 (s, 1H), 4.47 (d, *J* = 9.9 Hz, 1H), 4.39 (d, *J* = 9.9 Hz, 1H), 4.25 (s, 4H), 1.28 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 154.5, 153.1, 144.3, 143.8, 142.6, 134.1, 133.6, 129.2, 126.9, 126.2, 125.8, 119.3, 118.5, 117.7, 116.2, 114.4, 112.8, 77.2, 70.0, 64.2, 64.2, 56.2, 34.6, 31.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{29}H_{30}N_4O_2$: 467.2442; Found: 467.2448.

N-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-6-(4-methoxy)phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8g**): yellow oil. 33 mg, 37% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, *J* = 8 Hz, 1H), 7.42 – 7.40 (m, 3H), 7.31 (t, *J* = 8.4 Hz, 1H), 6.94 – 6.92 (m, 2H), 6.9 (d, *J* = 8.8 Hz, 1H), 6.80 – 6.78 (m, 3H), 6.73 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.73 (s, 1H), 4.52 – 4.45 (m, 2H), 4.23 (s, 4H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 162.1, 158.8, 156.3, 146.6, 145.7, 144.3, 135.4, 131.2, 129.7, 126.9, 112.0, 119.2, 118.6, 117.0, 115.4, 114.7, 113.6, 71.0, 65.7, 65.6, 57.2, 55.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{26}H_{24}N_4O_3$: 441.1921; Found: 441.1929.

6-Phenyl-*N*-(3-(trifluoromethyl)phenyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8h**): yellow oil. 49 mg, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 5H), 7.44 (s, 5H), 7.24 – 7.22 (m, 3H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.67 (s, 1H), 5.38 (s, 1H), 4.30 (d, *J* = 9.2 Hz, 1H), 4.17 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 143.7, 132.5, 131.4, 130.3, 129.3, 129.0, 127.9, 126.3, 126.3, 126.3, 125.1, 122.4, 120.3, 120.3, 120.1, 117.5, 117.5, 115.7, 102.0, 71.6, 58.3. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{19}F_3N_4$: 421.1635; Found: 421.1639. ^{19}F NMR (376 MHz, $CDCl_3$) -61.9 (s, 3F).

N-(3-bromophenyl)-6-phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8i**): yellow oil. 61mg, 71% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 – 7.59 (m, 4H), 7.48 – 7.33 (m, 7H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 2H), 5.92 (s, 1H), 5.83 (s, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.64 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.5, 152.1, 143.6, 137.1, 132.8, 131.9, 131.6, 129.7, 128.9, 127.2, 125.0, 124.6, 119.3, 117.1, 115.7, 113.7, 70.6, 57.6. HRMS (ESI) calcd for $[M+1]^+$: $C_{23}H_{19}BrN_4$: 431.0866; Found: 431.0877.

N,6-diphenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8j**): yellow oil. 51 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.48 – 7.38 (m, 7H), 7.36 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.26 (s, 1H), 6.82 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.64 (s, 1H), 5.59 (s, 1H), 4.44 (d, *J* = 9.8 Hz, 1H), 4.33 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 144.2, 136.3, 134.0, 130.5, 129.5, 129.5, 128.2, 127.7, 126.6, 125.8, 124.7, 120.0, 117.6, 116.1, 113.5, 77.2, 70.9, 56.4. HRMS (ESI) calcd for $[M+1]^+$: $C_{23}H_{20}N_4$: 353.1761; Found: 353.1769.

6-Phenyl-*N*-(*p*-tolyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8k**): yellow oil. 48 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 2H), 7.35 – 7.30 (m, 5H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8 Hz, 1H), 6.72 (t, *J* = 8 Hz, 1H), 5.59 (s, 1H), 5.49 (s, 1H), 4.34 (d, *J* = 9.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 153.2, 144.0, 137.2, 135.7, 135.6, 133.5, 129.9, 129.8, 129.1, 127.4, 125.4, 124.1, 119.4, 116.1, 113.5, 79.7, 70.5, 57.2, 20.9. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{22}N_4$: 367.1917; Found: 367.1913.

N-(3-methoxyphenyl)-6-phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[1,6-*c*]quinazolin-2-imine (**8l**): yellow oil. 61 mg, 80% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (s, 1H), 7.49 – 7.47 (m, 2H), 7.39 – 7.37 (m, 2H), 7.31 (t, *J* = 7.6Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8 Hz, 2H), 6.83 – 6.80 (m, 2H), 5.85 (s, 1H), 4.59 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 160.3, 158.9, 156.0, 146.3, 139.8, 135.5, 130.5, 130.1, 128.1, 127.2, 126.9, 120.0, 117.1, 116.2, 113.6, 71.0, 57.6, 56.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{24}H_{22}N_4O$: 383.1866; Found: 383.1869.

6-(4-(*Tert*-butyl)phenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-*N*-methyl-6,7-dihydro-4*H*-pyrimido[1,6-*c*]quinazolin-2-amine (**16**): yellow oil. 69 mg, 50% yield. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.77 (s, 1H), 6.72 – 6.64 (m, 2H), 6.46 (s, 1H), 5.60 (s, 1H), 5.13 (s, 1H), 4.64 – 4.62 (m, 2H), 4.30 (s, 4H), 3.54 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 152.5, 152.3, 144.1, 144.1, 143.4, 136.5, 134.7, 133.5, 126.6, 126.0, 125.2, 119.8, 118.7, 118.0, 116.3, 115.6, 79.6, 79.4, 77.3, 69.6, 64.2, 57.9, 41.3, 34.5, 31.1. HRMS (ESI) calcd for $[M+1]^+$: $C_{30}H_{32}N_4O_2$: 481.2598, Found: 481.2613.

4.2. Biology.

Tumor cell growth inhibitory activity test. Tumor cell growth inhibitory activities were tested against human cancer cell-lines, ZR-75-30 (breast cancer), HCT116 (colon cancer), and A549 (lung cancer), by the known procedure.[30] Briefly, For each well of a 96-well microplate, 100 μL of cell dilution was seeded, allowed to attach overnight, and then exposed to varying concentrations of compounds for 72 h (37 °C, 5% CO_2 atmosphere). The number of living cells was estimated by the MTT assay. The IC50 values were determined by a nonlinear regression analysis. Average values were reported.

Kinases inhibitory activity test. Kinases inhibitory activities were tested against several common kinases, such as ABL, FGFR1, FLT3, MET, INSR, EGFR, VEGFR-2, PDK1, CHK1, etc., by the known procedure.[31] The activities of the kinases were detected by mobility shift assay on EZ Caliper Reade. For the determination of IC50, the compounds were tested at 10 concentrations. Average values were reported.

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Supplementary data

Supplementary data related to this article can be found at.

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