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Discovery of quinazolin-4-amines bearing benzimidazole fragments as dual inhibitors of c-Met and VEGFR-2

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ABSTRACT

Both c-Met and VEGFR-2 are important targets for the treatment of cancers. In this study, a series of *N*-(2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4-amine derivatives were designed and identified as dual c-Met and VEGFR-2 inhibitors. Among these compounds bearing quinazoline and benzimidazole fragments, compound **7j** exhibited the most potent inhibitory activity against c-Met and VEGFR-2 with IC_{50} of 0.05 μM and 0.02 μM, respectively. It also showed the highest anticancer activity against the tested cancer cell lines with IC_{50} of 1.5 μM against MCF-7 and 8.7 μM against Hep-G2. Docking simulation supported the initial pharmacophoric hypothesis and suggested a common mode of interaction at the ATP-binding site of c-Met and VEGFR-2, which demonstrates that compound **7j** is a potential agent for cancer therapy deserving further researching.

1. Introduction

The receptor tyrosine kinase c-Met and its natural ligand hepatocyte growth factor (HGF) are involved in cell proliferation, migration, invasion, and survival and are essential for normal embryonic development and wound healing.[1,2] However, dysregulation of c-Met/HGF pathway can lead to tumorigenesis and metastasis.[3] Aberrant expression of c-Met/HGF axis has been identified in a wide range of human malignancies such as bladder, breast, colorectal, gastric, and lung cancers.[4–8]

VEGFR-2 (KDR), a member of vascular endothelial growth factor receptors (VEGFRs), also belongs to receptor tyrosine kinase family. Its activation by vascular endothelial growth factor (VEGF) initiates downstream signaling, ultimately leading to angiogenesis, vascular permeability enhancement, tumor proliferation, and tumor migration.[9–12]

c-Met has been shown to collaborate synergistically with VEGFR-2, resulting in promoting development of angiogenesis and progression of various human cancers.[10,13,14] Therefore, molecules that potently inhibit both c-Met and VEGFR-2 may have advantage over either c-Met-selective or VEGFR-2-selective inhibitor since they can target multiple signaling pathways involved in tumor angiogenesis, proliferation, and metastasis.[15] Thus, the combined inhibition of both c-Met and VEGFR signaling represents a promising approach to cancer treatment.

In recent years, some c-Met/VEGFR-2 dual inhibitors have been reported or have entered clinical trials.[16–22] Most of these tyrosine kinase inhibitors contain various heterocyclic scaffolds. In an attempt to pursue new antitumor agents potently inhibited both c-Met and VEGFR-2, a series of new quinazolin-4-amine derivatives containing benzimidazole moieties were synthesized and their inhibitory activities against c-Met and VEGFR-2 and two cancer cell lines were evaluated. In addition, the structure–activity relationships and possible enzyme binding modes were also illustrated.

2. Results and discussion

2.1. Chemistry

The synthesis route of the title *N*-(2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4-amine derivatives is outlined in Scheme 1. The preparation of these quinazolin-4-amines containing benzimidazole moiety started from a series of commercially available substituted benzoic acids **2a**–**2u**. Condensation of **2a**–**2u** with 4-nitro-*o*-phenylenediamine (**1**) in polyphosphoric acid (PPA) at 120–150 °C for 5 h gave the 5-nitro-benzimidazole intermediates **3a**–**3u**. Hydrogenation of 5-nitro-benzimidazole intermediates **3a**–**3u** with $Pd/C/H_2$ under normal pressure at room temperature for 5 h or with Fe/AcOH/EtOH under reflux for 2 h provided the

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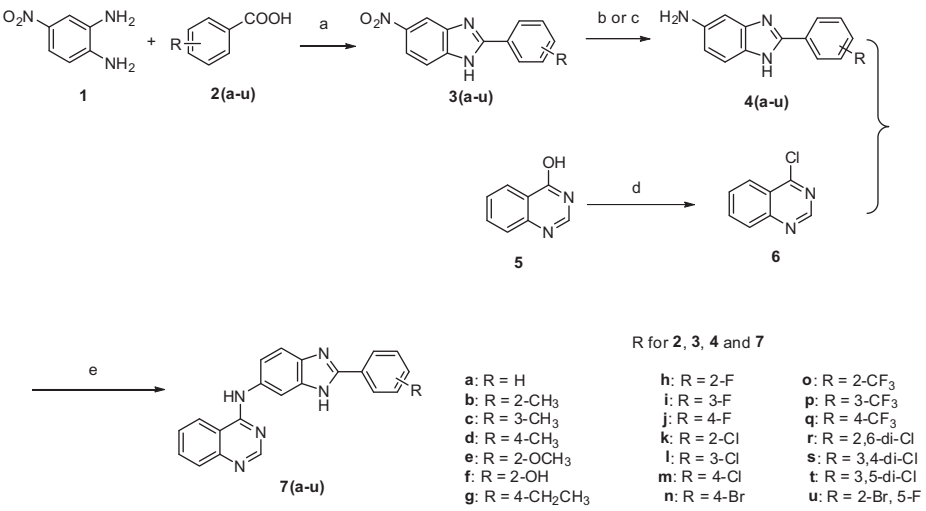


Scheme 1. General procedure for the synthesis of *N*-(2-phenyl-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine derivatives. Reagents and conditions: (a) PPA, 120–150 °C, 5 h; (b) Pd/C, H_2, CH_3OH, rt, 5 h; (c) Fe, AcOH, EtOH, reflux, 2 h; (d) $POCl_3$, 100 °C, 4 h; (e) isopropanol, reflux, 5 h.

5-amino-benzimidazole intermediates **4a**–**4u**. Condensation of **4a**–**4u** with 4-chloroquinazoline (**6**), which was prepared by quinazolin-4-ol (**5**) in $POCl_3$ at 100 °C for 4 h, in isopropanol under reflux for 5 h afforded the benzimidazole quinazolin-4-amines **7a**–**7u**.

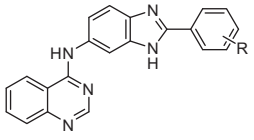
2.2. Biological evaluation

2.2.1. c-Met and VEGFR-2 inhibitory assay

All the synthesized quinazolin-4-amine derivatives containing benzimidazole moiety **7a**–**7u** were assayed with the enzymatic activities against c-Met and VEGFR-2. The results were summarized in Table 1. Also included was the activity of reference compound Golvatinib. Among these compounds, compound **7j** showed the most potent activities with IC_{50} of 0.02 μM and 0.05 μM against VEGFR-2 and c-Met, respectively, which is comparable to Golvatinib (IC_{50} = 0.02 μM against c-Met and 0.04 μM against VEGFR-2).

Structure–activity relationships (SARs) were inferred from data of enzymatic experiments reported in Table 1. The type, number and position of substituents on the phenyl ring linking to the benzimidazole moiety played important roles in the enzymatic activities. The inhibitory activities against c-Met and VEGFR-2 of compounds **7a**–**7u** with different single *para*-substituents increased in the following order: -F (**7j**)>-Cl (**7m**)>-Br (**7n**)>-H

Table 1
Enzymatic and cellular results for benzimidazole quinolin-4-amines



Compd	R	Enzymatic inhibition (IC_{50}, μM)		Proliferative inhibition (IC_{50}, μM)	
		c-Met	VEGFR-2	Hep-G2	MCF-7
7a	H	1.34	0.83	21.8	9.6
7b	2-CH_3	>10	9.35	>100	70.5
7c	3-CH_3	8.80	6.57	85.7	65.2
7d	4-CH_3	4.54	4.76	36.8	17.3
7e	2-OCH_3	>10	>10	>100	78.5
7f	2-OH	>10	>10	>100	64.6
7g	4-CH_2CH_3	7.30	8.69	80.3	54.0
7h	2-F	7.48	6.35	64.8	30.5
7i	3-F	1.50	0.82	37.6	12.6
7j	4-F	0.05	0.02	8.7	1.5
7k	2-Cl	>10	8.70	73.1	28.3
7l	3-Cl	4.24	1.58	31.6	14.4
7m	4-Cl	0.15	0.09	15.8	3.6
7n	4-Br	0.56	0.38	24.7	8.3
7o	2-CF_3	>10	>10	>100	86.5
7p	3-CF_3	>10	>10	92.6	52.3
7q	4-CF_3	>10	8.85	78.4	35.0
7r	2,6-Di-Cl	>10	>10	>100	74.7
7s	3,4-Di-Cl	1.53	0.76	19.5	9.0
7t	3,5-Di-Cl	3.58	1.84	28.4	7.5
7u	2-Br, 5-F	7.85	8.52	68.3	25.8
Golvatinib		0.02	0.04	65.5	49.6

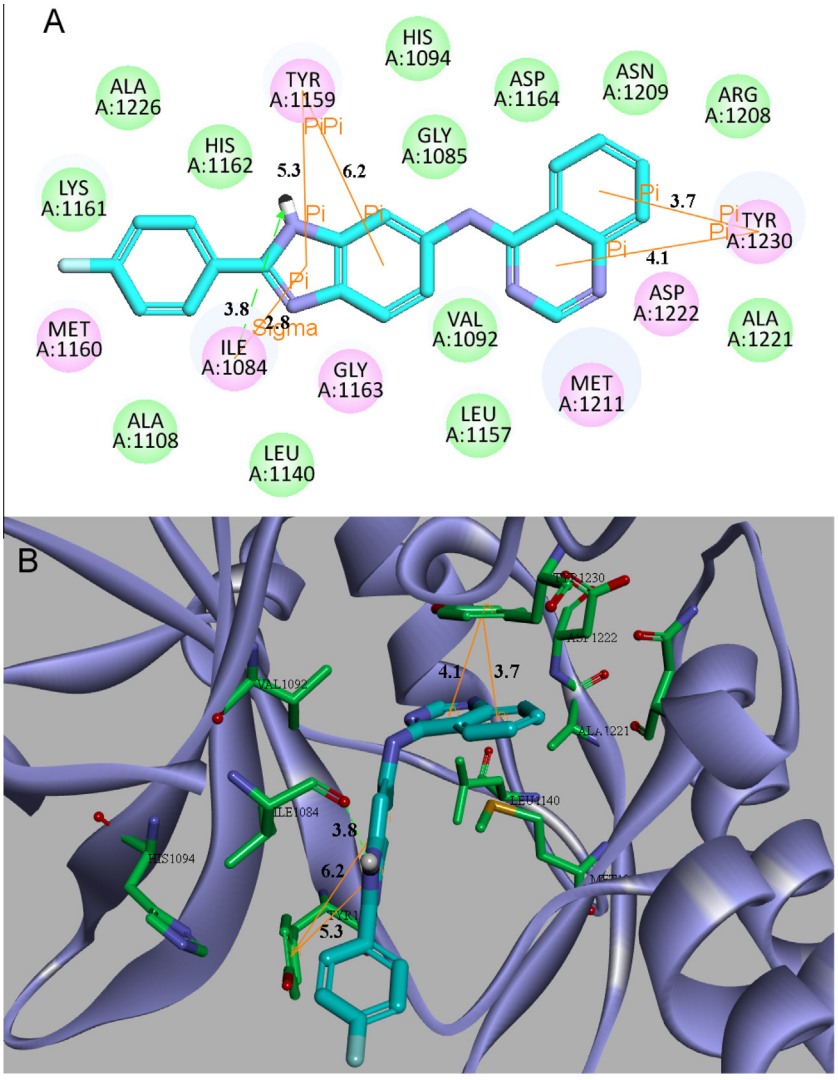


Figure 1. (A) 2D molecular docking modeling of compound **7j** with c-Met. The hydrogen bond is displayed as green dotted lines. The π–π interactions and π–σ interaction are shown as yellow line. (B) 3D model of the interaction between compound **7j** and c-Met ATP binding site.

(**7a**)>-CH_3 (**7d**)>-CH_2CH_3 (**7g**)>-CF3 (**7q**). The above results indicated that introduction of electron-withdrawing small substituent is favorable for the activities while introduction of electron-donating substituent or strongly electron-withdrawing bulk substituent causes obvious decrease of activities. This discipline was also observed in *ortho*-substituted and *meta*-substituted compounds.

Compounds **7h**, **7i** and **7j** with fluoro substituent at different position showed different inhibitory activity against c-Met and VEGFR-2. Compound **7j** with *para*-fluoro substituent showed more potent activity (IC_{50} = 0.05 μM against c-Met and 0.02 μM against VEGFR-2) than compound **7i** with *meta*-fluoro substituent (IC_{50} = 1.50 μM against c-Met and 0.82 μM against VEGFR-2). The activity of the latter was better than compound **7h** with *ortho*-chloro substituent (IC_{50} = 7.48 μM against c-Met and 6.35 μM against VEGFR-2). The result suggested that substituents in different positions led to different inhibitory activities (*para*- > *meta*- > *ortho*-). This rule was also found in other single substituted compounds. Comparing the activities of compounds **7r**, **7s** and **7t**, we found that compound **7s** with two chloro substituents at *para* and *meta* positions exhibited the most potent activity (IC_{50} = 1.53 μM against c-Met and 0.76 μM against VEGFR-2), and compound **7t** with two chloro substituents at two *meta* positions displayed weaker activity (IC_{50} = 3.58 μM against c-Met and 1.84 μM against VEGFR-2), however, introduction of two chloro substituents to two *ortho* positions caused the lost of activity (compound **7r**: IC_{50} >10 μM against c-Met and VEGFR-2). It also demonstrated that introduction of certain substituents at *para* position is more favorable.

2.2.2. Antiproliferation assay

All the synthesized compounds **7a**–**7u** were evaluated for their anticancer activity against MCF-7 (human breast cancer) and Hep-G2 (human liver cancer) cell lines by MTT assay. The results were also summarized in Table 1. It was clear that almost all the tested compounds showed better activities against MCF-7 than against Hep-G2. Among the tested compounds, compound **7j** with the most potent c-Met/VEGFR-2 inhibitory activities also showed the most potent anticancer activities with the IC_{50} value of 1.5 μM and 8.7 μM against MCF-7 and HepG-2, respectively, which is better than Golvatinib.

The SARs analysis result of antiproliferation activities of the tested compounds were consistent with that of their inhibitory activities against c-Met and VEGFR-2, which suggested that the

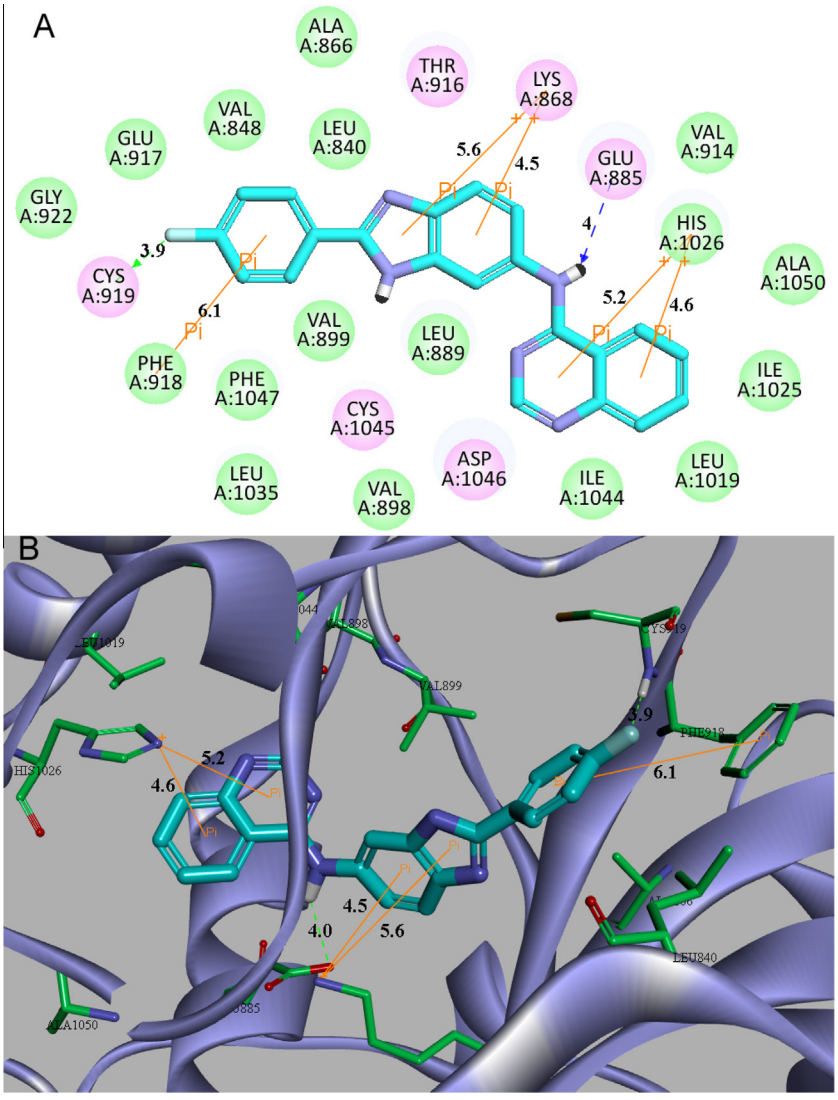


Figure 2. (A) 2D molecular docking modeling of compound **7j** with VEGFR-2. The hydrogen bonds are displayed as green or blue dotted lines. The π–π interaction and π–cation interactions are shown as yellow line. (B) 3D model of the interaction between compound **7j** and VEGFR-2 ATP binding site.

potent anticancer activities of the synthesized compounds were likely related to their dual c-Met/VEGFR-2 inhibitory activities.

2.3. Molecular docking studies

In order to better understand the interaction between compounds and kinases, molecular docking studies on the potent compound **7j** were performed using the Discovery Studio 3.1/CDOCKER protocol.

Figure 1 demonstrates the compound **7j** docking into the binding site of c-Met kinase (PDB: 3CD8).[23] In this binding model, the protonated nitrogen atom of benzimidazole ring in **7j** forms a hydrogen bond with ILE1084 (O...H–N: 3.8 Å). The π–π interactions are formed between the benzimidazole ring and TYR1159. Besides, π–π interactions are also formed between the quinazoline ring and TYR1230. In addition, the π–σ interaction is forged between the imidazole ring and ILE1084.

The binding model of compound **7j** into the ATP-binding cavity of VEGFR-2 kinase (PDB: 2QU5)[24] is depicted in Figure 2. In this binding model, the protonated nitrogen atom between quinazoline ring and benzimidazole ring and the fluorine atom of the phenyl ring in **7j** form hydrogen bonding interactions with GLU885 (O...H–N: 4.0 Å) and CYS 919 (F...H–N: 3.9 Å), respectively. The π–cation interactions are not only formed between the quinazoline ring and HIS1026 but also formed between the benzimidazole ring and LYS868. Additionally, the π–π interaction is forged between the phenyl ring and PHE918.

The nice binding model of compound **7j** with c-Met and VEGFR-2 is consistent with kinase assay data, which indicates that compound **7j** is a potent dual c-Met/VEGFR-2 inhibitor.

3. Conclusions

A series of quinazolin-4-amine derivatives containing benzimidazole moiety have been synthesized and discovered as dual inhibitors against c-Met and VEGFR-2 that displayed good antiproliferation activities against two tumor cell lines (MCF-7 and Hep-G2). Compound **7j** exhibited the most potent inhibitory activity against c-Met and VEGFR-2 with IC_{50} of 0.05 μM and 0.02 μM, respectively and also showed the greatest inhibitory activities against human breast cancer cell MCF-7 and human liver cancer cell Hep-G2 with IC_{50} of 1.5 μM and 8.7 μM, respectively. Molecular docking of the most potent inhibitor **7j** into ATP binding site of

c-Met and VEGFR-2 was performed and the result suggested that compound **7j** could bind well with the active site of c-Met and VEGFR-2. The above results demonstrated that compound **7j** could be a potential anticancer agent.

4. Experimental section

4.1. Chemistry

All solvents and reagents were commercially available and used without further purification. Melting points (uncorrected) were determined on a RY-1 MP apparatus. ESI-MS spectra were recorded on an Agilent/HP 1100 Series LC/MSD Trap SL Mass spectrometer., and ^{1}H NMR spectra were recorded on a Bruker AV-300 or AV-500 spectrometer at 25 °C with TMS and solvent signals allotted as internal standards. Chemical shifts were reported in ppm (δ). Elemental analyses were performed on a CHN-O-Rapid instrument.

4.1.1. General procedure for the preparation of the 5-nitro-2-phenyl-1*H*-benzo[*d*]imidazole derivatives 3a–3u

A mixture of 4-nitro-*o*-phenylenediamine (3.22 g, 21 mmol) and substituted benzoic acid **2a**–**2u** (20 mmol) in PPA (40 mL) was stirred at 120–150 °C for 5 h. The reaction was quenched with water and the pH was adjusted to 6 with saturated NaOH. The filter cake was washed with water and recrystallized from ethyl acetate to give corresponding compounds **3a**–**3u**.

4.1.1.1. 5-Nitro-2-phenyl-1*H*-benzo[*d*]imidazole (3a). Pale orange–red powder, yield: 88%, mp: 206–208 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.48–8.04 (m, 4H); 8.04–8.69 (m, 4H); 13.64 (s, 1H). MS (ESI $^+$) *m*/*z* 294.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.32; H, 3.82; N, 17.53.

4.1.1.2. 5-Nitro-2-*o*-tolyl-1*H*-benzo[*d*]imidazole (3b). Yellow powder, yield: 86%, mp: 146–148 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 2.58 (s, 3H); 7.46 (s, 3H); 7.77–7.85 (m, 2H); 8.16 (s, 1H); 8.40–8.59 (m, 1H); 13.37 (s, 1H). MS (ESI$^+$) *m*/*z* 254.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.34; H, 4.41; N, 16.64.

4.1.1.3. 5-Nitro-2-*m*-tolyl-1*H*-benzo[*d*]imidazole (3c). Yellow powder, yield: 99%, mp: 108–110 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 2.48 (s, 3H); 7.38–7.52 (m, 2H); 7.76 (d, *J* = 8.5 Hz, 1H); 8.00–8.15 (m, 3H); 8.47 (s, 1H); 13.58 (s, 1H). MS (ESI$^+$) *m*/*z* 254.2 (M+H)$^+$. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.42; N, 16.53.

4.1.1.4. 5-Nitro-2-*p*-tolyl-1*H*-benzo[*d*]imidazole (3d). Yellow powder, yield: 81%, mp: 219–221 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 2.32 (s, 3H); 7.29 (d, *J* = 7.9 Hz, 2H); 7.61 (d, *J* = 8.8 Hz, 1H); 7.98 (dd, *J* = 8.8, 2.2 Hz, 1H); 8.09 (d, *J* = 8.1 Hz, 2H); 8.35 (d, *J* = 2.1 Hz, 1H). MS (ESI$^+$) *m*/*z* 254.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.52; H, 4.35; N, 16.65.

4.1.1.5. 2-(2-Methoxyphenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3e). Brown powder, yield: 97%, mp: 208–209 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 4.08 (s, 3H); 7.17 (t, *J* = 7.4 Hz, 1H); 7.30 (d, *J* = 8.3 Hz, 1H); 7.57 (t, *J* = 7.4 Hz, 1H); 7.81 (d, *J* = 8.9 Hz, 1H); 8.13 (d, *J* = 8.7 Hz, 1H); 8.39 (d, *J* = 7.4 Hz, 1H); 8.54 (s, 1H); 12.67 (s, 1H). MS (ESI$^+$) *m*/*z* 270.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.66; H, 4.14; N, 15.67.

4.1.1.6. 2-(5-Nitro-1*H*-benzo[*d*]imidazol-2-yl)phenol (3f). Dark brown powder, yield: 37%, mp: 305–307 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 6.94–7.04 (m, 2H); 7.35 (t, *J* = 7.23 Hz, 1H); 7.71 (d, *J* = 8.8 Hz, 1H); 8.05 (dd, *J* = 8.8, 2.1 Hz, 1H); 8.26 (d, *J* = 7.0 Hz, 1H); 8.47 (d, *J* = 1.95 Hz, 1H). MS (ESI$^+$) *m*/*z* 256.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 61.35; H, 3.51; N, 16.50.

4.1.1.7. 2-(4-Ethylphenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3g). Orange powder, yield: 90%, mp: 84–86 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 1.22 (t, *J* = 7.5 Hz, 3H); 2.68 (d, *J* = 7.5 Hz, 2H); 7.42 (d, *J* = 8.1 Hz, 2H); 7.72 (d, J = 9.0 Hz, 1H); 8.08–8.13 (m, 3H); 8.42 (s, 1H); 13.48 (s, 1H). MS (ESI$^+$) *m*/*z* 268.1 (M+H)$^+$. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.52; H, 4.86; N, 15.68.

4.1.1.8. 2-(2-Fluorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3h). Orange powder, yield: 26%, mp: 171–173 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.41–7.52 (m, 2H); 7.60–7.68 (m, 1H); 7.81 (d, *J* = 8.7 Hz, 1H); 8.15 (dd, *J* = 8.7, 1.8 Hz, 1H); 8.27 (t, *J* = 7.2 Hz, 1H); 8.52 (s, 1H); 13.21 (s, 1H). MS (ESI$^+$) *m*/*z* 258.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_8FN_3O_2$: C, 60.70; H, 3.13; N, 16.34. Found: C, 60.78; H, 3.12; N, 16.30.

4.1.1.9. 2-(3-Fluorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3i). Pale yellow powder, yield: 42%, mp: 205–207 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.38–7.43 (m, 1H); 7.63–7.76 (m, 2H); 7.95–8.14 (m, 3H); 8.48 (s, 1H); 13.66 (s, 1H). MS (ESI$^+$) *m*/*z* 258.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_8FN_3O_2$: C, 60.70; H, 3.13; N, 16.34. Found: C, 60.55; H, 3.15; N, 16.39.

4.1.1.10. 2-(4-Fluorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3j). Golden powder, mp: yield: 96%, mp: 258–260 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.44 (t, *J* = 9.0 Hz, 2H); 7.75 (d, *J* = 8.7 Hz, 1H); 8.11 (dd, *J* = 9.0, 2.1 Hz, 1H); 8.23–8.27 (m, 2H); 8.45 (s, 1H); 13.59 (s, 1H). MS (ESI$^+$) *m*/*z* 258.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_8FN_3O_2$: C, 60.70; H, 3.13; N, 16.34. Found: C, 60.84; H, 3.16; N, 16.38.

4.1.1.11. 2-(2-Chlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3k). Brown powder, yield: 16%, mp: 168–170 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.52–7.62 (m, 2H); 7.67–7.70 (m, 1H); 7.80 (d, *J* = 9.0 Hz, 1H); 7.94 (dd, *J* = 7.2, 2.1 Hz, 1H); 8.15 (dd, *J* = 8.7, 2.1 Hz, 1H); 8.53 (s, 1H); 13.42 (s, 1H). MS (ESI$^+$) *m*/*z* 274.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_8ClN_3O_2$: C, 57.05; H, 2.95; N, 15.35. Found: C, 57.22; H, 2.97; N, 15.41.

4.1.1.12. 2-(3-Chlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3l). Orange powder, yield: 83%, mp: 220–222 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.61 (d, *J* = 5.1 Hz, 2H); 7.76 (d, *J* = 9.0 Hz, 1H); 8.10–8.17 (m, 2H); 8.22 (d, *J* = 0.9 Hz, 1H); 8.46 (d, *J* = 1.8 Hz, 1H); 13.69 (s, 1H). MS (ESI$^+$) *m*/*z* 274.0 (M+H)$^+$. Anal. Calcd for $C_{13}H_8ClN_3O_2$: C, 57.05; H, 2.95; N, 15.35. Found: C, 56.88; H, 3.01; N, 15.43.

4.1.1.13. 2-(4-Chlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3m). Yellow green powder, yield: 40%, mp: 301–303 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.66–7.77 (m, 3H); 8.13 (dd, *J* = 9.0, 2.1 Hz, 1H); 8.21 (d, *J* = 8.7 Hz, 2H); 8.49 (s, 1H); 13.66 (s, 1H). MS (ESI$^+$) *m*/*z* 274.0 (M+H)$^+$. Anal. Calcd for $C_{13}H_8ClN_3O_2$: C, 57.05; H, 2.95; N, 15.35. Found: C, 57.19; H, 2.92; N, 15.29.

4.1.1.14. 2-(4-Bromophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3n). Yellow powder, yield: 78%, mp: 296–298 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.77–7.85 (m, 3H); 8.13–8.18 (m, 3H); 8.50 (s, 1H). MS

(ESI$^+$) m/z 318.0 (M+H)$^+$. Anal. Calcd for $C_{13}H_8BrN_3O_2$: C, 49.08; H, 2.53; N, 13.21. Found: C, 49.24; H, 2.52; N, 13.26.

4.1.1.15. 5-Nitro-2-(2-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (3o). Pale orange powder, yield: 84%, mp: 190–191 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.80–7.91 (m, 4H); 7.98 (d, J = 7.5 Hz, 1H); 8.17 (d, J = 8.1 Hz, 1H); 8.54 (s, 1H), 13.52 (s, 1H). MS (ESI$^+$) m/z 308.2 (M+H)$^+$. Anal. Calcd for $C_{14}H_8F_3N_3O_2$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.78; H, 2.64; N, 13.65.

4.1.1.16. 5-Nitro-2-(3-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (3p). Brown crystal, yield: 56%, mp: 229–230 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.76–7.93 (m, 3H); 8.12 (dd, J = 9.0, 2.1 Hz, 1H); 8.47–8.52 (m, 3H); 13.79 (s, 1H). MS (ESI$^+$) m/z 308.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_8F_3N_3O_2$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.86; H, 2.59; N, 13.72.

4.1.1.17. 5-Nitro-2-(4-(trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazole (3q). Orange powder, yield: 21%, mp: 273–274 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.77 (d, J = 8.7 Hz, 1H); 7.94 (d, J = 8.7 Hz, 2H); 8.12 (dd, J = 9.0, 2.4 Hz, 1H); 8.37 (d, J = 8.1 Hz, 2H); 8.47 (d, J = 1.8 Hz, 1H); 13.78 (s, 1H). MS (ESI$^+$) m/z 308.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_8F_3N_3O_2$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.88; H, 2.60; N, 13.64.

4.1.1.18. 2-(2,6-Dichlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3r). Pale orange powder, yield: 80%, mp: 210–212 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.60–7.71 (m, 3H); 7.83 (d, J = 9.0 Hz, 1H); 8.17 (dd, J = 9.0, 2.1 Hz, 1H); 8.58 (s, 1H); 13.65 (s, 1H). MS (ESI$^+$) m/z 307.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_7Cl_2N_3O_2$: C, 50.67; H, 2.29; N, 13.64. Found: C, 50.80; H, 2.31; N, 13.68.

4.1.1.19. 2-(3,4-Dichlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3s). Pale orange powder, yield: 42%, mp: 232–235 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.75 (d, J = 8.4 Hz, 1H); 7.82–7.88 (m, 1H); 8.03–8.15 (m, 2H); 8.37 (d, J = 2.1 Hz, 1H); 8.45 (s, 1H); 13.67 (s, 1H). MS (ESI$^+$) m/z 307.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_7Cl_2N_3O_2$: C, 50.67; H, 2.29; N, 13.64. Found: C, 50.82; H, 2.28; N, 13.60.

4.1.1.20. 2-(3,5-Dichlorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3t). Pale orange powder, yield: 12%, mp: 290–292 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.77–7.82 (m, 2H); 8.14 (dd, J = 9.0, 2.1 Hz, 1H); 8.20 (d, J = 2.1 Hz, 2H); 8.49 (d, J = 2.1 Hz, 1H); 13.77 (s, 1H). MS (ESI$^+$) m/z 307.0 (M+H)$^+$. Anal. Calcd for $C_{13}H_7Cl_2N_3O_2$: C, 50.67; H, 2.29; N, 13.64. Found: C, 50.53; H, 2.26; N, 13.57.

4.1.1.21. 2-(2-Bromo-5-fluorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3u). Brown powder, mp: yield: 66%, mp: 218–220 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.43 (dd, J = 8.4, 3.0 Hz, 1H); 7.70–7.92 (m, 3H); 8.18 (d, J = 9.0 Hz, 1H); 8.60 (s, 1H); 13.55 (s, 1H). MS (ESI$^+$) m/z 336.0 (M+H)$^+$. Anal. Calcd for $C_{13}H_7BrFN_3O_2$: C, 46.45; H, 2.10; N, 12.50. Found: C, 46.53; H, 2.11; N, 12.55.

4.1.2. General procedure for the preparation of the 2-phenyl-1*H*-benzo[*d*]imidazol-5-amine derivatives 4a–4u

Method A: A suspension of **3** (5.0 mmol, R = CH_3, OCH_3, OH, CH_2CH_3, CF_3) and 10% Pd/C (0.13 g) in methanol (30 mL) was hydrogenated under normal pressure for 5 h at room temperature. Filtration and evaporation gave corresponding compound **4**.

Method B: Compound **3** (5.0 mmol, R = F, Cl, Br) and iron (1.1 g, 20 mmol) were suspended in aqueous ethanol (120 mL, 70% v/v) containing acetic acid (2 mL, 30 mmol) and heated at reflux for 2 h. The reaction mixture was cooled to room temperature. Filtration and evaporation gave corresponding compound **4**.

4.1.2.1. 2-Phenyl-1*H*-benzo[*d*]imidazol-5-amine (4a). Pink crystal, yield: 99%, mp: 292–293 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 3.17 (s, 2H); 6.54 (d, J = 8.5 Hz, 1H); 6.69 (s, 1H); 7.28 (d, J = 8.5 Hz, 1H); 7.41 (t, J = 7.0 Hz, 1H); 7.50 (t, J = 7.6 Hz, 2H); 8.07 (d, J = 7.8 Hz, 2H). MS (ESI$^+$) m/z 210.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.48; H, 5.26; N, 20.14.

4.1.2.2. 2-*o*-Tolyl-1*H*-benzo[*d*]imidazol-5-amine (4b). Brown powder, yield: 64.28%, mp: 63–64 °C. ^{1}H NMR (300 MHz; $CDCl_3$): 2.45 (s, 3H); 3.44 (s, 2H); 6.54 (t, J = 8.5 Hz, 1H); 7.08–7.46 (m, 6H). MS (ESI$^+$) m/z 224.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.52; H, 5.91; N, 18.77.

4.1.2.3. 2-*m*-Tolyl-1*H*-benzo[*d*]imidazol-5-amine (4c). Yellow powder, yield: 82.33%, mp: 231–233 °C. ^{1}H NMR (300 MHz; $CDCl_3$): 2.36 (s, 3H); 6.69 (dd, J = 8.7, 2.1 Hz, 1H); 6.85 (d, J = 1.8 Hz, 1H); 7.22 (d, J = 7.8 Hz, 1H); 7.32 (t, J = 7.5 Hz, 1H); 7.48 (d, J = 8.4 Hz, 1H); 7.79 (d, J = 7.8 Hz, 1H); 7.90 (s, 1H). MS (ESI$^+$) m/z 224.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.38; H, 5.84; N, 18.86.

4.1.2.4. 2-*p*-Tolyl-1*H*-benzo[*d*]imidazol-5-amine (4d). Orange powder, yield: 89.4%, mp: 112–114 °C. ^{1}H NMR (300 MHz; $CDCl_3$): 2.40 (s, 3H); 6.67 (dd, J = 8.7, 2.1 Hz, 1H); 6.84 (s, 1H); 7.88 (t, J = 1.8 Hz, 2H); 7.27 (s, 1H); 7.46 (d, J = 8.5 Hz, 1H); 7.88 (t, J = 1.8 Hz, 2H). MS (ESI$^+$) m/z 224.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.05; H, 5.91; N, 18.79.

4.1.2.5. 2-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazol-5-amine (4e). Brown powder, yield: 97%, mp: 193–194 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 3.99 (s, 3H); 6.54 (dd, J = 8.5, 1.6 Hz, 1H); 6.75 (s, 1H); 7.06 (t, J = 7.5 Hz, 1H); 7.18 (d, J = 8.3 Hz, 1H); 7.28 (d, J = 8.5 Hz, 1H); 7.37–7.42 (m, 1H); 8.24 (d, J = 7.7 Hz, 1H). MS (ESI$^+$) m/z 240.1 (M+H)$^+$. Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.46; H, 5.50; N, 17.51.

4.1.2.6. 2-(5-Amino-1*H*-benzo[*d*]imidazol-2-yl)phenol (4f). Yellow powder, yield: 46%, mp: 250–251 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 6.61 (d, J = 8.3 Hz, 1H); 6.74 (s, 1H); 6.97 (t, J = 8.4 Hz, 2H); 7.28–7.36 (m, 2H); 7.93 (d, J = 7.7 Hz, 1H); 12.63 (s, 1H); 13.22 (s, 1H). MS (ESI$^+$) m/z 226.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.16; H, 4.95; N, 18.72.

4.1.2.7. 2-(4-Ethylphenyl)-1*H*-benzo[*d*]imidazol-5-amine (4g). Orange powder, yield: 71%, mp: 102–104 °C. ^{1}H NMR (300 MHz; $CDCl_3$): 1.26 (t, J = 7.5 Hz, 3H); 2.67–2.71 (m, 2H); 5.30 (d, J = 0.5 Hz, 1H); 6.67 (dd, J = 8.5, 2.0 Hz, 1H); 6.84 (s, 1H); 7.28 (s, 1H); 7.45 (d, J = 8.0 Hz, 1H); 7.92 (d, J = 8.0 Hz, 2H). MS (ESI$^+$) m/z 238.1 (M+H)$^+$. Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 80.18; H, 6.33; N, 17.66.

4.1.2.8. 2-(2-Fluorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4h). White powder, yield: 61.9%, mp: 214–215 °C. ^{1}H NMR (300 MHz; $CDCl_3$): 6.72 (dd, J = 8.4, 2.1 Hz, 1H); 6.88 (s, 1H); 7.16–7.23 (m, 1H); 7.30–7.43 (m, 2H); 7.51 (d, J = 6.6 Hz, 1H); 8.46 (dd, J = 7.8, 1.8 Hz, 1H). MS (ESI$^+$) m/z 228.1 (M+H)$^+$. Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.56; H, 4.43; N, 18.45.

4.1.2.9. 2-(3-Fluorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4i). Pale orange powder, yield: 76%, mp: 245–246 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 4.98 (s, 2H); 6.54 (d, J = 8.4 Hz, 1H); 6.67

(s, 1H); 7.19–7.30 (m, 2H); 7.49–7.56 (m, 1H); 7.81–7.91 (m, 2H); 12.32 (s, 1H). MS (ESI^+) *m/z* 228.1 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.89; H, 4.46; N, 18.44.

4.1.2.10. 2-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4j). Orange crystal, yield: 73.86%, mp: 68–69 °C. ^1H NMR (300 MHz; $CDCl_3$): 3.50 (s, 2H); 6.66 (d, *J* = 8.4 Hz, 1H); 6.80 (s, 1H); 7.06 (t, *J* = 8.4 Hz, 2H); 7.42 (d, *J* = 8.4 Hz, 1H); 9.97 (m, 2H). MS (ESI^+) *m/z* 228.1 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.93; H, 4.41; N, 18.55.

4.1.2.11. 2-(2-Chlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4k). Brown powder, yield: 76.58%, mp: 87–89 °C. ^1H NMR (500 MHz; $CDCl_3$): 6.73 (dd, *J* = 8.0, 2.0 Hz, 1H); 6.89 (s, 1H); 7.33–7.41 (m, 2H); 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H); 7.52 (d, *J* = 8.0 Hz, 1H); 8.39 (dd, *J* = 7.5, 1.5 Hz, 1H). MS (ESI^+) *m/z* 244.1 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.25; H, 4.16; N, 17.26.

4.1.2.12. 2-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4l). Orange powder, yield: 38%, mp: 72–74 °C. ^1H NMR (300 MHz; $CDCl_3$): 6.69 (dd, *J* = 8.7, 2.1 Hz, 1H); 6.82 (d, *J* = 1.8 Hz, 1H); 7.33–7.35 (m, 2H); 7.47 (d, *J* = 8.4 Hz, 1H); 7.84–7.88 (m, 1H); 7.97–7.99 (m, 1H). MS (ESI^+) *m/z* 244.1 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 63.88; H, 4.17; N, 17.29.

4.1.2.13. 2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4m). Brown powder, yield: 57%, mp: 88–90 °C. ^1H NMR (300 MHz; $CDCl_3$): 2.17 (s, 2H); 6.63 (dd, *J* = 8.7, 2.1 Hz, 1H); 6.73 (d, *J* = 2.1 Hz, 1H); 7.31 (dd, *J* = 6.9, 2.4 Hz, 2H); 7.37 (d, *J* = 8.7 Hz, 1H); 8.85 (dd; *J* = 5.4, 1.8 Hz, 2H). MS (ESI^+) *m/z* 244.2 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.23; H, 4.12; N, 17.28.

4.1.2.14. 2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4n). Orange powder, yield: 64.45%, mp: 104–106 °C. ^1H NMR (300 MHz; DMSO-d_6): 6.54 (d, *J* = 8.4 Hz, 1H); 6.70 (s, 1H); 7.25 (d, *J* = 8.4 Hz, 1H); 7.64 (d, *J* = 8.4 Hz, 2H); 8.06 (d, *J* = 8.4 Hz, 2H). MS (ESI^+) *m/z* 288.0 $(M+H)^+$. Anal. Calcd for $C_{13}H_{10}BrN_3$: C, 54.19; H, 3.50; N, 14.58. Found: C, 54.34; H, 3.51; N, 14.62.

4.1.2.15. 2-(2-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-5-amine (4o). Brown powder, yield: 93%, mp: 153–155 °C. ^1H NMR (300 MHz; DMSO-d_6): 5.12 (s, 2H); 6.50 (d, *J* = 7.4 Hz, 1H); 6.80 (s, 1H); 7.45 (d, *J* = 8.4 Hz, 1H); 7.61–7.66 (m, 2H); 8.54–8.71 (m, 2H). MS (ESI^+) *m/z* 278.2 $(M+H)^+$. Anal. Calcd for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.64; N, 15.16. Found: C, 60.58; H, 3.69; N, 15.20.

4.1.2.16. 2-(3-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-5-amine (4p). Brown crystal, yield: 76%, mp: 93–95 °C. ^1H NMR (300 MHz; DMSO-d_6): 5.02 (s, 2H); 6.58 (d, *J* = 8.4 Hz, 1H); 6.70 (s, 1H); 7.33 (d, *J* = 8.3 Hz, 1H); 7.71–7.76 (m, 2H); 8.35–8.41 (m, 2H). MS (ESI^+) *m/z* 278.1 $(M+H)^+$. Anal. Calcd for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.64; N, 15.16. Found: C, 60.47; H, 3.61; N, 15.22.

4.1.2.17. 2-(4-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-5-amine (4q). White powder, yield: 82%, mp: 208–209 °C. ^1H NMR (300 MHz; DMSO-d_6): 5.09 (s, 2H); 6.57 (dd, *J* = 8.5, 1.6 Hz, 1H); 6.67 (s, 1H); 7.35(d, *J* = 8.5 Hz, 1H); 7.86 (d, *J* = 8.1 Hz, 2H); 8.26 (d, *J* = 8.1 Hz, 2H); 12.51 (s, 1H). MS (ESI^+) *m/z* 278.1 $(M+H)^+$. Anal. Calcd for $C_{14}H_{10}F_3N_3$: C, 60.65; H, 3.64; N, 15.16. Found: C, 60.83; H, 3.67; N, 15.13.

4.1.2.18. 2-(2,6-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4r). Brown crystal, yield: 64.25%, mp: 137–139 °C. ^1H NMR (300 MHz; DMSO-d_6): 6.56 (dd, *J* = 8.7, 2.1 Hz, 1H); 6.67 (s, 1H); 7.28 (d, *J* = 8.4 Hz, 1H); 7.51–7.63 (m, 3H). MS (ESI^+) *m/z* 278.0 $(M+H)^+$. Anal. Calcd for $C_{13}H_9Cl_2N_3$: C, 56.14; H, 3.26; N, 15.11. Found: C, 56.28; H, 3.23; N, 15.15.

4.1.2.19. 2-(3,4-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4s). Orange crystal, yield: 71%, mp: 100–102 °C. ^1H NMR (300 MHz; DMSO-d_6): 6.57 (d, *J* = 8.5 Hz, 1H); 6.68 (s, 1H); 7.31 (d, *J* = 8.5 Hz, 1H); 7.77 (d, *J* = 8.4 Hz, 1H); 8.03 (d, *J* = 8.4 Hz, 1H); 8.27 (s, 1H). MS (ESI^+) *m/z* 278.1 $(M+H)^+$. Anal. Calcd for $C_{13}H_9Cl_2N_3$: C, 56.14; H, 3.26; N, 15.11. Found: C, 56.32; H, 3.24; N, 15.15.

4.1.2.20. 2-(3,5-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4t). Brown powder, yield = 51%, mp: 241–243 °C. ^1H NMR (300 MHz; DMSO-d_6): 6.57 (d, *J* = 8.4 Hz, 1H); 6.60 (s, 1H); 7.30 (d, *J* = 8.4 Hz, 1H); 7.62 (s, 1H); 8.06 (s, 2H); 12.50 (s, 1H). MS (ESI^+) *m/z* 278.0 $(M+H)^+$. Anal. Calcd for $C_{13}H_9Cl_2N_3$: C, 56.14; H, 3.26; N, 15.11. Found: C, 56.30; H, 3.29; N, 15.08.

4.1.2.21. 2-(2-Bromo-5-fluorophenyl)-1*H*-benzo[*d*]imidazol-5-amine (4u). Yellow powder, yield: 92%, mp: 96–97 °C. ^1H NMR (300 MHz; $CDCl_3$): 6.74 (dd, *J* = 8.4, 2.1 Hz, 1H); 6.86 (d, *J* = 4.5 Hz, 1H); 7.01 (dd, *J* = 8.7, 3.0 Hz, 1H); 7.54–7.64 (m, 2H); 8.08 (dd, *J* = 9.9, 3.3 Hz, 1H). MS (ESI^+) *m/z* 306.0 $(M+H)^+$. Anal. Calcd for $C_{13}H_9FBrN_3$: C, 51.00; H, 2.96; N, 13.73. Found: C, 51.15; H, 2.99; N, 13.70.

4.1.3. Synthesis of 4-chloroquinazoline (6)

A suspension of quinazolin-4-ol (**5**) (2 g) in $POCl_3$ (30 mL) was heated at 100 °C for 4 h. After cooling, the mixture was concentrated under reduced pressure and the ice was added to the residue. The pH was adjusted to 6 with ammonia to allow precipitation. The filter cake was washed with water and dried to give 4-chloroquinazoline (**6**). White powder, yield: 92%, mp: 93–94 °C. ^1H NMR (300 MHz; $CDCl_3$): 7.69 (t, *J* = 7.5 Hz, 1H); 7.90–8.04 (m, 2H); 8.22 (d, *J* = 8.3 Hz, 1H); 8.99 (s, 1H). MS (ESI^+) *m/z* 165.0 $(M+H)^+$. Anal. Calcd for $C_8H_5ClN_2$: C, 53.38; H, 3.06; N, 17.02. Found: C, 53.54; H, 3.02; N, 17.08.

4.1.4. General procedure for the preparation of the quinolin-4-amine derivatives 7a–7u

A mixture of 4-chloroquinazoline (**6**, 5 mmol) and appropriate substituted anilines (**4a**–**4u**, 6 mmol) in isopropanol (40 mL) was stirred at reflux for 5 h. The reaction mixture was concentrated under reduced pressure and the solid residue was purified by column chromatography on silica gel, eluting with CH_2Cl_2/CH_3OH (10/1) to furnish title compound **7a**–**7u**.

4.1.4.1. *N*-(2-Phenyl-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7a). Yellow powder, yield: 92%, mp: 267–269 °C. ^1H NMR (300 MHz; DMSO-d_6): 7.55–7.65 (m, 4H); 7.73 (d, *J* = 8.7 Hz, 1H); 7.83 (t, *J* = 8.1 Hz, 1H); 7.94 (d, *J* = 7.8 Hz, 1H); 8.06 (t, *J* = 7.5 Hz, 1H); 8.13 (d, *J* = 1.8 Hz, 1H); 8.26 (dd, *J* = 7.8, 1.5 Hz, 2H); 8.86–8.90 (m, 2H); 11.50 (s, 1H). MS (ESI^+) *m/z* 338.1 $(M+H)^+$. Anal. Calcd for $C_{21}H_{15}N_5$: C, 74.76; H, 4.48; N, 20.76. Found: C, 74.62; H, 4.51; N, 20.80.

4.1.4.2. *N*-(2-*o*-Tolyl-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7b). Yellow powder, yield: 95%, mp: 303–304 °C. ^1H NMR (300 MHz; DMSO-d_6): 2.62 (s, 3H); 7.39–7.50 (m, 3H); 7.64 (dd, *J* = 8.7, 1.8 Hz, 1H); 7.74–7.86 (m, 3H); 7.92 (d, *J* = 8.4 Hz, 1H); 8.06 (d, *J* = 7.2 Hz, 1H); 8.15 (s, 1H); 8.84–8.87 (m, 2H); 11.40 (s, 1H). MS (ESI^+) *m/z* 352.2 $(M+H)^+$. Anal. Calcd for

$C_{22}H_{17}N_5$: C, 75.19; H, 4.88; N, 19.93. Found: C, 75.42; H, 4.85; N, 19.85.

4.1.4.3. *N*-(2-*m*-Tolyl-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7c). Yellow powder, yield: 82%, mp: 285–287 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 2.45 (s, 3H); 7.42 (d, J = 7.4 Hz, 1H); 7.51 (t, J = 7.6 Hz, 1H); 7.67 (d, J = 8.6 Hz, 1H); 7.77 (d, J = 8.6 Hz, 1H); 7.86 (t, J = 7.6 Hz, 1H); 7.97 (d, J = 8.1 Hz, 1H); 8.07–8.14 (m, 4H); 8.91 (d, J = 8.5 Hz, 2H); 11.59 (s, 1H). MS (ESI$^+$) m/z 352.3 (M+H)$^+$. Anal. Calcd for $C_{22}H_{17}N_5$: C, 75.19; H, 4.88; N, 19.93. Found: C, 75.35; H, 4.92; N, 20.01.

4.1.4.4. *N*-(2-*p*-Tolyl-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7d). Yellow powder, yield: 89%, mp: 238–240 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 2.42 (s, 3H); 7.43 (d, J = 8.0 Hz, 2H); 7.64–7.75 (m, 2H); 7.84 (t, J = 7.6 Hz, 1H); 7.94 (d, J = 8.2 Hz, 1H); 8.04–8.18 (m, 4H); 8.72–8.98 (m, 2H); 11.39 (s, 1H). MS (ESI$^+$) m/z 352.1 (M+H)$^+$. Anal. Calcd for $C_{22}H_{17}N_5$: C, 75.19; H, 4.88; N, 19.93. Found: C, 75.02; H, 4.91; N, 19.98.

4.1.4.5. *N*-(2-(2-Methoxyphenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7e). Brown powder, yield: 71%, mp: 349–350 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 4.07 (s, 3H); 7.20 (t, J = 7.4 Hz, 1H); 7.33 (d, J = 8.3 Hz, 1H); 7.57–7.68 (m, 2H); 7.77–7.83 (m, 2H); 7.91 (d, J = 7.8 Hz, 1H); 8.00–8.06 (m, 1H); 8.27 (s, 1H); 8.33 (d, J = 7.5 Hz, 1H); 8.81 (s, 2H); 11.10 (s, 1H). MS (ESI$^+$) m/z 368.0 (M+H)$^+$. Anal. Calcd for $C_{22}H_{17}N_5O$: C, 71.92; H, 4.66; N, 19.06. Found: C, 72.12; H, 4.63; N, 19.14.

4.1.4.6. 2-(6-(Quinazolin-4-ylamino)-1*H*-benzo[*d*]imidazol-2-yl)phenol (7f). Yellow powder, mp: yield: 53%, mp: 341–343 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.01–7.11 (m, 2H); 7.42 (t, J = 7.4 Hz, 1H); 7.65 (d, J = 8.6 Hz, 1H); 7.76–7.86 (m, 2H); 7.94 (d, J = 8.2 Hz, 1H); 8.07 (t, J = 7.6 Hz, 1H); 8.14 (d, J = 7.8 Hz, 2H); 8.88 (d, J = 8.3 Hz, 2H); 11.53 (s, 1H). MS (ESI$^+$) m/z 354.3 (M+H)$^+$. Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.38; H, 4.28; N, 19.82. Found: C, 71.25; H, 4.32; N, 19.88.

4.1.4.7. *N*-(2-(4-Ethylphenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7g). Yellow powder, yield: 68%, mp: 307–310 °C. ^{1}H NMR (500 MHz; DMSO-d_6): 1.23 (t, J = 7.6 Hz, 3H); 2.69 (q, J = 7.3 Hz, 2H); 7.44 (d, J = 8.2 Hz, 2H); 7.63 (dd, J = 8.6, 1.7 Hz, 1H); 7.72 (d, J = 8.7 Hz, 1H); 7.81 (t. J = 7.3 Hz, 1H); 7.92 (d, J = 8.4 Hz, 1H); 8.04 (t, J = 7.4 Hz, 1H); 8.17 (d, J = 8.3 Hz, 3H); 8.84 (d, J = 6.9 Hz, 2H); 11.33 (s, 1H). MS (ESI$^+$) m/z 366.2 (M+H)$^+$. Anal. Calcd for $C_{23}H_{19}N_5$: C, 75.59; H, 5.24; N, 19.16. Found: C, 75.64; H, 5.21; N, 19.20.

4.1.4.8. *N*-(2-(2-Fluorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7h). Yellow powder, yield: 64%, mp: 301–304 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.39–7.50 (m, 2H); 7.60 (d, J = 8.5 Hz, 2H); 7.75 (d, J = 8.6 Hz, 1H); 7.84 (t, J = 7.6 Hz, 1H); 7.97 (d, J = 8.2 Hz, 1H); 8.05–8.09 (m, 2H); 8.26 (t, J = 7.6 Hz, 1H); 8.88 (s, 1H); 8.95 (d, J = 8.3 Hz, 1H); 11.73 (s, 1H). MS (ESI$^+$) m/z 356.1 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}FN_5$: C, 70.98; H, 3.97; N, 19.71. Found: C, 70.76; H, 3.95; N, 19.75.

4.1.4.9. *N*-(2-(3-Fluorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7i). Green powder, yield: 77%, mp: 297–299 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.35 (t, J = 8.0 Hz, 1H); 7.57–7.65 (m, 2H); 7.70 (d, J = 8.6 Hz, 1H); 7.81 (t, J = 7.9 Hz, 1H); 7.92 (d, J = 8.3 Hz, 1H); 8.02–8.10 (m, 4H); 8.84–8.88 (m, 2H); 11.39 (s, 1H). MS (ESI$^+$) m/z 356.1 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}FN_5$: C, 70.98; H, 3.97; N, 19.71. Found: C, 70.82; H, 4.00; N, 19.63.

4.1.4.10. *N*-(2-(4-Fluorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7j). Yellow powder, yield: 65%, mp: 297–299 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.42 (t, J = 8.8 Hz, 2H); 7.56 (dd, J = 8.7, 1.7 Hz, 1H); 7.67 (d, J = 8.6 Hz, 1H); 7.77 (t, J = 7.9 Hz, 1H); 7.86 (d, J = 8.1 Hz, 1H); 8.00 (t, J = 7.3 Hz, 1H); 8.12 (s, 1H); 8.23–8.28 (m, 2H); 8.76–8.78 (m, 2H); 10.96 (s, 1H). MS (ESI$^+$) m/z 356.1 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}FN_5$: C, 70.98; H, 3.97; N, 19.71. Found: C, 80.26; H, 3.93; N, 19.78.

4.1.4.11. *N*-(2-(2-Chlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7k). Yellow crystal, yield: 44%, mp: 289–290 °C. ^{1}H NMR (500 MHz; DMSO-d_6): 7.52–7.61 (m, 3H); 7.67 (dd, J = 7.8, 1.9 Hz, 1H); 7.75 (d, J = 8.6 Hz, 1H); 7.85 (t, J = 7.6 Hz, 1H); 7.92–7.96 (m, 2H); 8.08 (t, J = 7.7 Hz, 2H); 8.88–8.92 (m, 2H); 11.65 (s, 1H). MS (ESI$^+$) m/z 372.1 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}ClN_5$: C, 67.83; H, 3.80; N, 18.84. Found: C, 67.98; H, 3.81; N, 18.87.

4.1.4.12. *N*-(2-(3-Chlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7l). Yellow powder, yield: 79%, mp: 327–329 °C. ^{1}H NMR (500 MHz; DMSO-d_6): 7.59–7.62 (m, 3H); 7.73 (d, J = 8.6 Hz, 1H); 7.85 (t, J = 7.8 Hz, 1H); 7.97 (d, J = 8.2 Hz, 1H); 8.06–8.11 (m, 2H); 8.21–8.23 (m, 1H); 8.31 (s, 1H); 8.89–8.96 (m, 2H); 11.75 (s, 1H). MS (ESI$^+$) m/z 372.1 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}ClN_5$: C, 67.83; H, 3.80; N, 18.84. Found: C, 68.02; H, 3.83; N, 18.92.

4.1.4.13. *N*-(2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7m). Yellow powder, yield: 59%, mp: 337–339 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.59–7.74 (m, 4H); 7.84 (t, J = 7.2 Hz, 1H); 7.96 (d, J = 8.3 Hz, 1H); 8.07 (t, J = 7.2 Hz, 2H); 8.27 (d, J = 8.5 Hz, 2H); 8.88–8.94 (m, 2H); 11.6 9(s, 1H). MS (ESI$^+$) m/z 372.2 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}ClN_5$: C, 67.83; H, 3.80; N, 18.84. Found: C, 67.65; H, 3.78; N, 18.78.

4.1.4.14. *N*-(2-(4-Bromophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7n). Yellow powder, yield: 78%, mp: 353–355 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.59 (dd, J = 8.7, 1.8 Hz, 1H); 7.70 (d, J = 8.7 Hz, 1H); 7.77–7.85 (m, 3H); 7.95(d, J = 8.7 Hz, 1H); 8.06 (t, J = 7.5 Hz, 2H); 8.18 (d, J = 8.4 Hz, 2H); 8.84–8.92 (m, 2H); 11.49 (s, 1H). MS (ESI$^+$) m/z 416.0 (M+H)$^+$. Anal. Calcd for $C_{21}H_{14}BrN_5$: C, 60.59; H, 3.39; N, 16.82. Found: C, 60.76; H, 3.41; N, 16.86.

4.1.4.15. *N*-(2-(2-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7o). Brown powder, yield: 54%, mp: 309–311 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.59 (d, J = 8.5 Hz, 1H); 7.71–7.85 (m, 5H); 7.94–8.09 (m, 4H); 8.89 (s, 1H); 8.91 (d, J = 8.2 Hz, 1H); 11.87 (s, 1H). MS (ESI$^+$) m/z 406.1 (M+H)$^+$. Anal. Calcd for $C_{22}H_{14}F_3N_5$: C, 65.18; H, 3.48; F, 14.06; N, 17.28. Found: C, 65.03; H, 3.50; N, 14.02.

4.1.4.16. *N*-(2-(3-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7p). Yellow powder, yield: 55%, mp: 343–345 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.60 (dd, J = 8.6, 1.3 Hz, 1H); 7.75 (d, J = 8.6 Hz, 1H); 7.80–7.90 (m, 3H); 7.97 (d, J = 8.3 Hz, 1H); 8.08–8.12 (m, 2H); 8.54–8.59 (m, 2H); 8.90–8.94 (m, 2H); 11.75 (s, 1H). MS (ESI$^+$) m/z 406.1 (M+H)$^+$. Anal. Calcd for $C_{22}H_{14}F_3N_5$: C, 65.18; H, 3.48; F, 14.06; N, 17.28. Found: C, 65.35; H, 3.51; N, 14.11.

4.1.4.17. *N*-(2-(4-(Trifluoromethyl)phenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7q). Yellow powder, yield: 64%, mp: 334–337 °C. ^{1}H NMR (300 MHz; DMSO-d_6): 7.60 (d, J = 8.0 Hz, 1H); 7.72 (d, J = 8.5 Hz, 1H); 7.82 (d, J = 7.1 Hz, 1H); 7.90–7.97 (m, 3H); 8.03–8.10 (m, 2H); 8.44 (d, J = 7.6 Hz, 2H);

8.87 (s, 1H); 8.94 (d, J = 7.9 Hz, 2H); 11.64 (s, 1H). MS (ESI^+) m/z 406.1 $(M+H)^+$. Anal. Calcd for $C_{22}H_{14}F_3N_5$: C, 65.18; H, 3.48; F, 14.06; N, 17.28. Found: C, 65.42; H, 3.46; N, 14.10.

4.1.4.18. *N*-(2-(2,6-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7r). Yellow powder, yield: 75%, mp: 336–339 °C. ^1H NMR (300 MHz; DMSO-d_6): 7.55–7.75 (m, 5H); 7.85 (t, J = 7.7 Hz, 1H); 7.98–8.12 (m, 3H); 8.89 (s, 1H); 9.01 (d, J = 8.3 Hz, 1H); 11.93 (s, 1H). MS (ESI^+) m/z 406.1 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}Cl_2N_5$: C, 62.08; H, 3.23; N, 17.24. Found: C, 62.31; H, 3.24; N, 17.29.

4.1.4.19. *N*-(2-(3,4-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7s). Brown powder, yield: 81%, mp: 327–329 °C. ^1H NMR (300 MHz; DMSO-d_6): 7.58 (dd, J = 8.7, 1.5 Hz, 1H); 7.70 (d, J = 8.6 Hz, 1H); 7.80–7.84 (m, 2H); 7.95 (d, J = 8.2 Hz, 1H); 8.03–8.06 (m, 2H); 8.20 (dd, J = 8.4, 1.6 Hz, 1H); 8.45–8.46 (d, J = 1.6 Hz, 2H); 8.86–8.93 (m, 2H); 11.60 (s, 1H). MS (ESI^+) m/z 406.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}Cl_2N_5$: C, 62.08; H, 3.23; N, 17.24. Found: C, 61.85; H, 3.25; N, 17.27.

4.1.4.20. *N*-(2-(3,5-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7t). Brown powder, yield: 65%, mp: 315–317 °C. ^1H NMR (300 MHz; DMSO-d_6): 7.66–7.92 (m, 4H); 7.95–8.15 (m, 2H); 8.18–8.31 (m, 3H); 8.85 (d, J = 8.2 Hz, 1H); 8.94 (d, J = 8.4 Hz, 1H); 11.88 (s, 1H). MS (ESI^+) m/z 406.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}Cl_2N_5$: C, 62.08; H, 3.23; N, 17.24. Found: C, 62.28; H, 3.21; N, 17.20.

4.1.4.21. *N*-(2-(2-Bromo-5-fluorophenyl)-1*H*-benzo[*d*]imidazol-6-yl)quinazolin-4-amine (7u). Yellow powder, yield: 73%, mp: 328–331 °C. ^1H NMR (300 MHz; DMSO-d_6): 7.39 (dd, J = 8.5, 2.8 Hz, 1H); 7.59 (d, J = 8.8 Hz, 1H); 7.70–7.76 (m, 2H); 7.81–7.90 (m, 2H); 7.98 (d, J = 8.1 Hz, 1H); 8.06–8.11 (m, 2H); 8.89 (s, 1H); 8.99 (d, J = 8.2 Hz, 1H); 11.84 (s, 1H). MS (ESI^+) m/z 434.0 $(M+H)^+$. Anal. Calcd for $C_{21}H_{13}BrFN_5$: C, 58.08; H, 3.02; N, 16.13. Found: C, 58.32; H, 3.04; N, 16.18.

4.2. Cell proliferative assay

The antiproliferative activities of the prepared *N*-(2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)quinazolin-4-amine derivatives against Hep-G2 and MCF-7 cells were evaluated by MTT assay.[25] Briefly, target tumor cells were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2×10^4 cells mL^{-1} with the complete medium, 100 μL of the obtained cell suspension was added to each well of 96-well culture plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before the antiproliferative assessments. Tested samples at pre-set concentrations were added to 6 wells. After 48 h exposure period, 40 μL of PBS containing 2.5 mg mL^{-1} of MTT was added to each well. Four hours later, 100 μL extraction solution (10% SDS-5% isobutyl alcohol-0.010 M HCl) was added. After an overnight incubation at 37 °C, the optical density was measured at a wavelength of 570 nm on an ELISA microplate reader.

4.3. In vitro kinase assay

In vitro kinase inhibitory ability was determined using HTScan VEGF Receptor 2 Kinase Assay Kit and HTScan MET Kinase Assay Kit (purchased from Cell Signaling Technology, Inc.) by colorimetric ELISA assay according to the manufacturer's instructions.[26] Briefly, reaction cocktail containing recombinant human VEGFR-2 or Met kinase was incubated with various concentrations of tested compounds or DMSO (0.1%) for 5 min at room temperature, and then ATP/substrate peptide cocktail was added to the pre-incubated reaction cocktail. After incubation at room temperature for 30 min, the reaction was stopped and transferred to a 96-well streptavidin-coated plate, and incubated for 1 h at room temperature. Primary antibody [phosphorylated tyrosine monoclonal antibody [(pTyr-100), 1:1000 in PBS/T with 1% bovine serum albumin (BSA)] was added into per well until the wells were washed thrice with PBS/T. After incubated at room temperature for 1 h, phosphorylation of the substrate was monitored with HRP-labeled anti-mouse IgG antibody (1:500 in PBS/T with 1% BSA), followed by a chromogenic reaction. Finally, the kinase assay was detected at 450 nm with microplate reader. The reaction processed with only DMSO (0.1%) served as a vehicle control. The results were expressed as percent kinase activity of the vehicle control, and IC_{50} was defined as the compound concentration that resulted in 50% inhibition of enzyme activity. The kinase assay was performed thrice independently.

4.4. Molecular docking

Molecular docking of compound **7j** into the three dimensional X-ray structure of c-Met (PDB code: 3CD8) and VEGFR-2 (PDB code: 2QU5) was carried out using the Discovery Studio (version 3.1) as implemented through the graphical user interface Discovery Studio CDOCKER protocol.

The three-dimensional structure of the compound **7j** was constructed using ChemBio 3D Ultra 11.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2008)], then it was energetically minimized by using MMFF94 with 5000 iterations and minimum RMS gradient of 0.10. The crystal structures of VEGFR-2 kinase were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.-do). All bound waters and ligands were eliminated from the protein and the polar hydrogen was added. The whole 3CD8 or 2QU5 was defined as a receptor and the site sphere was selected based on ATP binding site of 3CD8 or 2QU5. Compound **7j** were placed during the molecular docking procedure. Types of interactions of the docked protein with ligand were analyzed after the end of molecular docking.

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