

# Synthesis, Molecular Docking Study, and Anticancer Activity of 7-Azaindole-1,2,3-triazol Bearing *N*-Benzamide Derivatives

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**Abstract**—In this study, a novel series of 7-azaindole-1,2,3-triazole bearing *N*-benzamide derivatives **3a–3r** were synthesized and fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and MS. The prepared compounds were tested against A549 and HepG2 cell lines by using MTT assay in vitro anticancer activity. Compounds **3d**, **3l**, **3q**, and **3r** exhibited the most promising, with IC<sub>50</sub> (7.83, 7.58, 9.47, and 8.65 μM, respectively) against A549 compared with Gefitinib (IC<sub>50</sub>, 6.77 μM) and IC<sub>50</sub> (6.98, 6.69, 10.18, and 7.97 μM, respectively) against HepG2 compared with Sorafenib (IC<sub>50</sub>, 5.65 μM). Further molecular docking studies showed that compounds **3d**, **3l**, **3q**, and **3r** can bind well to protein targets 3LXY, 4AGD, and 3WZE, so these compounds have the potential to be developed into multi-targeted kinase inhibitor.

**Keywords:** 7-azaindole, 1,2,3-triazol, synthesis, molecular docking study, anticancer activity

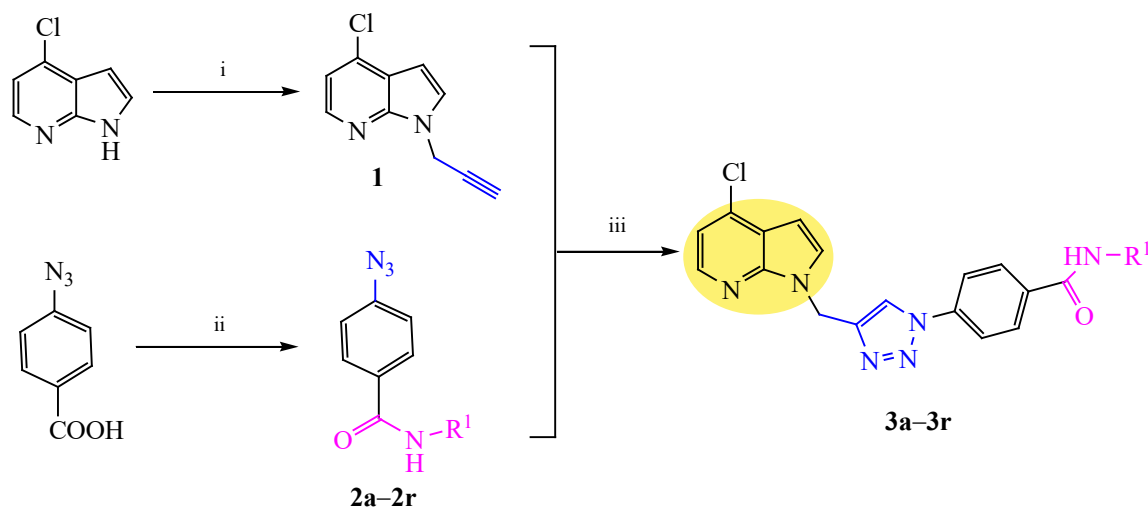
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Cancer continues to be a leading health hazard for human being due to its high morbidity and mortality rates worldwide [1]. Traditional cancer treatment methods include surgery, radiotherapy and chemotherapy, but in view of their shortcomings in treatment, researchers have been working on developing new cancer treatment methods. During this period, targeted therapy stood out in cancer treatment due to its strong specificity and low side effects [2]. Small molecule kinase inhibitors are a major category of cancer targeted drugs. With the deepening of people's understanding of genes and carcinogenic molecular mechanisms, scientists have discovered that protein kinases play a key role in the growth, proliferation, differentiation, migration, and apoptosis of tumor cells [2, 3]. It has stimulated people's enthusiasm for the research and development of small molecule kinase inhibitor drugs. However, from the perspective of current clinical treatment effect, kinase inhibitors have shown good efficacy in the initial treatment of cancer patients. With the passage of treatment time, the vast majority of cancer patients have shown obvious resistance to kinase inhibitors, such as the increase in the dosage of the drug and the decrease in the treatment effect, which seriously affects the treatment index of cancer patients. Therefore,

it is necessary to develop new small molecule kinase inhibitors to overcome shortcomings.

Designing drugs for multiple protein kinase targets is a major method to overcome the resistance of kinase inhibitors [4]. This kind of drugs is called multi-target kinase inhibitors. In recent years, molecular hybridization methods have become an important strategy for drug molecular design. Molecular hybridization refers to the combination of two or more pharmacophores with biological activity to form a single molecular structure with higher biological activity [5]. Since these pharmacophores have different mechanisms of action and different binding targets, the drug molecules obtained by combining them will play a role in multiple aspects, thereby reducing the risk of drug resistance [6].

The mechanism of action of most kinase inhibitors is to competitively bind to the ATP-binding site of the N- and C-terminal clefts in the catalytic domain of protein kinases, thereby preventing the phosphorylation of proteins [7, 8]. 7-azaindole is a common pharmacophore with a variety of pharmacological activities, such as anti-microbial, anti-cancer, anti-HIV and anti-influenza [9]. In the 7-azaindole ring, the N on the pyridine structure is the hydrogen bond acceptor and the NH on the pyrrole

**Scheme 1.** Synthesis of the target compounds **3a–3r**.

Reagents and conditions: (i) 3-bromoprop-1-yne, K<sub>2</sub>CO<sub>3</sub>, DMF, reflux at 35°C, 12 h, 80%, **1**; (ii) HATU, DIPEA, DMF, reflux at 35–50°C, 6–7 h, 58–65%, **2a–2r**; (iii) CuSO<sub>4</sub>·5H<sub>2</sub>O, sodium ascorbate, THF : H<sub>2</sub>O = 1 : 1, N<sub>2</sub>, reflux at 50°C, 9–10 h, 45–70%, **3a–3r**.

structure is the hydrogen bond acceptor and donor which will form bidentate hydrogen bonds with the hinge region of the kinase [7, 8]. This enhances the binding ability between kinase and drug molecule. Meanwhile, it's reported that more than 90 kinds of protein kinases have shown sensitivity to drugs containing 7-azaindole structure [7]. Therefore, 7-azaindole fragments are often introduced into the drug molecule as inhibitors of multiple protein kinases. Especially in the treatment of cancer, 7-azaindole has shown great advantages. Whether it is vemurafenib (BRAF kinase inhibitor) for the treatment of melanoma, or a variety of anti-cancer drugs targeting different kinase targets (such as JAK3 [10], CSF1R [11], STK [12] and ROCK1 [13]) that are currently undergoing clinical research, they are all designed based on the 7-azaindole structure.

1,2,3-Triazole is another important type of nitrogen-containing heterocyclic compound. In terms of structure, 1,2,3-triazole has the ability to form various non-covalent bindings such as hydrogen bonds,  $\pi$ - $\pi$  stacking effect, hydrophobic interaction, van der Waals force and dipole-dipole interaction and it is less toxic and has stability under physiological conditions, which induces it being abundant in pharmacological activity [6, 14–16]. The antibacterial [17], antimalarial [18], antifungal [19], antiviral [20],

antitubercular [21], anti-HIV [22], and anticancer [23] activities of 1,2,3-triazole make it play an important role in a variety of drugs. On the anticancer activity, 1,2,3-triazole works by inhibiting different enzymes such as carbonic anhydrases (CAs) [24], thymidylate synthase (TS) [25], aromatase [26], tryptophan, 2, 3-dioxygenase (TDO) [27], vascular endothelial growth factor receptor (VEGFR) [28], and epidermal growth factor receptor (EGFR) [29]. Moreover, some of theazole derivatives such as cefatrizine, carboxyamidotriazole, anastrozole, and letrozole have already been used in clinics or are under clinical evaluation for the treatment of cancers, revealing their potential as putative anticancer drugs [6, 15].

Based on the above, a series of compounds containing 7-azaindole and 1,2,3-triazole fragments were designed and synthesized. Subsequently, these compounds were tested for their anticancer activity in order to find a better anticancer structure.

## RESULTS AND DISCUSSION

**Chemistry.** In this study, the target compounds **3a–3r** were synthesized by a three-step reaction (Scheme 1). The first step is to synthesize compound **1** (4-chloro-1-(prop-

**Table 1.** The structure of compound **3a–3r**

Compound	Structure	Compound	Structure
<b>3a</b>		<b>3j</b>	
<b>3b</b>		<b>3k</b>	
<b>3c</b>		<b>3l</b>	
<b>3d</b>		<b>3m</b>	
<b>3e</b>		<b>3n</b>	
<b>3f</b>		<b>3o</b>	
<b>3g</b>		<b>3p</b>	
<b>3h</b>		<b>3q</b>	
<b>3i</b>		<b>3r</b>	

**Table 2.** In vitro anticancer activity of the target compounds **3a–3r** and the positive control drugs. Values are mean  $\pm$  SD expressed in  $\mu\text{M}$ 

Compound	IC <sub>50</sub> , $\mu\text{M}$ A549	HepG2	Compound	IC <sub>50</sub> , $\mu\text{M}$ A549	HepG2
<b>3a</b>	15.79 $\pm$ 0.11	15.06 $\pm$ 0.32	<b>3k</b>	17.79 $\pm$ 2.64	16.86 $\pm$ 1.89
<b>3b</b>	14.96 $\pm$ 1.35	13.57 $\pm$ 1.41	<b>3l</b>	7.58 $\pm$ 0.87	6.69 $\pm$ 0.69
<b>3c</b>	18.35 $\pm$ 0.76	17.09 $\pm$ 1.01	<b>3m</b>	13.14 $\pm$ 1.21	12.93 $\pm$ 1.45
<b>3d</b>	7.83 $\pm$ 0.36	6.98 $\pm$ 0.19	<b>3n</b>	15.49 $\pm$ 0.93	14.32 $\pm$ 0.52
<b>3e</b>	13.61 $\pm$ 0.49	14.88 $\pm$ 0.81	<b>3o</b>	15.99 $\pm$ 2.10	15.38 $\pm$ 1.76
<b>3f</b>	19.63 $\pm$ 2.74	18.38 $\pm$ 2.98	<b>3p</b>	11.29 $\pm$ 0.13	12.07 $\pm$ 0.84
<b>3g</b>	26.58 $\pm$ 1.54	24.37 $\pm$ 2.39	<b>3q</b>	9.47 $\pm$ 0.96	10.18 $\pm$ 0.57
<b>3h</b>	12.55 $\pm$ 0.67	12.79 $\pm$ 1.04	<b>3r</b>	8.65 $\pm$ 0.82	7.97 $\pm$ 0.43
<b>3i</b>	16.36 $\pm$ 2.43	17.89 $\pm$ 1.98	Gefitinib	6.77 $\pm$ 0.65	
<b>3j</b>	17.05 $\pm$ 1.32	16.81 $\pm$ 1.67	Sorafenib		1.65 $\pm$ 0.71

2-yn-1-yl)-1*H*-pyrrolo[2,3-*b*]pyridine) by substitution reaction. In the second step, compounds **2a–2r** were synthesized by amide condensation reaction. In the last step, the target compounds **3a–3r** were synthesized by utilizing the azide-alkyne cycloaddition reaction of appropriate precursors **1** and **2a–2r** in the presence of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /sodium ascorbate in THF :  $\text{H}_2\text{O}$  (1 : 1) mixture. The azide-alkyne cycloaddition reaction is known as the click reaction and it need to be catalyzed by Cu(I) ions. This reaction has many advantages such as good selectivity, strong stereospecificity [30], mild reaction conditions and high yield. Therefore, it is widely used in the regio- and stereo- specific synthesis of 1,4-substituted-1,2,3-triazoles which is a structure with various pharmacological activity.

Through the above reaction, we obtained a series of hybrid compounds **3a–3r** containing 7-azaindole structure and 1,2,3-triazole structure (see Table 1 for specific structure). Then the  $^1\text{H}$  NMR spectra,  $^{13}\text{C}$  NMR spectra and Mass spectra analysis test methods had been used to characterize the structures of the compounds and characterization results had confirmed the chemical structures of the target compounds **3a–3r**.

**In vitro anticancer activity.** The prepared target compounds **3a–3r** were further screened for their potential that inhibits the growth of cancer cells against lung cancer (A549) and hepatic cancer (HepG2) cell lines by MTT colorimetric assay [31]. In this study, Gefitinib and Sorafenib were used as positive control drugs for lung cancer and hepatic cancer cells, respectively. And the IC<sub>50</sub> values which are some different concentrations

of the compounds that induces 50% death of the cancer cells of the test compounds were determined from dose-response curves and the results are summarized in Table 2. And the inversely proportional relationship between the ability of the sample to inhibit cancer growth and the IC<sub>50</sub> values.

The results presented in Table 2 reveal that the synthetic series of compounds **3a–3r** have shown an obvious inhibitory effect on the growth of lung cancer cell (A549) and hepatic cancer cell (HepG2). Among these compounds, compound **3l** exhibits the strongest inhibitory effect on cancer cells A549 and HepG2, and its IC<sub>50</sub> values are 7.58  $\pm$  0.87  $\mu\text{M}$  and 6.69  $\pm$  0.69  $\mu\text{M}$ , respectively, while compound **3g** exhibits the weakest inhibitory effect, and its IC<sub>50</sub> values for the two cancer cells are 26.58  $\pm$  1.54  $\mu\text{M}$  and 24.37  $\pm$  2.39  $\mu\text{M}$ , respectively. At the same time, compared with the positive control, although the IC<sub>50</sub> values of compounds **3d** (7.83  $\pm$  0.36  $\mu\text{M}$ ; 6.98  $\pm$  0.19  $\mu\text{M}$ ), **3l**, **3q** (9.47  $\pm$  0.96  $\mu\text{M}$ ; 10.18  $\pm$  0.57  $\mu\text{M}$ ) and **3r** (8.65  $\pm$  0.82  $\mu\text{M}$ ; 7.97  $\pm$  0.43  $\mu\text{M}$ ) are larger than the positive control (IC<sub>50</sub> of Gefitinib for A549 = 6.77  $\pm$  0.65  $\mu\text{M}$ ; IC<sub>50</sub> of Sorafenib for HepG2 = 5.65  $\pm$  0.71  $\mu\text{M}$ ), their IC<sub>50</sub> values are all less than 10  $\mu\text{M}$ . Therefore, the inhibitory effects of these four compounds on cancer cells are at the same level of inhibition as the positive control, which indicates that compounds **3d**, **3l**, **3q** and **3r** have greater anti-cancer activity potential. However, the IC<sub>50</sub> values of compounds **3g** is more than 20  $\mu\text{M}$ , which suggests that there is little anticancer activity potential of compound **3g**. In addition, the IC<sub>50</sub> values of other compounds are between 10 and 20  $\mu\text{M}$ ,

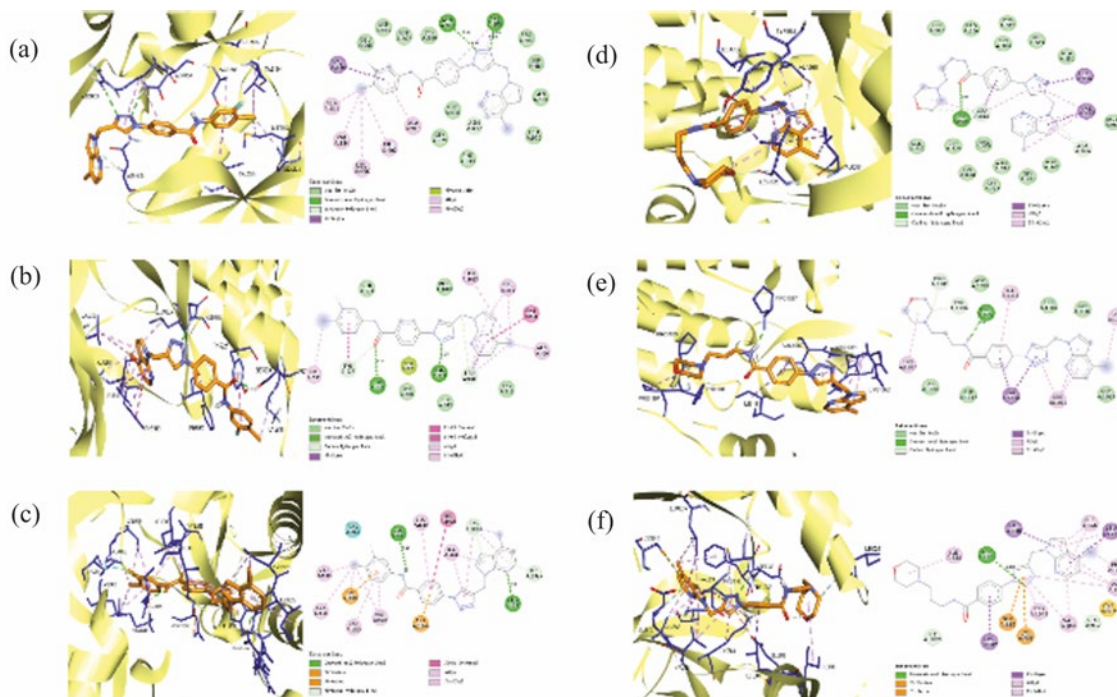
**Table 3.** The lowest binding energies of compounds **3a–3r** with different protein targets

Compound	Lowest binding energy, kcal/mol							
	4R7H	3EYG	3TJD	3LXK	4WKQ	3WZD	3WZE	4AGD
<b>3a</b>	-5.44	-5.63	-5.03	-6.38	-6.14	-6.32	-6.21	-5.40
<b>3b</b>	-6.56	-4.76	-4.32	-5.46	-6.58	-5.02	-6.41	-6.75
<b>3c</b>	-5.42	-5.79	-3.90	-5.66	-5.47	-5.78	-6.54	-6.17
<b>3d</b>	-6.24	-4.95	-3.21	-7.32	-5.78	-7.19	-6.65	-7.51
<b>3e</b>	-6.36	-5.24	-3.64	-7.03	-5.16	-6.09	-5.64	-6.73
<b>3f</b>	-4.87	-5.25	-3.41	-5.47	-5.23	-5.18	-6.27	-6.37
<b>3g</b>	-4.08	-3.84	-3.20	-5.36	-4.51	-4.18	-3.96	-4.95
<b>3h</b>	-6.19	-5.92	-4.13	-6.28	-6.50	-6.17	-6.55	-6.99
<b>3i</b>	-6.33	-5.30	-3.84	-6.14	-5.86	-6.14	-6.29	-6.53
<b>3j</b>	-6.98	-6.68	-4.07	-5.95	-6.30	-5.45	-6.26	-6.75
<b>3k</b>	-5.75	-5.11	-3.47	-5.52	-6.02	-6.82	-6.44	-5.86
<b>3l</b>	-6.22	-6.95	-3.64	-8.22	-6.85	-6.25	-7.26	-7.23
<b>3m</b>	-5.44	-4.44	-3.77	-6.27	-6.54	-6.43	-7.11	-6.40
<b>3n</b>	-6.56	-4.78	-4.90	-6.69	-6.58	-5.27	-6.14	-6.25
<b>3o</b>	-5.42	-5.03	-4.92	-6.83	-5.87	-5.58	-6.74	-6.39
<b>3p</b>	-6.24	-5.62	-3.86	-6.09	-6.98	-6.90	-6.88	-7.14
<b>3q</b>	-6.36	-4.33	-3.69	-7.07	-6.81	-6.23	-6.92	-7.05
<b>3r</b>	-4.87	-5.24	-4.12	-7.05	-7.03	-6.81	-6.71	-7.13

which reveals that they also have an inhibitory effect on cancer cells, but the inhibitory effect is worse than that of the positive control and compounds **3d**, **3l**, **3q**, and **3r**. The possible reason for the better activity of compounds **3d**, **3l**, **3q**, and **3r** is that they bind to multiple protein kinase targets in lung cancer cells A549 and hepatic cancer cells HepG2, thereby inhibiting the growth and reproduction of cancer cells.

**Molecular docking studies.** Tyrosine kinase is one of the main members of the protein kinase family. Because it can participate in the regulation of various physiological processes of cancer cells, including growth, proliferation, differentiation, metastasis and apoptosis, it is often used as a drug target for cancer treatment. In order to further investigate the possible binding modes and corresponding interaction energies between the synthesized compounds **3a–3r** and various tyrosine kinase targets in cancer cells, we docked the synthesized compounds **3a–3r** with CSF1R (PDB: 4R7H), JAK1 (PDB: 3EYG), JAK2 (PDB: 3TJD), JAK3 (PDB: 3LXK), EGFR1 [32] (PDB: 4WKQ) and VEGFR2 [33] (PDB: 3WZD, 3WZE, 4AGD) targets, respectively. The lowest binding energies between compounds and different targets were obtained, as shown in Table 3.

As we can see from the docking results, on the one hand, the synthesized series of compounds have weak binding ability against 3TJD (JAK2 target) and the lowest binding energy ranges from  $-3.20$  to  $-5.03$  kcal/mol, while the synthesized compounds have strong binding ability against 3LXK (JAK3 target), 3WZE (VEGFR2 target) and 4AGD (VEGFR2 target) and the lowest binding energy is approximately around  $-6$  and  $-7$  kcal/mol. That is to say, the synthesized series of compounds have the best selectivity for protein targets 3LXK, 3WZE, and 4AGD, and the worst selectivity for protein target 3TJD. On the other hand, among all the compounds, the lowest binding energy values of compound **3l** against protein targets 3EYG, 3LXK, 3WZE, and 4AGD are the smallest. In addition, the lowest binding energy values of compound **3l** against other targets are also in the range of  $-6$  to  $-7$  kcal/mol. Therefore, the binding ability between compound **3l** and the selected protein targets is stronger than that of other compounds on the whole. On the contrary, the lowest binding energy values of compound **3g** against every selected protein targets are larger than that of other compounds. So there is weak binding ability between compound **3g** and the selected protein targets.



**Fig. 1.** The 2D and 3D binding model diagrams of compounds **3g**, **3l** against the protein targets (3LXK, 4AGD, 3WZE). (a) Compound **3l** with the protein target 3LXK. (b) Compound **3l** with the protein target 4AGD. (c) Compound **3l** with the protein target 3WZE. (d) Compound **3g** with the protein target 3LXK. (e) Compound **3g** with the protein target 4AGD. (f) Compound **3g** with the protein target 3WZE.

Moreover, comparing the lowest binding energy data with the anticancer activity data of compounds, it can be found that the smaller the lowest binding energy data between the compound and each target, the better the anticancer activity it shown. Therefore, the lowest binding energy data can be used to explain the anticancer activity of compounds.

In order to more clearly observe the interactions between compounds **3g**, **3l** and protein targets 3LXK, 3WZE, 4AGD, respectively, the 2D and 3D binding model diagrams of compounds **3g**, **3l** with the protein targets (3LXK, 4AGD, 3WZE) were made by drawing software (Discovery Studio) and the results were shown in Fig. 1.

In the interaction between drug molecules and protein targets, hydrogen bonding is the most important mode of action, and its number determines the binding ability of drug molecules against protein targets. Furthermore, hydrophobic bonds are another important role in the interaction. When the number of hydrogen bonds is the same, the binding ability of different drug molecules with protein targets is mainly affected by hydrophobic

bonds. According to the above content, analyzing Fig. 1 can find that in the binding of compound **3l** with protein targets 3LXK, 4AGD and 3WZE, we can clearly see the formation of two hydrogen bonds between compound and the protein target, while compound **3g** forms only one hydrogen bond with them respectively. Therefore, from the perspective of the number of hydrogen bonds, the binding ability of compound **3l** with the three targets is stronger than that of compound **3g**. Meanwhile, the hydrogen bond distance between compound **3l** and the three targets is relatively short, with an average length of 2.54 Å, which is much smaller than 3.5 Å of the traditional hydrogen bond. This further indicates that compound **3l** has strong binding ability with the three targets. Besides, we can also see from the figure that compound **3l** interacts with many amino acid residues on the three protein targets, thus forming a strong hydrophobic interaction force. And the presence of these strong interactions can effectively improve the stability of the compound **3l** with the active pocket on the protein target, so compound **3l** is a potentially active small molecule for the three protein targets.

In contrast, in the binding of compound **3g** with the three protein targets, both the number of hydrogen bonds and the number of hydrophobic bonds are less than those of compound **3l**, which implies that compound **3g** has a weak inhibitory effect on the three selected protein targets.

Why is there such a difference in the binding of compounds **3l** and **3g** with protein targets? Based on the structure of the compounds, we infer that compound **3g** can not be better embedded into the protein targets due to the presence of a long alkyl structure in the compound **3g**. As a result, the strong interaction between the protein and the target can't be formed, resulting in the decreased inhibitory activity of compound **3g** on the targets.

## EXPERIMENTAL

Starting materials and solvents were purchased from Aladdin, Macklin, Adamas, Bidepharm and were used without purification. Compound **1** and **2a–2r** were purified by column chromatography before being used for the next reaction. Reaction progress were monitored by thin layer chromatography on silica gel 60 GF254 (Qingdao Haiyang Chemical Co., Ltd., China). Melting points were determined on a  $\chi$ -4 precision micro melting point apparatus and were uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on Avance AV-400 spectrometer (Bruker, Germany, 400 and 101 MHz). And tetramethylsilane (TMS) was used as an internal standard for spectra obtained in  $\text{DMSO}-d_6$  and  $\text{CDCl}_3$  solvent. Chemical shifts are given in parts per million (ppm). Mass spectra were recorded on Agilent 6224 instrument.

**General procedure for the synthesis of 4-chloro-1-(prop-2-yn-1-yl)-1H-pyrrolo[2,3-*b*]pyridine (1).** To 4-chloro-1H-indole (13.11 mmol) dissolved in DMF (30 mL) anhydrous potassium carbonate (39.33 mmol) was added. Then, 3-bromopropyne (15.73 mmol) was slowly added dropwise to the mixed system while stirring. The mixture was heated at 35°C for 12 h. Reaction was monitored by TLC until TLC showed that the reactants were completely consumed, eluent (PE–EA, 2 : 1). The cooled mixture was partitioned with Ethyl acetate (3×20 mL). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated in vacuo. The residue was purified on a short  $\text{SiO}_2$  column using the eluent PE–EA (4 : 1) to give the desired compound **1**.

**General procedure for the synthesis of compound 2a–2r.** To 4-azidobenzoic acid (1.20 mmol) dissolved in DMF (30 mL) HATU (1.44 mmol), DIPEA (2.40 mmol) and substituted aromatic amine (1.20 mmol) were

added. The mixture was warmed and held at 35–50°C under  $\text{N}_2$  with stirring for 6–7 h. When TLC showed the reaction was complete, ethyl acetate (3×20 mL) and water (20 mL) was used to extract the solution containing product. Finally, the resulting organic phases was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using the eluent PE–EA (8 : 1) to give the desired compound **2a–2r**.

**General procedure for the synthesis of target compound 3a–3r.** To compound **1** (0.74 mmol) dissolved in THF (20 mL) anhydrous copper sulfate (0.22 mmol) and sodium ascorbate (0.37 mmol) dissolved in water (5 mL) as catalyst were added. Then, compound **2a–2r** (0.74 mmol) was dropped into the mixture with stirring. The mixture was heated and refluxed at 50°C under  $\text{N}_2$  for 9–10 h. The reaction was monitored by TLC. After the completion of reaction, the solution was filtered and the filtrate was portioned between ethyl acetate (3×20 mL) and water (20 mL) and the combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to dryness. The residue was purified on a short column of silica gel, using  $\text{CH}_2\text{Cl}_2$ –MeOH (160 : 1) to give the pure desired target compound **3a–3r**. And these obtained compounds were characterized by  $^1\text{H}$  NMR spectra,  $^{13}\text{C}$  NMR spectra and MS.

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorobenzyl)-benzamide (3a).** Compound **3a** was obtained from the reaction of compound **1** with compound **2a**. Yield: 52%, white solid; mp 255–256°C.  $^1\text{H}$  NMR (400MHz,  $\text{DMSO}-d_6$ ):  $\delta$ , ppm: 9.27 t ( $J = 5.8$  Hz, 1H, NH), 8.91 s (1H,  $\text{C}^9\text{H}$ ), 8.32 d ( $J = 5.2$  Hz, 1H, Ar-H), 8.13 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.06 d ( $J = 8.6$  Hz, 2H, Ar-H), 7.86 d ( $J = 3.5$  Hz, 1H, Ar-H), 7.43 d. d ( $J = 8.1, 5.9$  Hz, 2H, Ar-H), 7.33 d ( $J = 5.1$  Hz, 1H,  $\text{C}^7\text{H}$ ), 7.26–7.17 m (2H, Ar-H), 6.66 d ( $J = 3.5$  Hz, 1H,  $\text{C}^6\text{H}$ ), 5.74 s (2H,  $\text{C}^8\text{H}_2$ ), 4.53 d ( $J = 5.8$  Hz, 2H,  $\text{C}^{24}\text{H}_2$ ).  $^{13}\text{C}$  NMR spectrum (101 MHz,  $\text{DMSO}-d_6$ ),  $\delta_{\text{C}}$ , ppm: 165.02 (C-17), 162.36 (C-22), 159.95 (C-5), 153.02 (C-3), 147.51 (C-16), 144.66 (C-1), 143.31 (C-15), 138.30 (C-10), 135.65 (C-23), 134.39 (C-18,19), 129.29 (C-12,14), 122.95 (C-11,13), 121.73 (C-7), 119.60 (C-4), 118.88 (C-9), 118.81 (C-2), 116.98 (C-20,21), 115.90 (C-6), 57.88 (C-8), 42.01 (C-24). MS (ESI,  $m/z$ ): 461.1 ( $[M + \text{H}]^+$ ).

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1H-1,2,3-triazol-1-yl)-N-(4-chlorobenzyl)-benzamide (3b).** Compound **3b** was obtained from

the reaction of compound **1** with compound **2b**. Yield: 51.30%, white solid; mp 265–267°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 9.26 t (1H, NH), 8.88 s (1H, C<sup>9</sup>H), 8.28 d (*J* = 3.9 Hz, 1H, Ar-H), 8.09 d (*J* = 7.4 Hz, 2H, Ar-H), 8.03 d (*J* = 7.7 Hz, 2H, Ar-H), 7.82 s (1H, Ar-H), 7.39 d (*J* = 8.5 Hz, 4H, Ar-H), 7.30 d (*J* = 4.0 Hz, 1H, C<sup>7</sup>H), 6.59 d (*J* = 22.9 Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>), 4.50 d (*J* = 4.2 Hz, 2H, C<sup>24</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>), δ<sub>C</sub>, ppm: 165.09 (C-17), 147.52 (C-5), 144.67 (C-3), 143.31 (C-16), 138.51 (C-23), 138.33 (C-18,19), 134.40 (C-1), 133.92 (C-15), 131.34 (C-10), 130.15 (C-22), 129.14 (C-20,21), 128.96 (C-12,14), 122.25 (C-11,13), 121.74 (C-7), 119.62 (C-4), 118.89 (C-9), 115.82

***N*-(4-Bromobenzyl)-4-(4-((4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-benzamide (3c)**. Compound **3c** was obtained from the reaction of compound **1** with compound **2c**. Yield: 48.82%, white solid; mp 247–248°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 8.87 t (1H, NH), 8.28 s (1H, C<sup>9</sup>H), 8.16–7.98 m (4H, Ar-H), 7.82 d (*J* = 3.5 Hz, 1H, Ar-H), 7.72 d (*J* = 8.4 Hz, 1H, Ar-H), 7.57–7.51 m (2H, Ar-H), 7.37–7.20 m (3H, Ar-H, C<sup>7</sup>H), 6.59 d (*J* = 23.8, 3.5 Hz, 1H, C<sup>6</sup>H), 5.73 s (2H, C<sup>8</sup>H<sub>2</sub>), 4.48 d (*J* = 5.2 Hz, 2H, C<sup>24</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>), δ<sub>C</sub>, ppm: 165.09 (C-17), 147.52 (C-5), 144.67 (C-3), 143.31 (C-16), 138.93 (C-23), 138.33 (C-1), 134.39 (C-15), 133.91 (C-10), 131.16 (C-20,21), 130.14 (C-18,19), 129.51 (C-12,14), 128.95 (C-22), 124.90 (C-4), 122.52 (C-11,13), 121.74 (C-7), 119.80 (C-9), 119.62 (C-2), 115.81 (C-6), 57.89 (C-8), 42.14 (C-24). MS (ESI, *m/z*): 521.0 ([*M* + H]<sup>+</sup>).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-cyanobenzyl)-benzamide (3d)**. Compound **3d** was obtained from the reaction of compound **1** with compound **2d**. Yield: 55.32%, white solid; mp 289–291°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 9.34 t (*J* = 5.9 Hz, 1H, NH), 8.88 s (1H, C<sup>9</sup>H), 8.31–8.25 m (1H, Ar-H), 8.11 t (*J* = 7.5 Hz, 2H, Ar-H), 8.0 d (*J* = 8.7 Hz, 2H, Ar-H), 7.83 d. d (*J* = 10.9, 6.4 Hz, 3H, Ar-H), 7.55 t (*J* = 7.8 Hz, 2H, Ar-H), 7.27 t (*J* = 9.3 Hz, 1H, C<sup>7</sup>H), 6.60 d (*J* = 16.8 Hz, 1H, C<sup>6</sup>H), 5.71 s (2H, C<sup>8</sup>H<sub>2</sub>), 4.61 d (*J* = 10.3 Hz, 2H, C<sup>24</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>), δ<sub>C</sub>, ppm: 165.27 (C-17), 147.50 (C-5), 145.33 (C-3), 144.67 (C-23), 143.27 (C-16), 138.40 (C-1), 134.41 (C-15), 133.72 (C-10), 132.26 (C-20,21), 130.07 (C-18,19), 128.99 (C-12,14), 122.04 (C-11,13), 121.72 (C-7), 119.61

(C-4), 118.89 (C-9), 118.45 (C-25), 115.79 (C-2), 115.21 (C-22), 114.87 (C-6), 59.73 (C-8), 42.54 (C-24). MS (ESI, *m/z*): 469.1 ([*M* + H]<sup>+</sup>).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(pyridin-4-ylmethyl)-benzamide (3e)**. Compound **3e** was obtained from the reaction of compound **1** with compound **2e**. Yield: 53.02%, yellow solid; mp 298–299°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 9.26 t (*J* = 5.9 Hz, 1H, NH), 8.87 s (1H, C<sup>9</sup>H), 8.58 s (1H, Ar-H), 8.48 d (*J* = 3.8 Hz, 1H, Ar-H), 8.27 d (*J* = 5.2 Hz, 1H, Ar-H), 8.09 d (*J* = 8.8 Hz, 2H, Ar-H), 8.02 d (*J* = 8.8 Hz, 2H, Ar-H), 7.78 d. d (*J* = 22.6, 5.7 Hz, 2H, Ar-H), 7.38 d. d (*J* = 7.7, 4.8 Hz, 1H, Ar-H), 7.28 d (*J* = 5.2 Hz, 1H, C<sup>7</sup>H), 6.61 d (*J* = 3.6 Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>), 4.53 d (*J* = 5.8 Hz, 2H, C<sup>23</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>), δ<sub>C</sub>, ppm: 165.70 (C-17), 149.35 (C-20, 21), 148.62 (C-5), 148.02 (C-22), 145.16 (C-3), 143.80 (C-16), 138.85 (C-1), 135.67 (C-15), 135.38 (C-10), 134.89 (C-12,14), 134.36 (C-11,13), 130.63 (C-18,19), 129.47 (C-4), 123.98 (C-9), 121.75 (C-7), 119.39 (C-2), 116.30 (C-6), 58.39 (C-8), 42.09 (C-23). MS (ESI, *m/z*): 444.0 ([*M* + H]<sup>+</sup>).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(thiophen-3-ylmethyl)benzamide (3f)**. Compound **3f** was obtained from the reaction of compound **1** with compound **2f**. Yield: 65.34%, yellow solid; mp 243–245°C. <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) δ, ppm: 8.23 t (*J* = 5.4 Hz, 1H, NH), 7.95 s (1H, C<sup>9</sup>H), 7.94–7.84 m (2H, Ar-H), 7.79–7.70 m (2H, Ar-H), 7.46 d (*J* = 3.5 Hz, 1H, Ar-H), 7.32 d. d (*J* = 12.4, 9.1 Hz, 2H, Ar-H), 7.25 d (*J* = 13.7 Hz, 1H, Ar-H), 7.12 t (*J* = 6.1 Hz, 1H, Ar-H), 7.03 t (*J* = 8.5 Hz, 1H, C<sup>7</sup>H), 6.61 d (*J* = 5.9 Hz, 1H, C<sup>6</sup>H), 5.62 s (2H, C<sup>8</sup>H<sub>2</sub>), 4.63 d (*J* = 16.1, 5.5 Hz, 2H, C<sup>22</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>, ppm: 165.87 (C-17), 163.56 (C-5), 147.81 (C-3), 145.20 (C-16), 143.34 (C-21), 138.78 (C-1), 136.32 (C-15), 134.41 (C-10), 129.75 (C-18), 128.71 (C-12,14), 128.53 (C-19), 122.43 (C-11,13), 122.88 (C-7), 120.59 (C-4), 120.23 (C-20), 120.05 (C-9), 116.32 (C-2), 115.83 (C-6), 59.13 (C-8), 43.58 (C-22).- MS (ESI, *m/z*): 449.0 ([*M* + H]<sup>+</sup>).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3-morpholino-propyl)benzamide (3g)**. Compound **3g** was obtained from the reaction of compound **1** with compound **2g**. Yield: 67.54%, white solid; mp 260–261°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 8.84 t (*J* =



5.7 Hz, 1H, NH), 8.60 s (1H, C<sup>9</sup>H), 8.28 d ( $J = 5.1$  Hz, 1H, Ar-H), 8.04 d ( $J = 8.8$  Hz, 2H, Ar-H), 8.00 d ( $J = 8.7$  Hz, 2H, Ar-H), 7.80 d ( $J = 3.5$  Hz, 1H, Ar-H), 7.29 d ( $J = 5.1$  Hz, 1H, C<sup>7</sup>H), 6.60 d ( $J = 11.9$  Hz, 1H, C<sup>6</sup>H), 5.67 s (2H, C<sup>8</sup>H<sub>2</sub>), 3.61–3.55 m (4H, C<sup>18</sup>H<sub>2</sub>, C<sup>20</sup>H<sub>2</sub>), 2.44–2.23 m (8H, C<sup>21</sup>H<sub>2</sub>-C<sup>24</sup>H<sub>2</sub>), 1.76–1.69 m (2H, C<sup>19</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 165.43 (C-17), 148.04 (C-5), 145.12 (C-3), 143.80 (C-16), 138.63 (C-1), 134.90 (C-15), 130.61 (C-10), 129.28 (C-12,14), 122.22 (C-11,13), 121.06 (C-7), 120.39 (C-4), 119.40 (C-9), 116.30 (C-2), 115.43 (C-6), 98.39 (C-23,24), 66.67 (C-21,22), 56.52 (C-20), 53.81 (C-8), 38.34 (C-18), 26.37 (C-19). MS (ESI, *m/z*): 480.2 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl)benzamide (3h).** Compound **3h** was obtained from the reaction of compound **1** with compound **2h**. Yield: 69.63%, white solid; mp 228–230°C. <sup>1</sup>H NMR spectrum (600 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.45 s ( $J = 24.2$  Hz, 1H, NH), 8.89 s (1H, C<sup>9</sup>H), 8.26 t ( $J = 5.3$  Hz, 1H, Ar-H), 8.14 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.07 d ( $J = 8.7$  Hz, 2H, Ar-H), 7.83–7.75 m (3H, Ar-H), 7.28 d ( $J = 5.1$  Hz, 1H, C<sup>7</sup>H), 7.21 t ( $J = 8.9$  Hz, 2H, Ar-H), 6.61 d ( $J = 5.3$  Hz, 1H, C<sup>6</sup>H), 5.68 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 164.22 (C-17), 159.58 (C-22), 157.19 (C-5), 147.52 (C-3), 144.68 (C-16), 143.29 (C-1), 138.63 (C-15), 138.50 (C-23), 135.30 (C-10), 134.42 (C-12,14), 130.10 (C-18,19), 122.39 (C-11,13), 121.77 (C-7), 120.34 (C-4), 119.59 (C-9), 115.80 (C-2), 115.31 (C-20,21), 115.09 (C-6), 57.90 (C-8). MS (ESI, *m/z*): 444.0 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-chlorophenyl)benzamide (3i).** Compound **3i** was obtained from the reaction of compound **1** with compound **2i**. Yield: 58.0%, white solid; mp 222–223°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.24 s ( $J = 11.7$  Hz, 1H, NH), 8.89 s (1H, C<sup>9</sup>H), 8.27 d ( $J = 5.1$  Hz, 1H, Ar-H), 8.18 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.07 d ( $J = 8.7$  Hz, 2H, Ar-H), 7.81 d ( $J = 3.6$  Hz, 1H, Ar-H), 7.62–7.52 m (2H, Ar-H), 7.41 t ( $J = 7.1$  Hz, 1H, Ar-H), 7.36 s (1H, Ar-H), 7.25 s (1H, C<sup>7</sup>H), 6.61 d ( $J = 3.6$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 164.28 (C-17), 147.53 (C-5), 144.73 (C-3), 143.33 (C-16), 138.68 (C-23), 134.85 (C-1), 134.41 (C-15), 133.67 (C-10), 130.17 (C-22), 129.70 (C-21), 129.59 (C-18), 129.45 (C-12,14), 128.66 (C-19), 127.72 (C-20), 122.52 (C-11,13), 121.79 (C-7), 119.73 (C-4),

118.90 (C-9), 116.83 (C-2), 115.43 (C-6), 57.91 (C-8). MS (ESI, *m/z*): 443.0 ( $[M + H]^+$ ).

**N-(3-Bromophenyl)-4-(4-((4-chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzamide (3j).** Compound **3j** was obtained from the reaction of compound **1** with compound **2j**. Yield: 52.0%, yellow solid; mp 235–237°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.53 s (1H, NH), 8.92 s (1H, C<sup>9</sup>H), 8.28 s (1H, Ar-H), 8.16 t ( $J = 9.4$  Hz, 3H, Ar-H), 8.09 d ( $J = 8.6$  Hz, 2H, Ar-H), 7.81 d ( $J = 11.4$ , 5.6 Hz, 2H, Ar-H), 7.37–7.23 m (3H, Ar-H, C<sup>7</sup>H), 6.62 d ( $J = 3.5$  Hz, 1H, C<sup>6</sup>H), 5.72 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 164.51 (C-17), 147.52 (C-5), 143.27 (C-3), 140.58 (C-16), 138.64 (C-23), 134.82 (C-1), 134.42 (C-15), 134.18 (C-10), 130.61 (C-20), 130.09 (C-12,14), 129.48 (C-22), 126.40 (C-21), 122.65 (C-11,13), 121.82 (C-4), 121.41 (C-7), 119.61 (C-18,19), 119.07 (C-9), 118.94 (C-2), 115.83 (C-6), 57.91 (C-8). MS (ESI, *m/z*): 508.9 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(3,4-dichlorophenyl)benzamide (3k).** Compound **3k** was obtained from the reaction of compound **1** with compound **2k**. Yield: 46.03%, white solid; mp 280–281°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.56 s (1H, NH), 8.90 s (1H, C<sup>9</sup>H), 8.27 d ( $J = 5.1$  Hz, 1H, Ar-H), 8.14 d ( $J = 8.8$  Hz, 2H, Ar-H), 8.10–8.07 m (3H, Ar-H), 7.81 d ( $J = 3.6$  Hz, 1H, Ar-H), 7.76–7.71 m (1H, Ar-H), 7.44 t ( $J = 9.1$  Hz, 1H, Ar-H), 7.27 d ( $J = 19.7$ , 5.1 Hz, 1H, C<sup>7</sup>H), 6.61 d ( $J = 6.7$  Hz, 1H, C<sup>6</sup>H), 5.69 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 164.22 (C-17), 159.58 (C-5), 157.19 (C-3), 147.52 (C-16), 144.68 (C-23), 143.29 (C-1), 138.50 (C-15), 135.30 (C-10), 135.28 (C-21), 134.45 (C-19), 134.42 (C-22), 130.10 (C-12,14), 129.39 (C-18), 122.34 (C-11,13), 121.77 (C-7), 119.59 (C-4), 118.90 (C-20), 118.80 (C-9), 118.31 (C-2), 115.09 (C-6), 57.90 (C-8). MS (ESI, *m/z*): 498.9 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1H-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-chloro-3-fluorophenyl)benzamide (3l).** Compound **3l** was obtained from the reaction of compound **1** with compound **2l**. Yield: 48.33%, white solid; mp 275–276°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.56 s (1H, NH), 8.90 s (1H, C<sup>9</sup>H), 8.27 d ( $J = 5.1$  Hz, 1H, Ar-H), 8.14 d ( $J = 8.8$  Hz, 2H, Ar-H), 8.10–8.07 m (3H, Ar-H), 7.81 d ( $J = 3.6$  Hz, 1H, Ar-H), 7.73 d ( $J = 6.4$  Hz, 1H, Ar-H), 7.44 t ( $J = 9.1$  Hz, 1H, Ar-H), 7.27 d ( $J = 19.7$ ,

5.1 Hz, 1H, C<sup>7</sup>H), 6.61 d ( $J = 6.7$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_C$ , ppm: 164.40 (C-17), 154.65 (C-21), 152.23 (C-5), 147.46 (C-3), 143.32 (C-16), 138.63 (C-23), 136.16 (C-1), 134.50 (C-15), 134.09 (C-10), 130.14 (C-20), 129.43 (C-12,14), 122.21 (11,13), 121.88 (C-7), 121.81 (C-4), 120.69 (C-18), 119.66 (C-9), 118.90 (C-22), 118.87 (C-2), 116.88 (C-19), 116.66 (C-6), 57.92 (C-8). MS (ESI,  $m/z$ ): 498.9 ( $[M + H]^+$ ).

***N*-(4-Bromo-2-fluorophenyl)-4-(4-((4-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)benzamide (3m).** Compound **3m** was obtained from the reaction of compound **1** with compound **2m**. Yield: 65.0%, white solid; mp 283–284°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.33 s (1H, NH), 8.88 s (1H, C<sup>9</sup>H), 8.27 d ( $J = 5.2$  Hz, 1H, Ar-H), 8.16 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.07 d ( $J = 8.7$  Hz, 2H, Ar-H), 7.80 d ( $J = 3.6$  Hz, 1H, Ar-H), 7.68–7.57 m (2H, Ar-H), 7.46 d ( $J = 8.5$  Hz, 1H, Ar-H), 7.26 t ( $J = 9.9$  Hz, 1H, C<sup>7</sup>H), 6.61 d ( $J = 3.6$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_C$ , ppm: 164.30 (C-19), 156.83 (C-17), 154.33 (C-5), 147.53 (C-3), 144.74 (C-16), 143.32 (C-1), 138.75 (C-15), 134.41 (C-10), 133.37 (C-12,14), 130.14 (C-20), 129.60 (C-18), 122.51 (C-11,13), 121.78 (C-7), 120.66 (C-4), 120.38 (C-21), 119.90 (C-22), 119.80 (C-9), 118.64 (C-23), 118.52 (C-2), 116.93 (C-6), 53.58 (C-8). MS (ESI,  $m/z$ ): 482.1 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(*m*-tolyl)benzamide (3n).** Compound **3n** was obtained from the reaction of compound **1** with compound **2n**. Yield: 62.68%, yellow solid; mp 287–288°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.31 s (1H, NH), 8.90 s (1H, C<sup>9</sup>H), 8.28 d ( $J = 5.2$  Hz, 1H, Ar-H), 8.16 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.07 d ( $J = 8.7$  Hz, 2H, Ar-H), 7.81 t ( $J = 5.5$  Hz, 1H, Ar-H), 7.60 d ( $J = 19.5, 11.3$  Hz, 2H, Ar-H), 7.35 s (1H, Ar-H), 7.19 s (1H, Ar-H), 6.95 d ( $J = 7.5$  Hz, 1H, C<sup>7</sup>H), 6.62 d ( $J = 3.5$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>), 2.31 d ( $J = 11.2$  Hz, 3H, C<sup>24</sup>H<sub>3</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_C$ , ppm: 164.71 (C-17), 148.03 (C-5), 145.18 (C-3), 143.81 (C-6), 139.36 (C-21), 138.94 (C-23), 138.28 (C-1), 135.19 (C-15), 134.91 (C-10), 130.64 (C-20), 129.88 (C-12,14), 128.96 (C-19), 125.04 (C-22), 122.28 (C-11,13), 121.47 (C-7), 120.09 (C-4), 119.40 (C-9), 119.12 (C-18), 118.32 (C-2), 116.89 (C-6), 58.40 (C-8), 21.68 (C-24). MS (ESI,  $m/z$ ): 526.9 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3,5-dimethylphenyl)-benzamide (3o).** Compound **3o** was obtained from the reaction of compound **1** with compound **2o**. Yield: 55.0%, white solid; mp 249–251°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.20 s (1H, NH), 8.88 s (1H, C<sup>9</sup>H), 8.28 d ( $J = 5.2$  Hz, 1H, Ar-H), 8.15 d ( $J = 8.8$  Hz, 2H, Ar-H), 8.06 d ( $J = 8.8$  Hz, 2H, Ar-H), 7.81 d ( $J = 3.6$  Hz, 1H, Ar-H), 7.43 s (2H, Ar-H), 7.28 d ( $J = 5.2$  Hz, 1H, Ar-H), 6.77 s (1H, C<sup>7</sup>H), 6.62 d ( $J = 3.6$  Hz, 1H, C<sup>6</sup>H), 5.71 s (2H, C<sup>8</sup>H<sub>2</sub>), 2.28 s (6H, C<sup>24</sup>H<sub>3</sub>, C<sup>25</sup>H<sub>3</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_C$ , ppm: 164.14 (C-17), 147.53 (C-5), 144.68 (C-3), 143.31 (C-16), 138.77 (C-20,21), 138.41 (C-23), 137.56 (C-1), 134.73 (C-15), 134.42 (C-10), 130.13 (C-12,14), 129.35 (C-22), 122.37 (C-11,13), 122.13 (C-18,19), 121.78 (C-7), 119.59 (C-4), 118.91 (C-9), 118.22 (C-2), 115.82 (C-6), 57.91 (C-8), 21.10 (C-24,25). MS (ESI,  $m/z$ ): 457.1 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-ethylphenyl)-benzamide (3p).** Compound **3p** was obtained from the reaction of compound **1** with compound **2p**. Yield: 62.0%, white solid; mp 241–242°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.08 s (1H, NH), 8.91 s (1H, C<sup>9</sup>H), 8.29 d ( $J = 4.8$  Hz, 1H, Ar-H), 8.19 d ( $J = 8.5$  Hz, 2H, Ar-H), 8.08 d ( $J = 8.6$  Hz, 2H, Ar-H), 7.83 d ( $J = 3.5$  Hz, 1H, Ar-H), 7.29 ddd ( $J = 14.6, 9.0, 5.2$  Hz, 5H, Ar-H, C<sup>7</sup>H), 6.63 d ( $J = 3.5$  Hz, 1H, C<sup>6</sup>H), 5.72 s (2H, C<sup>8</sup>H<sub>2</sub>), 2.67 d ( $J = 15.7, 8.2$  Hz, 2H, C<sup>24</sup>H<sub>2</sub>), 1.16 t ( $J = 7.5$  Hz, 3H, C<sup>25</sup>H<sub>3</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_C$ , ppm: 164.54 (C-17), 147.54 (C-5), 144.72 (C-3), 143.31 (C-16), 139.89 (C-1), 138.48 (C-15), 138.22 (C-10), 135.53 (C-19), 134.42 (C-23), 134.25 (C-22), 130.14 (C-12,14), 129.32 (C-20), 128.52 (C-21), 122.52 (C-11,13), 121.80 (C-7), 119.68 (C-4), 118.92 (C-9), 118.82 (C-2), 118.34 (C-18), 116.80 (C-6), 57.91 (C-8), 23.95 (C-24), 14.13 (C-25). MS (ESI,  $m/z$ ): 457.1 ( $[M + H]^+$ ).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxyphenyl)-benzamide (3q).** Compound **3q** was obtained from the reaction of compound **1** with compound **2q**. Yield: 45.22%, white solid; mp 270–272°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.23 s (1H, NH), 8.90 s (1H, C<sup>9</sup>H), 8.28 d ( $J = 5.2$  Hz, 1H, Ar-H), 8.16 d ( $J = 8.6$  Hz, 2H, Ar-H), 8.06 d ( $J = 8.5$  Hz, 2H, Ar-H), 7.79 t ( $J = 5.3$  Hz, 1H, Ar-H), 7.59 d ( $J = 19.8, 11.3$  Hz, 2H,

Ar-H), 7.36–7.20 m (2H, Ar-H), 6.99 d ( $J = 7.4$  Hz, 1H, C<sup>7</sup>H), 6.65 d ( $J = 3.4$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>), 3.81 s (3H, C<sup>24</sup>H<sub>3</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 167.45 (C-17), 164.30 (C-22), 156.22 (C-5), 148.03 (C-3), 144.98 (C-16), 135.67 (C-1), 134.89 (C-15), 132.48 (C-10), 132.19 (C-23), 130.27 (C-12,14), 122.48 (C-11,13), 122.27 (C-18,19), 121.06 (C-7), 120.63 (C-4), 119.25 (C-9), 118.28 (C-2), 116.90 (C-20,21), 116.83 (C-6), 58.91 (C-8), 55.09 (C-24). MS (ESI, *m/z*): 459.0([*M* + H]<sup>+</sup>).

**4-(4-((4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(pyridin-4-yl)-benzamide (3r).** Compound **3r** was obtained from the reaction of compound **1** with compound **2r**. Yield: 49.0%, yellow solid; mp 234–236°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 10.70 s (1H, NH), 8.89 s (1H, C<sup>9</sup>H), 8.27 d ( $J = 5.1$  Hz, 1H, Ar-H), 8.17 d ( $J = 8.7$  Hz, 2H, Ar-H), 8.04 d ( $J = 8.6$  Hz, 3H, Ar-H), 7.80 d ( $J = 3.5$  Hz, 2H, Ar-H), 7.28 t ( $J = 6.1$  Hz, 3H, Ar-H, C<sup>7</sup>H), 6.61 d ( $J = 3.5$  Hz, 1H, C<sup>6</sup>H), 5.70 s (2H, C<sup>8</sup>H<sub>2</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>),  $\delta_c$ , ppm: 165.38 (C-17), 165.26 (C-22), 147.57 (C-20,21), 144.71 (C-5), 143.31 (C-3), 138.86 (C-16), 134.42 (C-1), 133.92 (C-15), 130.55 (C-10), 130.12 (C-12,14), 122.85 (C-11,13), 121.82 (C-7), 119.70 (C-4), 119.08 (C-9), 118.91 (C-2), 116.35 (C-18,19), 115.82 (C-6), 57.91 (C-8). MS (ESI, *m/z*): 430.0 ([*M* + H]<sup>+</sup>).

**Biological activity.** *Cell culture maintenance.* A549 (lung cancer) and HepG2 (hepatic cancer) cells were cultured in the DMEM growth media with 10% heat inactivated fetal bovine serum (FBS), 1% (v/v) of penicillin and streptomycin solution. All cell lines were cultured at 37°C in a 5% CO<sub>2</sub>, fully humidified atmosphere for 3–4 days.

*Cytotoxicity assay.* 100  $\mu$ L of culture media containing cells were seeded into 96-well plates. After 24 h of incubation, the culture medium was removed. Then the fresh medium alone or the tested compounds dissolved in DMSO at increasing concentrations from 0.625 to 160  $\mu$ M for cancerous cell lines were added into 96-well plates in which cancerous cells existed. The positive control drugs included Gefitinib and Sorafenib (0.625–160  $\mu$ M, final concentration less than 0.4%) and DMSO was as blank control.

After 72 h, 20  $\mu$ L/well of media having MTT (5 mg/mL) was added for 4h at incubated at 37°C. At last, the 100  $\mu$ L of media was discarded and 100  $\mu$ L of Dimethyl sulfoxide (DMSO) was added to solubilize the

purple-colored formazan. All experimental conditions were tested in triplicate and the experiment was performed three times.

Finally, the absorbance of plate was recorded at 490 nm using Microplate Reader. Then using SPSS18 software, IC<sub>50</sub> values were calculated. IC<sub>50</sub> values were reported as mean  $\pm$  SD.

**Dock and virtual screening.** *Preparation of proteins.* Three-dimensional structure of the target proteins (PDB file format) was obtained from RCSB database. Then using PymolWin software, the original water and ligands on the protein were removed and saved as PDB file format. Next, the obtained protein was added hydrogens (Polar Only), added the atomic type (Assign AD4 type) by AutoDock Tools–1.5.6 software and saved as PDBQT file format.

*Preparation of ligands.* ChemDraw 14.0 software was utilized to generate the 2D structures of the synthesized compounds. Then the 2D structures were converted into 3D structures with the best dominant conformation by Chem3D software and saved as PDB file format. Next, using AutoDock Tools–1.5.6 software, the PDB file format of ligands were converted to the PDBQT file format. This process required calculating the charge (Compute Gasteiger), adding the atomic type (Assign AD4 type), choosing root and torsions on the ligand.

*Grid map calculations.* AutoDock grid maps were calculated for each compound using AutoDock Tools–1.5.6 software, based on the active site coordinates of each protein crystal structure. The size of all grid boxes 126 $\times$ 126 $\times$ 126 xyz points with a grid spacing of 0.375 Å. Then the GPF file format was output and the file was calculated by running AutoGrid program.

*Molecular docking simulations.* Using Docking program of AutoDock Tools–1.5.6 software, the Genetic Algorithm (GA) was used for pose sampling and DPF file format was output. Then the file was calculated by running AutoDock program. Finally, the configuration with the lowest binding energy was obtained from the Analyze program and saved as PDB file format. The results of molecular docking were visualized in Discovery Studio 4.5 client software and then analyzed the docking results.

## CONCLUSIONS

In summary, utilizing substitution reaction, amide condensation reaction and click reaction, we have synthesized and characterized a combinatorial library of 7-azaindole with 1,2,3-triazole. All the newly synthesized compounds **3a–3r** were subjected to in vitro anti-cancer activity against lung cancer cell lines and hepatic cancer cell lines. The studies reveal that compound **3d**, **3l**, **3q** and **3r** have obvious inhibitory activity on lung cancer and hepatic cancer cell lines and exhibit IC<sub>50</sub> values comparable to the positive control. Molecular docking studies indicate that compound **3d**, **3l**, **3q** and **3r** can effectively bind to multiple protein targets especially to the target 3LXK, 4AGD and 3WZE. Of all the compounds, compound **3l** shows the strongest inhibitory activity and the lowest values of binding energy. In view of this, we investigate the binding of compound **3l** to the protein target 3LXK 4AGD and 3WZE. And the results show that compound **3l** can form two strong hydrogen bonds with the protein target, and can form hydrophobic interactions with multiple amino acid residues on the target, so as to effectively embed into the active pocket of the target. Overall, the synthesized compounds demonstrate inhibition against multiple targets, indicating great potential as multi-kinase target inhibitors in cancer chemotherapy. Our work illustrates lead molecules for anticancer chemotherapy.

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#### CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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