有机化学 DOI: 10.6023/cjoc201805005 研究论文
Chinese Journal of Organic Chemistry ARTICLE

吡咯并三嗪衍生物的合成及其对肿瘤细胞增殖的抑制活性

张娅玲 马沙沙 李夏冰* 侯巧丽
吕梦娇 郝云霞 王 伟 李宝林*
(陕西师范大学化学化工学院 教育部药用资源与天然药物化学重点实验室 西北濒危药材资源开发国家工程实验室 西安 710062)

摘要 为发现高效、低毒的抗肿瘤药物, 以吡咯并[2,1-*f*][1,2,4]三嗪为母核, 通过给母核的 4,6-位引入不同的结构单元, 设计、合成了 11 个新的吡咯并三嗪衍生物, 并对其抑制肿瘤细胞增殖的活性进行了评价. 目标化合物的合成先是以氰基乙酸甲酯为原料, 经肟化、还原、酯的氨解三步反应制得 2-氨基-2 氰基乙酰胺(**1**); 同时通过乙酰乙酸乙酯和 *N*,*N*-二甲基甲酰胺二甲缩醛之间的缩合反应制得 2-乙酰基-3-(二甲基氨基)丙烯酸乙酯(**2**); 经化合物 **1** 与 **2** 之间的环化反应获得 5-氰基-4-甲基吡咯-3-甲酸乙酯(**4**). 化合物 **4** 经氨化、脒的生成、Dimroth 重排、水解和酰化反应分别获得目标化合物. 利用噻唑蓝比色(MTT)法测试了目标化合物对肿瘤细胞的抗增殖活性, 结果显示大部分合成化合物对高表达野生型表皮生长因子受体(EGFR)的人表皮鳞癌细胞 A431 具有一定的抗增殖作用. 特别是 4-(3-乙炔基苯氨基)-5-甲基吡咯并[2,1-*f*][1,2,4]三嗪-6-甲酸乙酯(**7c**)、4-(3-氯-4-(3-氟苄氧基)苯氨基)-5-甲基吡咯并[2,1-*f*][1,2,4]三嗪-6-甲酸(**8a**)和 4-(3-乙炔基苯氨基)-5-甲基吡咯并[2,1-*f*][1,2,4]三嗪-6-(*N*-(2-(甲磺酰基)乙基))甲酰胺(**9c**)对 A431 肿瘤细胞的抗增殖活性较高, IC_{50} 值分别为 20.05, 21.98 和 23.87 μmol•L^{-1}. 初步的构效关系分析表明 4-位芳氨基为 3-氯-4-(3-氟苄氧基)苯氨基和 3-乙炔基苯氨基时, 能够增强 4-芳氨基吡咯并三嗪-6-甲酸或其酯对 A431 肿瘤细胞增殖的抑制活性.

关键词 吡咯并三嗪; 4-芳氨基吡咯并三嗪; Dimroth 重排; 肿瘤; 抗增殖活性

Synthesis and Antiproliferative Activities of Novel Pyrrolotriazine Derivatives

Zhang, Yaling Ma, Shasha Li, Xiabing* Hou, Qiaoli
Lü, Mengjiao Hao, Yunxia Wang, Wei Li, Baolin*
(*Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062*)

Abstract In order to find novel antitumor agents with high efficiency and low toxicity, 11 novel pyrrolo[2,1-*f*][1,2,4]triazine derivatives were designed and synthesized through the introduction of varied structural moieties to the 4,6-positions of pyrrolotriazine core. The antiproliferative activities of synthesized compounds were also evaluated against human tumor cells. Firstly, 2-amino-2-cyanoacetamide (**1**) was prepared from methyl cyanoacetate as a starting material through three step reactions of oximation, reduction and ammonolysis. Meanwhile, ethyl 2-acetyl-3-(dimethylamino)acrylate (**2**) was obtained from the reaction of ethyl acetoacetate with *N*,*N*-dimethylformamide dimethyl acetal. Then the cyclization reaction of **1** with **2** gave ethyl 5-cyano-4-methylpyrrole-3-carboxylate (**4**). Finally, pyrrolotriazine derivatives as target compounds were synthesized from **4** through the ammoniation, generating amidine, Dimroth rearrangement, and subsequent hydrolyzation and acylation. The antiproliferative activities of target compounds against human tumor cell lines were investigated by methyl thiazolyl tetrazolium (MTT) colorimetric assay. The results demonstrated that most synthesized compounds had obviously selective inhibitory effects against A431 cells with highly expressed wild type epidermal growth factor receptor (EGFR). Ethyl 4-(3-ethynylphenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**7c**), 4-(3-chloro-4-(3-fluorobenzyloxy)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (**8a**) and 4-(3-ethynylphenylamino)-5-methylpyrrolo[2,1-*f*]-

* Corresponding authors. E-mail: xiabingli@snnu.edu.cn; baolinli@snnu.edu.cn
Received May 2, 2018; revised June 18, 2018; published online August 22, 2018.
Project supported by the National Natural Science Foundation of China (No. 21272144) and the Fundamental Research Funds for the Central Universities (Nos. GK201603034, GK201706005, X2015YB06).
国家自然科学基金(No. 21272144)及中央高校基本科研业务费专项资金(Nos. GK201603034, GK201706005, X2015YB06)资助项目.

[1,2,4]triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamide (**9c**) were the most potent agents with IC_{50} values of 20.05, 21.98 and 23.87 μmol•L^{-1} in the synthesized compounds, respectively. Preliminary structure-activity relationship analysis indicated that the introduction of 3-chloro-4-(3-fluorobenzyloxy)phenylamino and 3-ethynylphenylamino to 4-position of pyrrolotriazine-6- carboxylic acids or its esters can lead to enhance antiproliferative activities against A431 tumour cells.

Keywords pyrrolotriazine; 4-arylaminopyrrolotriazine; Dimroth rearrangement; tumor; antiproliferative activity

1 Introduction

Cancer is set to become a major cause of morbidity and mortality in the coming decades, and is a major public health problem in every region of the world.[1,2] Fighting cancer has been the life mission for generations of biologists and clinicians,[3] and there is increasing interest in strategies for the prevention and treatment of cancer. Nowdays, there are kinds of approaches to treat cancer, the treatment using small molecular compounds as anti-cancer drugs was one of them. Small molecular anti-cancer drugs such as gefitinib, erlotinib and lapatinib (Figure 1) are based on a quinazoline core scaffold. Gefitinib and erlotinib are selective tyrosine kinase inhibitors (TKIs), and effective in clinical therapies for non-small cell lung cancer (NSCLC) that harbors activating mutations in the epidermal growth factor receptor (EGFR) kinase domain.[4~6] Lapatinib is a dual target TKI of human epidermal growth factor receptor 2 (HER-2) and EGFR for use in combination with capecitabine for the treatment of patients with HER-2-overexpressing metastatic breast cancer.[7] However, they have some limites in clinical using, such as drug resistence of gefitinib and erlotinib[4,8,9] and hepatotoxicity of lapatinib.[10,11] Brivanib is also a small molecular selective receptor TKI with potential antineoplastic activity. It is based on a pyrrolo[2,1-*f*][1,2,4]triazine core scaffold, and targets the key angiogenesis receptors VEGF-R2, FGF-R1 and FGF-R2.[12,13] Nevertheless, the clinical efficacy of brivanib has been limited by corresponding fatigue, hypertension and diarrhea.[14] Based on the above, there is an urgent demand for discovering novel lead compounds for anti-cancer drugs.

Recently, several groups further proved pyrrolo[2,1-*f*][1,2,4]triazine core to be a key structure unit of antitumor agents,[15,16] although brivanib appeared some side effect in clinical treatment. Meanwhile, it is suggested that the pharmacodynamics of pyrrolo[2,1-*f*][1,2,4]triazine derivatives can be improved through replacing substituent in core.[17] As reported in our previous studies, a brivanib analogue, ethyl 4-(3-chloro-4-(3-fluorobenzyloxy)phenylamino)-5-methylpyrrolotriazine-6-carboxylate (**7a**) with pyrrolotriazine core[18] (Figure 1) had been synthesized, and exhibited

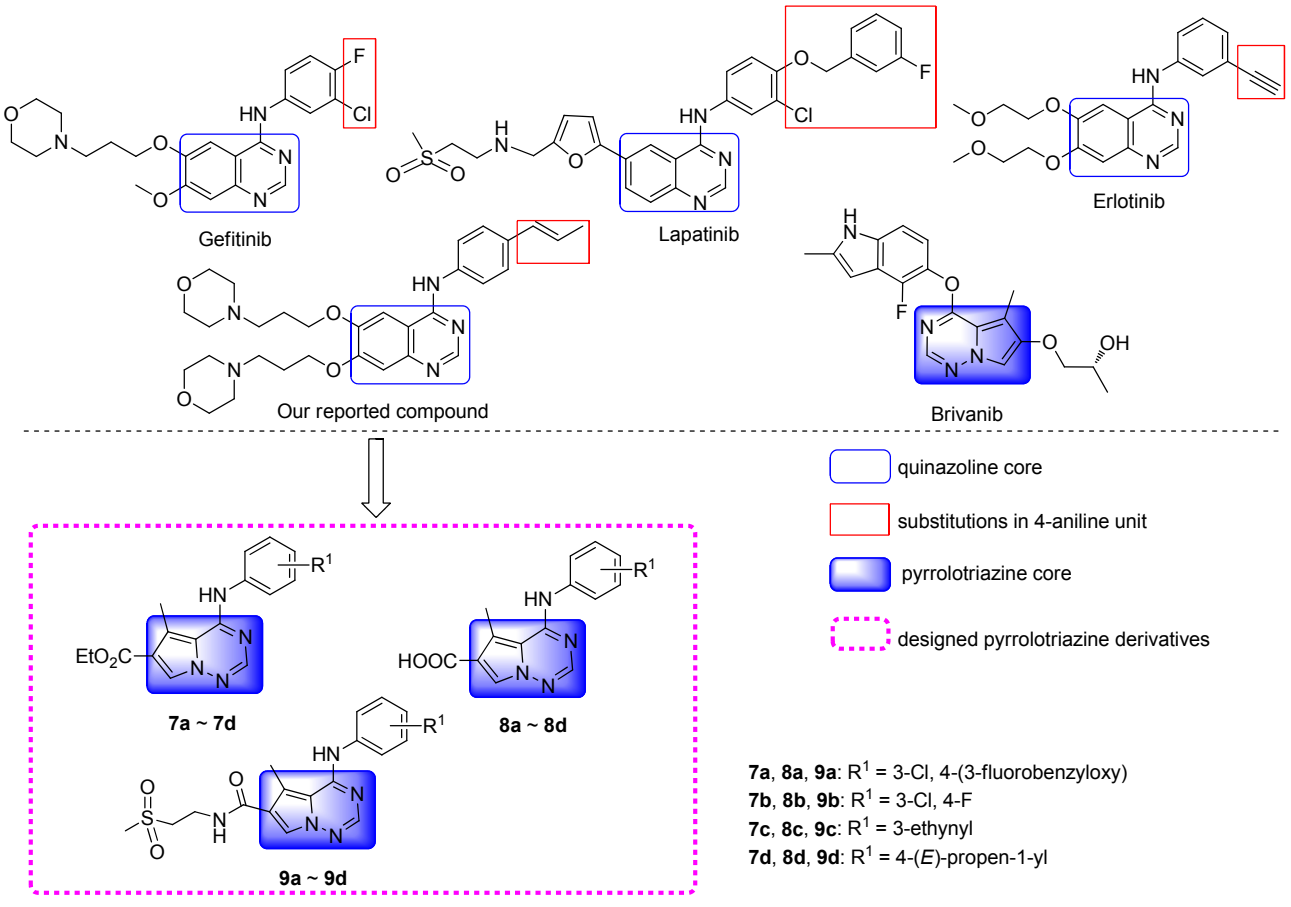


Figure 1 Structures of reported antitumor agents and design of target compounds

antiproliferative effects against tumor cells. We also introduced a series of hydrophobic arylamino groups to the 4-position of quinazoline core, and obtained several high active antitumor compounds such as 4-(4-(*E*)-(propen-1-yl)-phenylamino)-6,7-bis(3-morpholinopropoxy)quinazoline (Figure 1) *etc*.[10,19] Encouraging by these results, to find novel antitumor agent, we further optimized the structure of **7a** to give 11 novel pyrrolotriazine derivatives by introducing four hydrophobic arylamino at the 4-position, and two hydrophilic carboxyl and *N*-(2-(methylsulfonyl)ethyl)-carboxamide moiety at the 6-position of pyrrolotriazine core, respectively (Figure 1). Herein, the synthesis and preliminary evaluation for the antiproliferative activities of these pyrrolo[2,1-*f*][1,2,4]triazine derivatives are represented.

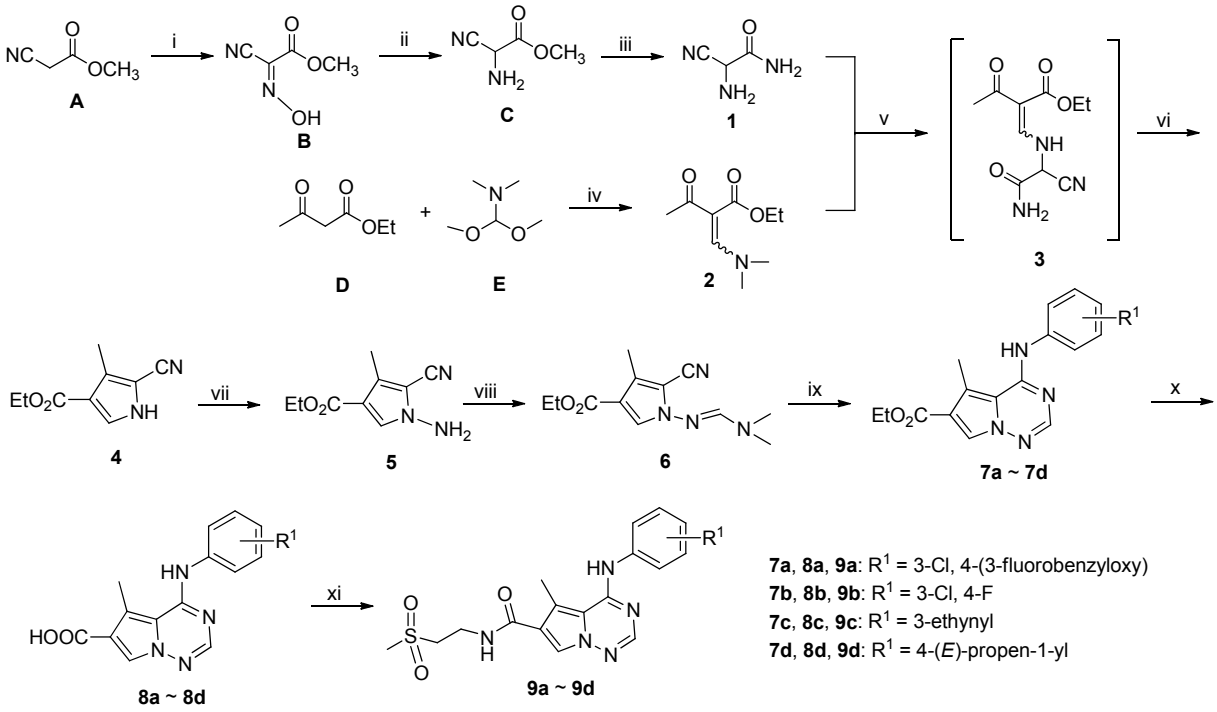
2 Results and discussion

2.1 Synthesis of designed compounds

The synthetic route of designed pyrrolotriazine derivatives is outlined in Scheme 1. Methyl cyanoacetate (**A**) was used as starting material, and methyl 2-cyano-2-(hydroxylimino)acetate (**B**) was prepared in 93.8% yield through the oximation reaction of compound **A** and $NaNO_2$ in the presence of acetic acid. Then methyl 2-cyano-2-aminoacetate (**C**) was obtained in 82.6% yield from the reduction reaction of compound **B** with $Na_2S_2O_4$ in the mixture solvent of ethanol and water. The obtained compound **C** reacted with NH_3•H_2O to give 2-amino-2-cyanoacetamide (**1**) in 93.1% yield. Meanwhile, ethyl 2-acetyl-3-(dimethylamino)acrylate (**2**) was prepared in 84.3% yield by the reaction of ethyl acetoacetate and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA, **E**) in the presence of *p*-toluenesulfonic acid (*p*-TsOH).

Subsequently, ethyl 3-methyl-2-cyanopyrrole-4-carboxylate (**4**) was got in 83.5% yield through intermediate **3** generated from the reaction of compounds **1** and **2** in acetic acid. After the deprotonation of **4** with NaH as strong base in DMF, it reacted with NH_2Cl to give amination resultant ethyl *N*-amino-3-methyl-2-cyanopyrrole-4-carbo- xylate (**5**) in 91.5% yield under our previous optimization condition.[18,20] The condensation reaction of **5** and DMF- DMA gave the important intermediate of *N*,*N*-dimethylformamidine derivative **6** in 89.2% yield.

Then, target compounds ethyl 4-arylamino-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylates (**7a**～**7d**) were synthesized in 25.7～45.2% yields by Dimroth rearrangement reaction of **6** and four arylamines in the presence of *p*-TsOH, respectively (Scheme 1). Previously, the synthesis of pyrrolo[2,1-*f*][1,2,4]triazine derivatives from **5** needed three step continuous reactions including the formation of pyrrolotriazin-4(3*H*)-one, halogenation with $POCl_3$, and the substitution with arylamine at 4-position of pyrrolotri azine.[21,22] In this process, use of $POCl_3$ leads to anhydrous



Reagents and conditions: (i) $NaNO_2$, HOAc, 0～5 ℃, 1 h; r.t., 1 h, 93.8%. (ii) $Na_2S_2O_4$, EtOH-H_2O, 50 °C, 82.6%. (iii) NH_3•H_2O, 0 °C, 20 min, 93.1%. (iv) *p*-TsOH, 80 °C, 70 min, 84.3%. (v) HOAc, r.t., 18 h. (vi) 106 ℃, 6 h, 83.5%. (vii) (1) NaH, DMF, −20 ℃, 45 min; (2) NH_2Cl, Et_2O, −20 °C, 2 h; 91.5%. (viii) DMF-DMA, 30 °C, 5 min; H_2SO_4, 30 °C, 1 h; 89.2%. (ix) R^1-aniline, *p*-TsOH, 112 ℃, 21 h, 25.7%～45.2%. (x) (1) THF/CH_3OH, NaOH, 60 °C, 2 h; (2) 2 mol•L^{-1} H_2SO_4; 75.0%～93.5%. (xi) 2-(methylsulfonyl)ethylamine•HCl, EDCl, DMAP, Et_3N, r.t., 12 h, 86.1%～90.3%.

Scheme 1 Synthetic route of target compounds **7a**～**7d**, **8a**～**8d** and **9a**～**9d**

operation as a necessary condition. Herein, Dimroth rearrangement reaction[19] was used to construct triazine ring, simultaneously, arylamino moiety was introduced to 4-position of pyrrolotriazine core in cyclization process. Apparently, this is a convenient procedure with fewer steps. According to the synthetic mechanisms of gefitinib,[23] 6-bromo-*N*-arylthieno[2,3-*d*]pyrimidin-4-amines[24] and naphthylazuleno[2,1-*d*]pyrimidin-4-amines,[25] we proposed the mechanism of Dimroth rearrangement reaction from **6** to **7** as scheme 2.

Next series of target compounds **8a**～**8d** was prepared in 75.0%～93.5% yields by the hydrolysis of **7**. Finally, compound **8** reacted with 2-(methylsulfonyl)ethanamine hydrochloride to give **9a**～**9d** in 86.1%～90.3% yields in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP). All the structures of synthesized target compounds, 4-arylaminopyrrolotriazine derivatives, were characterized by ^{1}H NMR, ^{13}C NMR and HRMS, *etc*.

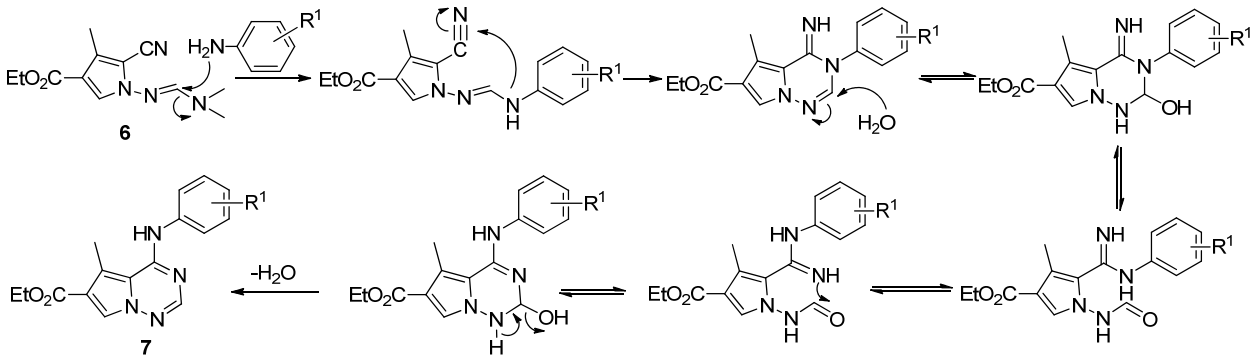
2.2 Antiproliferative activity

All the synthesized compounds were evaluated for their ability to inhibit the proliferation of three human tumor cell lines, including colon cancer SW480, epidermoid carcinoma A431 and NSCLC A549, using methyl thiazolyl tetrazolium (MTT) assay.[10,26～28] Clinical drugs, gefitinib and lapatinib were used as reference compounds. The indicated compound was serially diluted with dimethyl sulfoxide (DMSO), and then diluted with the cell culture medium. The IC_{50} values of these compounds are listed in Table 1.

When SW480 and A549 cells were treated with targeted compounds, all tested compounds showed less antiproliferative activities with IC_{50} values more than 100 μmol•L^{-1} (Table 1). Except compounds **7d**, **9a** and **9d**, other tested compounds showed certain inhibitory activities against A431 cells, the IC_{50} values of them were in the range of 20.05～75.41 μmol•L^{-1}. Although they were all less potent than gefitinib and lapatinib (with IC_{50} values of 4.45 and 4.80 μmol•L^{-1}, respectively) (Table 1). Compounds **7c**, **8a** and **9c** were the most potent agents (with IC_{50} values of 20.05, 21.98 and 23.87 μmol•L^{-1}, respectively) in the synthesized compounds. Pyrrolotriazine derivatives with 4-(*E*)-propen-1-yl at 4-anilino moiety were less potent than that with other substituents in the same position. In pyrrolotriazine derivatives harboring ethyl 6-carboxylate moiety (**7a**～**7d**) or 6-carboxylic acid moiety (**8a**～**8d**), when 3-chloro-4-(3-fluorobenzyloxy)phenylamino or 3-ethynylphenylamino as a synergy group was introduced to 4-position of pyrrolotriazine core, compounds could give higher inhibitory effects to A431 cells. In derivatives harboring *N*-(2-(methylsulfonyl)ethyl)carboxamide moiety (**9a**～**9d**), 3-ethynylphenylamino unit at 4-position of pyrrolotriazine core could enhance antiproliferative activity of pyrrolotriazine derivatives against A431 cells. In addition, the data in Table 1 indicated that most of synthesized pyrrolotriazine derivatives showed obviously selective antiproliferative effects against epidermoid carcinoma A431 cells with highly expressed wild type EGFR.[10] This suggested that these compounds may display its activity through the inhibition of EGFR signaling pathway. The related evidence need further accumulate.

3 Conclusions

A series of novel pyrrolotriazine derivatives with different substituents at 4,6-positions were designed and synthesized through multi-step reactions. It is noteworthy that Dimroth rearrangement was used to construct pyrrolotriazine core, and led to achieve a shorter synthetic route. Meanwhile, their antiproliferative activities against human tumor cell lines *in vitro* were investigated. The results demonstrated that most synthesized compounds exhibited obviously selective antiproliferative effects against epidermoid carcinoma A431 cells with highly expressed wild type EGFR. Among the synthesized compounds, compounds **7c**, **8a** and **9c** were the most potent agents with IC_{50} values of 20.05, 21.98 and 23.87 μmol•L^{-1}, respectively. This selective inhibition suggest that these novel pyrrolotriazine derivatives may be a kind of EGFR inhibitors and the further structural optimization of these compounds may find more high antiproliferative active agents against epidermoid carcinoma A431 cells. Preliminary structure-activity relationship analysis indicated that 3-chloro-4-(3-fluoro-benzyloxy)phenylamino and 3-ethynylphenylamino units maybe synergy groups for antiproliferative activities



Scheme 2 Proposed mechanism of Dimroth rearrangement reaction from **6** to **7**

Table 1 Antiproliferative activities [IC_{50}/(μmol•L^{-1})] of synthesized compounds against human cancer cell lines[a]

Compd.	R^1	SW480	A431	A549
Gefitinib		12.50±0.28	4.45±0.25	21.17±0.47
Lapatinib		12.58±1.35	4.80±0.71	14.90±1.21
7a	3-Cl-4-(3-fluorobenzyloxy)	>100[b]	35.05±0.53	>100[b]
7b	3-Cl-4-F	>100[b]	55.48±17.60	>100[b]
7c	3-Ethynyl	>100[b]	20.05±2.00	>100[b]
7d	4-(*E*)-Propen-1-yl	>100[b]	>100[b]	>100[b]
8a	3-Cl,4-(3-fluorobenzyloxy)	>100[b]	21.98±4.30	>100[b]
8b	3-Cl-4-F	>100[b]	37.41±3.36	>100[b]
8c	3-Ethynyl	>100[b]	36.13±2.75	>100[b]
8d	4-(*E*)-Propen-1-yl	>100[b]	75.41±12.20	>100[b]
9a	3-Cl-4-(3-Fluorobenzyloxy)	>100[b]	>100[b]	>100[b]
9b	3-Cl-4-F	>100[b]	42.75±4.00	>100[b]
9c	3-Ethynyl	>100[b]	23.87±1.54	>100[b]
9d	4-(*E*)-Propen-1-yl	>100[b]	>100[b]	>100[b]

[a] The values are mean±SD at least three independent experiments. [b] IC_{50} was not calculated because less than 50% inhibition was observed at the highest concentration (100 μmol•L^{-1}).

of pyrrolotriazine derivatives against epidermoid carcinoma A431 cells. The obtained structure-activity relationships will provide an important reference for the modification of pyrrolotriazines. Further investigations of this novel class of compounds are underway in our laboratory.

4 Experimental section

4.1 General

Human cancer cell lines SW480, A431 and A549 were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Dulbecco's Modified Eagle's Medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco. Trypsin, penicillin-streptomycin (P/S) and *L*-glutamate were purchased from Sigma-Aldrich. All other reagents and solvents were analytical grade. They were supplied by local commercial suppliers and used without further purification unless otherwise noted.

^{1}H NMR and ^{13}C NMR spectra were obtained using a Super-conducting Fourier Digital NMR spectrometer 300, 400, 600 MHz (Bruker Avance III) instrument at room temperature. The high-resolution mass spectra (HRMS) were measured using Bruker Esquire 3000plus mass spectrometer. Melting point (m.p.) was determined on X-6 micro melting point apparatus and was uncorrected.

4.2 Chemistry

4.2.1 Synthesis of methyl 2-cyano-2-(hydroxyimino)-acetate (**B**)

To mixture of methyl cyanoacetate (**A**) (3.00 g, 30.0 mmol) and sodium nitrite (2.48 g, 36.0 mmol) in water, acetic acid (2.5 mL) was dropwise added at 0～5 ℃ for 1 h. Then the resulting mixture continued to react at room temperature for 1 h. The mixture was extracted with ethyl acetate, the organic layer was then concentrated to dry. The residue was washed with cyclohexane to give **B** (3.60 g) as a pale yellow solid, yield 93.8%.[29]

4.2.2 Synthesis of methyl 2-cyano-2-aminoacetate (**C**)

Compound **B** (10.00 g, 78.0 mmol) was dissolved in the mixture of water (240.0 mL) and ethanol (110.0 mL). Sodium hydrosulfite (61.11 g, 351.0 mmol) was added in batches to the mixture, and the obtained mixture was heated at 50 ℃ until reaction completion as indication by thin layer chromatography (TLC). The mixture was extracted with CH_2Cl_2, then concentrated, filtered and evaporated to give **C** (7.35 g) as yellow oil, yield 82.6%.

4.2.3 Synthesis of 2-amino-2-cyanoacetamide (**1**)

Compound **C** (7.35 g, 64.4 mmol) was dissolved in methanol (40.0 mL), then ammonium hydroxide (20 mL) was added in ice bath under the protection of nitrogen. The mixture was stirred for 20 min, then concentrated and filtered to give **1** (5.94 g) as orange red solid, yield 93.1%.[30]

4.2.4 Synthesis of ethyl 2-acetyl-3-(dimethylamino)-acrylate (**2**)

p-TsOH (0.12 g, 0.7 mmol) was dissolved in ethyl acetoacetate (**D**) (6.00 g, 46.1 mmol), then DMF-DMA (6.04 g, 50.7 mmol) was added. The mixture was refluxed at 80 ℃ for 70 min. Then evaporated under reduced pressure to give deep red oily mixture, which was purified by silica column chromatography with ethyl acetate as a eluent to provide **2** as yellow oil (7.20 g) with yield of 84.3%.[31]

4.2.5 Synthesis of ethyl 3-methyl-2-cyanopyrrole-4-carboxylate (**4**)

Compound **2** (11.09 g, 59.9 mmol) was dissolved in acetic acid (90 mL), then **1** (5.94 g, 59.9 mmol) was added. The mixture was reacted at room temperature for 18 h. The mixture appeared orange red when **1** was utterly dissolved. Then the mixture was refluxed at 106 ℃ for 6 h, and evaporated under reduced pressure to give black viscose, which was purified by silica column chromatography [*V*(ethyl acetate)∶*V*(petroleum ether)=1∶10～1∶2] to provide **4** as pale yellow solid (6.43 g) with yield of 83.5%.[18,32]

4.2.6 Synthesis of ethyl *N*-amino-3-methyl-2-cyano-pyrrole-4-carboxylate (**5**)

Compound **4** (1.25 g, 7.0 mmol) was dissolved in DMF

(6.0 mL), and cooled to −20 ℃, then sodium hydride was added. The mixture was reacted for 45 min with stirring. Ether solution of chloramine (140.0 mL, 21.0 mmol) in a constant pressure funnel was slowly added. The reaction mixture was stirred at −20 ℃ for 2 h, then room temperature for 1 h. The solution changed to transparent clear after saturated sodium thiosulfate aqueous solution was added. Water (10.0 mL) was added to dilute the solution. The obtained mixture was extracted with ethyl ether (30.0 mL×3), then the organic phase was combined and washed with water and saturated brine, dried over anhydrous sodium sulfate, concentrated and purified by silica column chromatography [*V*(ethyl acetate)∶*V*(petroleum ether)=1∶4] to provide **5** as pale yellow solid (1.24 g) with yield of 91.5%.[18] m.p. 130.4～131.0 ℃; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.49 (s, 1H), 6.48 (s, 2H), 4.19 (q, J=7.1 Hz, 2H), 2.30 (s, 3H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.4, 133.2, 131.8, 114.0, 113.1, 108.0, 61.1, 15.9, 12.9; HRMS calcd for $C_9H_{12}N_3O_2$ [M+H]$^+$ 194.0930, found 194.0930.

4.2.7 Synthesis of *N*,*N*-dimethylformamidine derivative (**6**)

Compound **5** (0.58 g, 3.0 mmol) was dissolved in toluene (9.0 mL), then DMF-DMA (0.9 mL, 6.6 mmol) was added. The mixture solution was stirred at 30 ℃ for 5 min. Acetic acid (0.3 mL) was added to the mixture, and reacted for 10 min. Then, toluene was removed under reduced pressure to give orange red oil. Water was added, and the pH of the mixture was adjusted to 3 by the addition of 2 mol•L^{-1} H_2SO_4 aqueous solution. The obtained orange red solid was changed to yellow after stirring for 1 h at 30 ℃. The yellow solid was filtered and washed with water, then purified by silica column chromatography [*V*(ethyl acetate)∶*V*(petroleum ether)=1∶4] to give **6** (0.66 g) as off-white powder with yield of 89.2%.[18] m.p. 86.8～87.9 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.32 (s, 1H), 4.25 (q, J=7.1 Hz, 2H), 3.04 (s, 3H), 3.02 (s, 3H), 2.40 (s, 3H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.7, 159.7, 132.6, 126.2, 113.6, 113.3, 104.9, 60.8, 42.0, 36.1, 15.4, 12.6; HRMS calcd for $C_{12}H_{16}N_4O_2Na$ [M+Na]$^+$ 271.1171, found 271.1165.

4.2.8 Synthesis of ethyl 4-arylamino-5-methylpyrrolo-[2,1-*f*][1,2,4]triazine-6-carboxylates **7a**～**7d**

R^1-aniline (4.4 mmol) and *p*-TsOH (0.10 g, 0.6 mmol) were added to the solution of **6** in toluene (25 mL), then heated up to 112 ℃ to reflux for 21～38 h. After completion of the reaction as indicated by TLC, the reaction solution was evaporated under reduced pressure. The residue was purified by silica column chromatography [*V*(ethyl acetate)∶*V*(chloroform)=1∶15] to give **7a**～**7d** with yield of 25.7%～45.2%.

Ethyl 4-(3-chloro-4-(3-fluorobenzyloxy)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**7a**): Off-white powder, 0.59 g, yield 32.4%. m.p. 184.8～185.9 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.91 (s, 1H), 7.78 (s, 1H),7.43 (d, J=10.6 Hz, 1H), 7.37～7.33 (m, 1H), 7.26～7.29 (m, 2H), 7.03～7.00 (m, 1H), 6.94 (d, J=8.8 Hz, 1H), 5.14 (s, 2H), 4.34 (q, J=7.1 Hz, 2H), 2.89 (s, 3H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 164.6, 163.0 (d, $^1J_{C\text{-}F}$=246.4 Hz), 154.5, 151.4, 148.5, 138.9 (d, $^3J_{C\text{-}F}$=7.6 Hz), 131.1, 130.2 (d, $^3J_{C\text{-}F}$=8.3 Hz), 128.8, 124.9, 123.7, 122.4 (d, $^4J_{C\text{-}F}$=3.1 Hz), 122.0, 121.9, 115.5, 115.0 (d, $^2J_{C\text{-}F}$=21.2 Hz), 114.3, 114.0 (d, $^2J_{C\text{-}F}$=22.1 Hz), 113.3, 70.4, 60.2, 14.4, 11.9; HRMS calcd for $C_{23}H_{21}ClFN_4O_3$ [M+H]$^+$ 455.1286, found 455.1281.

Ethyl 4-(3-chloro-4-fluorophenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**7b**): Off-white powder, 0.63 g, yield 45.2%. m.p. 145.8～146.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.92 (s, 1H), 7.89 (dd, J=6.4, 2.5 Hz, 1H), 7.49～7.43 (m, 1H), 7.15 (t, J=8.7 Hz, 1H), 4.34 (q, J=7.1 Hz, 2H), 2.90 (s, 3H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 164.5, 155.3 (d, $^1J_{C\text{-}F}$=247.8 Hz), 154.4, 148.4, 133.8 (d, $^4J_{C\text{-}F}$=2.9 Hz), 124.4, 122.0, 121.8 (d, $^3J_{C\text{-}F}$=6.9 Hz), 121.3 (d, $^2J_{C\text{-}F}$=18.8 Hz), 116.7 (d, $^3J_{C\text{-}F}$=22.4 Hz), 115.7, 114.3, 113.1, 60.3, 14.4, 11.8; HRMS calcd for $C_{16}H_{15}ClFN_4O_2$ [M+H]$^+$ 349.0868, found 349.0868.

Ethyl 4-(3-ethynylphenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**7c**): Pale yellow solid, 0.49 g, yield 38.3%. m.p. 133.2～133.8 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.93 (s, 1H), 7.81 (s, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 7.28 (d, J=7.7 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 3.11 (s, 1H), 2.90 (s, 3H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C NMR (151 MHz,$CDCl_3$) δ: 164.6, 154.5, 148.6, 137.6, 129.2, 128.7, 125.2, 123.2, 122.4, 122.1, 115.6, 114.3, 113.4, 83.1, 78.0, 60.6, 14.5, 11.9; HRMS calcd for $C_{18}H_{17}N_4O_2$ [M+H]$^+$ 321.1352, found 321.1353.

Ethyl 4-(4-(*E*)-(propen-1-yl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**7d**): Pale yellow solid, 0.26 g, yield 25.7%. m.p. 120.2～121.0 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.92 (s, 1H), 7.58 (d, J=8.5 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 6.37 (d, J=15.8 Hz, 1H), 6.18～6.24 (m, 1H), 4.34 (q, J=7.1 Hz, 2H), 2.90 (s, 3H), 1.88 (dd, J=6.6, 1.5 Hz, 3H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 164.6, 154.4, 148.7, 135.7, 135.0, 130.2, 126.5, 125.7, 122.1, 121.8, 115.3, 114.1, 113.5, 60.2, 18.5, 14.4, 11.8; HRMS calcd for $C_{19}H_{21}N_4O_2$ [M+H]$^+$ 337.1665, found 337.1661.

4.2.9 Synthesis of 4-arylamino-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acids **8a**～**8d**

Sodium hydroxide aqueous solution (3 mol•L^{-1}, 0.9 mL, 3.0 mmol) was added to the mixture of **7** (1.0 mmol) in 5 mL of THF/MeOH (*V*∶*V*=1∶1). The reaction mixture was refluxed for 2 h at 60 ℃. The organic solvents was removed under reduced pressure. The residues was dissolved in water, and pH was adjusted to 2 by the addition of 2 mol•L^{-1} H_2SO_4 aqueous solution. The obtained white solid was filtered and washed with water, then dried *in vacuo* to give **8a**～**8d** with yield of 75.0%～93.5%.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (**8a**):

Off-white powder, 0.39 g, yield 90.7%. m.p. 260.7～261.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.05 (s, 1H), 7.88 (s, 1H), 7.73 (s, 1H), 7.45～7.50 (m, 2H), 7.28～7.34 (m, 3H), 7.23～7.15 (m, 1H), 5.27 (s, 2H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.4, 164.5, 162.2 (d, $^1J_{C\text{-}F}$=247.8 Hz), 161.0, 150.6, 139.6 (d, $^3J_{C\text{-}F}$=7.5 Hz), 130.6 (d, $^3J_{C\text{-}F}$=8.2 Hz), 125.7, 124.0, 123.3 (d, $^4J_{C\text{-}F}$=2.8 Hz), 122.1, 121.2, 117.6, 115.6, 114.7 (d, $^2J_{C\text{-}F}$=21.1 Hz), 114.6, 114.3, 114.0 (d, $^2J_{C\text{-}F}$=22.0 Hz), 113.4, 69.4, 11.6; HRMS calcd for $C_{21}H_{17}ClFN_4O_3$ [M＋H]$^+$ 427.0973, found 427.0948.

4-(3-Chloro-4-fluorophenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (**8b**): Off-white powder, 0.24 g, yield 75.0%. m.p. 249.6～250.1 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 12.42 (s, 1 H), 8.80 (s, 1H), 8.08 (s, 1H), 7.97 (s, 2H), 7.67 (d, J=2.9 Hz, 1H), 7.44 (t, J=8.9 Hz, 1H), 2.83 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 165.4, 154.4, 154.1 (d, $^1J_{C\text{-}F}$=243.4 Hz), 148.1, 135.2, 125.4, 124.3 (d, $^3J_{C\text{-}F}$=6.5 Hz), 121.6, 116.7 (d, $^2J_{C\text{-}F}$=21.7 Hz), 116.4 (d, $^2J_{C\text{-}F}$=21.5 Hz), 115.7 (d, $^4J_{C\text{-}F}$=2.9 Hz), 114.1, 113.3 (d, $^3J_{C\text{-}F}$=6.1 Hz), 11.6; HRMS calcd for $C_{14}H_{10}ClFN_4O_2Na$ [M＋Na]$^+$ 343.0374, found 343.0362.

4-(3-Ethynylphenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazine-6-carboxylic acid (**8c**): Pale yellow solid, 0.25 g, yield 86.2%. m.p. 243.1～244.2 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.07 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 7.39 (t, J=7.8 Hz, 1H), 7.26 (d, J=5.3 Hz, 1H), 4.21 (s, 1H), 2.83 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 170.7, 159.6, 153.5, 153.4, 143.6, 134.1, 132.8, 131.5, 129.3, 127.0, 126.8, 120.9, 118.6, 88.5, 86.0, 16.8; HRMS calcd for $C_{16}H_{12}N_4O_2Na$ [M＋Na]$^+$ 315.0858, found 315.0844.

4-(4-(*E*)-(Propen-1-yl)phenylamino)-5-methylpyrrolo-[2,1-*f*][1,2,4]triazine-6-carboxylic acid (**8d**). Pale yellow solid, 0.29 g, yield 93.5%. m.p. 252.3～253.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.04 (s, 1H), 8.03 (s, 1H), 7.89 (d, J=9.0 Hz, 2H), 7.40 (d, J=8.6 Hz, 2H), 6.42 (d, J=15.9 Hz, 1H), 6.34～6.20 (m, 1H), 2.80 (s, 3H), 1.86 (dd, J=6.5, 1.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 165.4, 133.9, 131.4, 130.3, 125.8, 125.3, 124.9, 123.5, 121.9, 121.8, 116.3, 115.5, 113.7, 18.2, 11.6; HRMS calcd for $C_{17}H_{17}N_4O_2$ [M＋H]$^+$ 309.1352, found 309.1338.

4.2.10 Synthesis of 4-arylamino-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamides **9a**～**9d**

8a～**8d** (0.1 mmol) and EDCI (0.2 mmol, 0.0384 g) were dissolved in the mixture of DMF (1 mL) and CH_2Cl_2 (2 mL), then triethylamine (0.25 mL) was added. The reaction mixture was stirring for 1 h at room temperature, then DMAP (0.12 mmol, 0.0148 g) and 2-methyl sulfonyl ethylamine hydrochloride (0.2 mmol, 0.0320 g) were added and reacted 12 h. After completion of the reaction as indicated by TLC, the water was added. Then it was extraced with CH_2Cl_2. The organic layer was directly concentrated and purified by silica column chromatography [*V*(methanol)∶*V*(chloroform＝1∶30) to give **9a**～**9d** with yield of 86.9%～90.3%.

4-(3-Chloro-4-(3-fluorobenzyloxy)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamide (**9a**): Off-white powder, 0.0469 g, yield 88.2%. m.p. 259.0～259.9 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.62 (s, 1H), 8.39 (t, J=5.4 Hz, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.83 (d, J=2.5 Hz, 1H), 7.59～7.53 (m, 1H), 7.47 (dd, J=14.0, 7.9 Hz, 1H), 7.34～7.29 (m, 2H), 7.25 (d, J=9.0 Hz, 1H), 7.20～7.15 (m, 1H), 5.26 (d, J=10.6 Hz, 2H), 3.60～3.68 (m, 2H), 3.38 (s, 2H), 3.04 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 164.3, 164.2, 162.2 (d, $^1J_{C\text{-}F}$=243.2 Hz), 154.2, 150.3, 148.0, 139.6 (d, $^3J_{C\text{-}F}$=7.2 Hz), 131.9, 130.6 (d, $^3J_{C\text{-}F}$=8.5 Hz), 125.6, 123.9, 123.3 (d, $^4J_{C\text{-}F}$=2.9 Hz), 120.9, 118.5, 118.4, 114.7 (d, $^2J_{C\text{-}F}$=21.2 Hz), 114.1, 114.0 (d, $^2J_{C\text{-}F}$=21.9 Hz), 112.8, 69.3, 53.0, 40.8, 32.8, 11.4; HRMS calcd for $C_{24}H_{24}ClFN_5O_4S$ [M＋H]$^+$ 532.1222, found 532.1207.

4-(3-Chloro-4-fluorophenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamide (**9b**): Off-white powder, 0.0367 g, yield 86.1%. m.p. 249.8～250.6 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.41 (t, J=5.5 Hz, 1H), 8.15 (s, 1H), 7.98 (dd, J=6.8, 2.4 Hz, 1H), 7.96 (s, 1H), 7.68 (dd, J=8.5, 3.3 Hz, 1H), 7.44 (t, J=9.1 Hz, 1H), 3.63～3.66 (m, 2H), 3.39 (s, 2H), 3.05 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 164.1, 154.2, 154.0 (d, $^1J_{C\text{-}F}$=243.7 Hz), 147.8, 135.3 (d, $^4J_{C\text{-}F}$=3.0 Hz), 125.3, 124.2 (d, $^3J_{C\text{-}F}$=7.0 Hz), 118.8 (d, $^2J_{C\text{-}F}$=19.8 Hz), 118.7, 116.6, 116.5 (d, $^2J_{C\text{-}F}$=21.8 Hz), 114.3, 112.8, 53.0, 40.8, 32.9, 11.5; HRMS calcd for $C_{17}H_{18}ClFN_5O_3S$ [M＋H]$^+$ 426.0803, found 426.0805.

4-(3-Ethynylphenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]-triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamide (**9c**): Off-white powder, 0.0345 g, yield 86.9%. m.p. 199.6～200.3 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.69 (s, 1H), 8.42 (t, J=5.6 Hz, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.88 (t, J=1.6 Hz, 1H), 7.78～7.74 (m, 1H), 7.40 (t, J=7.9 Hz, 1H), 7.27 (d, J=7.7 Hz, 1H), 4.22 (s, 1H), 3.62～3.68 (m, 2H), 3.40 (s, 2H), 3.06 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 164.1, 154.1, 147.9, 128.8, 127.5, 126.1, 124.0, 121.8, 121.7, 118.6, 118.6, 114.2, 112.9, 83.2, 80.8, 53.0, 40.8, 32.9, 11.4; HRMS calcd for $C_{19}H_{19}N_5O_3$-SNa [M＋Na]$^+$ 420.1106, found 420.1076.

(4-(*E*)-(Propen-1-yl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-(*N*-(2-(methylsulfonyl)ethyl))carboxamide (**9d**): Pale yellow solid, 0.0373 g, yield 90.3%. m.p. 185.9～186.4 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.49 (s, 1H), 8.34 (t, J=5.6 Hz, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.66 (dd, J=33.3, 8.5 Hz, 2H), 7.38 (dd, J=8.6, 2.5 Hz, 2H), 6.40 (d, J=15.8 Hz, 1H), 6.31～6.22 (m, 1H), 3.62～3.66 (m, 2H), 3.38 (s, 2H), 3.04 (s, 3H), 2.80 (s, 3H), 1.85 (d, J=5.7 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 164.3, 156.3, 153.4, 148.0, 137.1, 133.3, 130.3, 125.7, 124.6, 123.3, 122.8, 118.5, 118.0, 53.0, 40.9, 32.8, 18.2, 11.4; HRMS calcd for $C_{20}H_{23}N_5O_3SNa$ [M＋Na]$^+$ 436.1419, found 436.1408.

4.3 Biology

4.3.1 Cell culture

SW480, A431, and A549 cells were maintained on 60 mm cell culture dishes and cultured using DMEM supplemented with 10% (wt%) FBS, 100 units/mL penicillin, 100 μg/mL streptomycin and 2 mmol•L^{-1} *L*-glutamate at 37 ℃ and 5% (vol%) CO_2 with 95% humidity.

4.3.2 Antiproliferative activity *in vitro*

The antiproliferative activities of targeted compounds against SW480, A549, and A431 cells were evaluated *in vitro* by the MTT assay according to reported methods.[10,28,33]

Supporting Information ^{1}H NMR, ^{13}C NMR and HRMS spectra of all the target compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

References

[1] Bray, F.; Jemal, A.; Grey, N.; Ferlay, J.; Forman, D. *Lancet Oncol.* **2012**, *13*, 790.
[2] Siegel, R. L.; Miller, K. D.; Jemal, A. *Ca-Cancer J. Clin.* **2017**, *67*, 7.
[3] Anon, T. *Cell* **2017**, *168*, 545.
[4] Zhou, W.; Ercan, D.; Chen, L.; Yun, C. H.; Li, D.; Capelletti, M.; Cortot, A. B.; Chirieac, L.; Iacob, R. E.; Padera, R.; Engen, J. R.; Wong, K. K.; Eck, M. J.; Gray, N. S.; Janne, P. A. *Nature* **2009**, *462*, 1070.
[5] Dhillon, S. *Targeted Oncol.* **2015**, *10*, 153.
[6] Cohen, M. H.; Williams, G. A.; Sridhara, R.; Chen, G.; Pazdur, R. *Oncologist* **2003**, *8*, 303.
[7] Ryan, Q.; Ibrahim, A.; Cohen, M. H.; Johnson, J.; Ko, C. W.; Sridhara, R.; Justice, R.; Pazdur, R. *Oncologist* **2008**, *13*, 1114.
[8] Kuwano, M.; Sonoda, K.; Murakami, Y.; Watari, K.; Ono, M. *Pharmacol. Therapeut.* **2016**, *161*, 97.
[9] Jia, Y.; Yun, C. H.; Park, E.; Ercan, D.; Manuia, M.; Juarez, J.; Xu, C.; Rhee, K.; Chen, T.; Zhang, H.; Palakurthi, S.; Jang, J.; Lelais, G.; Didonato, M.; Bursulaya, B.; Michellys, P. Y.; Epple, R.; Marsilje, T. H.; Mcneill, M.; Lu, W.; Harris, J.; Bender, S.; Wong, K. K.; Janne, P. A.; Eck, M. J. *Nature* **2016**, *534*, 129.
[10] Chen, L.; Zhang, Y.; Liu, J.; Wang, W.; Li, X.; Zhao, L.; Wang, W.; Li, B. *Eur. J. Med. Chem.* **2017**, *138*, 689.
[11] Towles, J. K.; Clark, R. N.; Wahlin, M. D.; Uttamsingh, V.; Rettie, A. E.; Jackson, K. D. *Drug Metab. Dispos.* **2016**, *44*, 1584.
[12] Dempke, W. C.; Zippel, R. *Anticancer Res.* **2010**, *30*, 4477.
[13] Chou, T.; Finn, R. S. *Future Oncol.* **2012**, *8*, 1083.
[14] Finn, R. S.; Kang, Y. K.; Mulcahy, M.; Polite, B. N.; Lim, H. Y.; Walters, I.; Baudelet, C.; Manekas, D.; Park, J. W. *Clin. Cancer Res.* **2012**, *18*, 2090.
[15] Wu, X.; Yang, M.; Shu, Q.; Zhu, C. *WO 2013178021*, **2013** [*Chem. Abstr.* **2013**, *187*, 5272].
[16] Li, Q.; Lescrinier, E.; Groaz, E.; Persoons, L.; Daelemans, D.; Herdewijn, P.; De Jonghe, S. *ChemMedChem* **2018**, *13*, 97.
[17] Degorce, S. L.; Anjum, R.; Dillman, K. S.; Drew, L.; Groombridge, S. D.; Halsall, C. T.; Lenz, E. M.; Lindsay, N. A.; Mayo, M. F.; Pink, J. H.; Robb, G. R.; Scott, J. S.; Stokes, S.; Xue, Y. *Bioorg. Med. Chem.* **2018**, *26*, 913.
[18] Ma, S.-S.; Zhang, Y.-L.; Zhang, X.-Q.; Gu, H.-M.; Li, B.-L. *Chem. Res. Appl.* **2015**, *27*, 870 (in Chinese).
(马沙沙, 张娅玲, 张喜全, 顾红梅, 李宝林, 化学研究与应用, **2015**, *27*, 870.)
[19] Zhang, Y.; Chen, L.; Xu, H.; Li, X.; Zhao, L.; Wang, W.; Li, B.; Zhang, X. *Eur. J. Med. Chem.* **2018**, *147*, 77.
[20] Li, B.; Ma, S.; Li, J.; Wang, L.; Liu, J.; Chen, L. *CN 104788460*, **2015** [*Chem. Abstr.* **2015**, *119*, 3561].
[21] Gavai, A. V.; Wen-Ching, H.; Ping, C.; Ruediger, E. H.; Harold, M.; Fink. B. E.; Norris, D. J. *WO 2005065266*, **2005** [*Chem. Abstr.* **2005**, *638*, 632].
[22] Borzilleri, R. M.; Cai, Z. W.; Ellis, C.; Fargnoli, J.; Fura, A.; Gerhardt, T.; Goyal, B.; Hunt, J. T.; Mortillo, S.; Qian, L.; Tokarski, J.; Vyas, V.; Wautlet, B.; Zheng, X.; Bhide, R. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1429.
[23] Chandregowda, V.; Rao, G. V.; Reddy, G. C. *Org. Process Res. Dev.* **2007**, *11*, 813.
[24] Zhan, D.; Li, S.; Zhao, H.; Lan, M. *Chin. J. Org. Chem.* **2011**, *31*, 207 (in Chinese).
(詹冬梅, 李思远, 赵红莉, 蓝闽波, 有机化学, **2011**, *31*, 207.)
[25] Wang, D.; Yu, J.; Li, W.; Cui, Q.; Feng, S. *Chin. J. Org. Chem.* **2012**, *32*, 1547 (in Chinese).
(王道林, 于家懿, 李伟, 崔庆涛, 冯姗姗, 有机化学, **2012**, *32*, 1547.)
[26] Wong, R.; Turlova, E.; Feng, Z. P.; Rutka, J. T.; Sun, H. S. *Oncotarget* **2017**, *8*, 11239.
[27] Chen, W. L.; Turlova, E.; Sun, C. L.; Kim, J. S.; Huang, S.; Zhong, X.; Guan, Y. Y.; Wang, G. L.; Rutka, J. T.; Feng, Z. P.; Sun, H. S. *Mar. Drugs* **2015**, *13*, 2505.
[28] Zhang, Y.; Zhang, Y.; Liu, J.; Chen, L.; Zhao, L.; Li, B.; Wang, W. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1584.
[29] Bhaskar, B. S.; Singh, S. G.; Neeraj, G.; Kumar, T. P.; Srinivasan, C. V.; Lalit, W. *WO 2010140168*, **2010** [*Chem. Abstr.* **2010**, *153*, 0544].
[30] Wu, Z.; Wang, X.; Zhou, J. *CN 1250773*, **2000** [*Chem. Abstr.* **2000**, *862*, 111].
[31] Ogan, M. D.; Tran, S. B.; Rinehart, J. K. *J. Labelled Compd. Radiopharm.* **2006**, *49*, 139.
[32] Cohnen, E.; Dewald, R. *Synthesis* **1987**, 566.
[33] Zhang, Y.; Lü, M.; Zhang, Y.; Chen, L.; Wang, W.; Li, B. *Chin. J. Org. Chem.* **2017**, *37*, 1787 (in Chinese).
(张颖, 吕梦娇, 张娅玲, 陈丽, 王伟, 李宝林, 有机化学, **2017**, *37*, 1787.)

(Zhao, C.)

