RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2014, **4**, 11168

Copper(II)-catalyzed cascade approach for the synthesis of pyrrolo[2,1-*f*][1,2,4]triazine-fused isoquinolines†

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Received 5th December 2013
Accepted 4th February 2014

DOI: 10.1039/c3ra47324d

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We report herein a one-pot copper(II)-catalyzed coupling-cyclization leading to small molecules based on a novel structural motif, *i.e.* the pyrrolo[2,1-*f*][1,2,4]triazine moiety fused with an isoquinoline ring. The reaction is easy to perform in good to excellent yields with high atom economy and exhibits a broad substrate scope.

Introduction

The development of synthetic organic chemistry in pharmaceutical science provides new opportunities to synthesize new bioactive chemical entities. The transition-metal-catalyzed cascade cyclization reaction has been used as a major method to construct heterocyclic scaffolds from readily accessible organic compounds.[1] In the past few years, Lewis acids (complexes of Ag, Cu, Fe, Au, Pd *etc.*) have emerged as powerful catalysts for the purpose. The feasibility of activating C-heteroatom bonds like C–O, C–N, C–S bond by coordination to these catalysts has led to the development of a variety of catalytic reactions involving C-heteroatom bond formation with high atom economy.[2]

As a privileged fragment, pyrrolo[2,1-*f*][1,2,4]triazine skeleton is an important moiety that has been found to be present in several pharmaceutical candidates, exhibiting anticancer,[3] anti-inflammatory[4] activities (Fig. 1). For example, EGFR tyrosine kinase inhibitors BMS690514,[5] BMS599626 [6] and IGF1R inhibitor BMS754807 [7] all contain a pyrrolo[2,1-*f*][1,2,4]triazine scaffold. Therefore, the design and synthesis of novel pyrrolo-[2,1-*f*][1,2,4]triazine scaffolds attract the attention of both organic and medicinal chemists.[8]

Isoquinoline-fused polycyclic compounds are important structural moieties that appear in both natural products and therapeutic agents and have wide applications in pharmaceutical research (Fig. 1).[9] Considerable efforts have been made to develop efficient methods for the synthesis of this class of compounds. Using cascade addition of nucleophiles and cyclization, many reports in the literature[9b,10] have showed the successful synthesis of fused 1,2-dihydroisoquinolines in the presence or absence of Lewis acid catalysts like AgOTf,[11] AuCl,[12] or $Yb(OTf)_3$ (ref. 13) (Scheme 1 eqn 1).

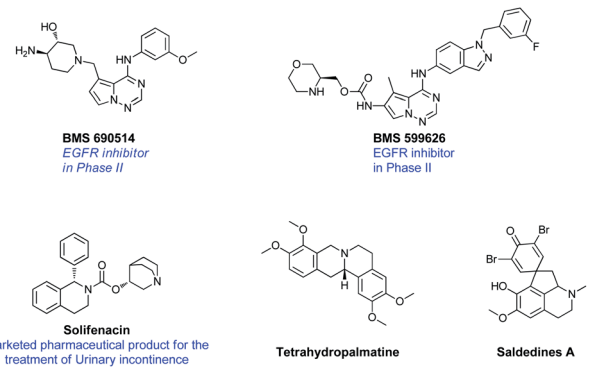
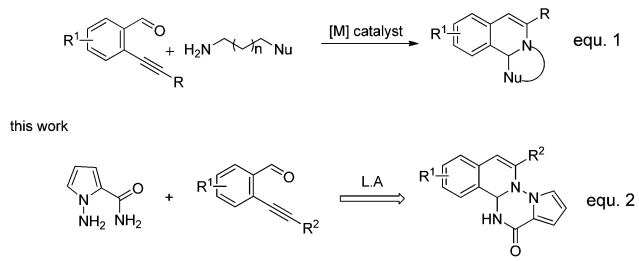


Fig. 1 Examples of pyrrolo[2,1-*f*][1,2,4]triazine derivatives and isoquinolines.

As a part of our interest in the construction of heterocyclic scaffolds using substituted *N*-amino pyrroles as building blocks to expand medicinal chemistry space,[8a,14] in this paper we



Scheme 1 A possible route for the construction of diverse 4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one.

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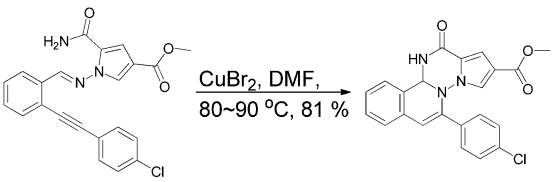
† Electronic supplementary information (ESI) available. CCDC 909484. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra47324d

hypothesized that the condensation reaction of 2-alkynylbenzaldehydes and *N*-amino pyrrole-2-carboxyamide would provide the corresponding imine intermediate, which would follows cascade addition of nucleophiles and cyclization to afford fused isoquinolines in the presence of appropriate Lewis acids (Scheme 1 eqn (2)).

Results and discussion

In order to explore this proposal, methyl 1-amino-5-carbamoyl-1*H*-pyrrole-3-carboxylate (**1a**) was treated with 1.2 equiv. of 2-((4-chlorophenyl)ethynyl)benzaldehyde (**2a**) in the presence of a variety of transition metal catalysts and solvents. The results were summarized in Table 1. When the reaction was treated by AuCl (0.1 equiv.) in the presence of 4 Å MS in dichloroethane (DCE) at room temperature, the expected product **3a** was not obtained, but imine **4a** was isolated in 59% yield (Table 1, entry 1). Elevating the temperature to 80–90 °C gave the product **3a** in 30% yield and the imine **4a** in 20% yield (Table 1, entry 2). When gold(I) chloride was replaced by more cheaper copper catalyst $Cu(OTf)_2$, the same yield was obtained (Table 1, entry 3 *vs.* entry 2). In order to improve the solubility of reactants, dimethyl formamide (DMF) was employed as the solvent and the product **3a** was obtained in 65% yield (Table 1, entry 4). Then other catalysts such as $CuCl_2 \cdot 2H_2O$ and $CuBr_2$ were screened. **3a** was obtained in 72% and 83% yields, respectively (Table 1, entries 5 and 6). Without the catalyst the target product **3a** was not afforded, with a result of imine **4a** obtained in 73% yield (Table 1, entry 12). However, CuCl, $Cu(NO_3)_2 \cdot 3H_2O$, anhydrous $FeCl_3$ did not make this transformation proceed under the conditions (Table 1, entries 7–9), and only the imine **4a** was obtained. We speculate the transformation may proceed through the imine intermediate. So we conducted an experiment using imine **4a** and $CuBr_2$ in DMF at 80–90 °C to prove the proposition. Fortunately the imine can transform to the target compound in 81% yield (shown in Scheme 2). However, addition of base and ligand failed to give the desired product **3a** (Table 1, entries 10 and 11). Finally we also investigated the effect of reaction time. The yield was slightly lowered when monitored the progress in 2 hours, and the yield did not change when extending reaction time to 7 hours (Table 1, entries 13 and 14). The compound **3a** was characterized by the ^{1}H NMR, ^{13}C NMR and DEPT spectra analysis.

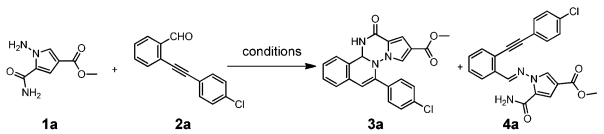


4a **3a**

Scheme 2 Transformation of **4a** to the target compound **3a**.

With the optimal conditions in hand, we examined the scope of the copper(II)-catalyzed annulation strategy with the results shown in Table 2. We first investigated the electron effects of substituents of 2-(phenylethynyl)benzaldehydes. When R was phenyl, it was found that the electron-withdrawing groups (–Cl, –F, $–CO_2CH_3$, $–NO_2$) on the R afforded the target products in good to excellent yields (60–85%, Table 2, entries 1, 4, 5, 8, 12, 13, and 16). And the electron-donating groups ($–CH_3$, $–OCH_3$)

Table 1 Selected optimization studies[a]

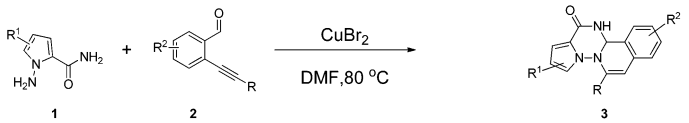


1a **2a** **3a** **4a**

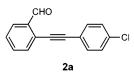
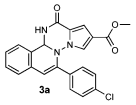
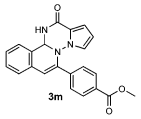
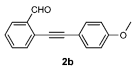
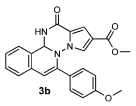
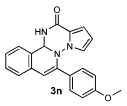
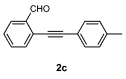
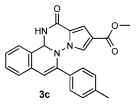
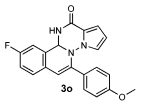
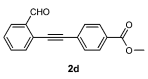
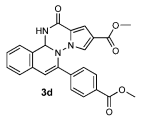
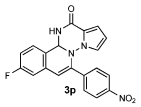
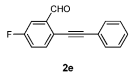
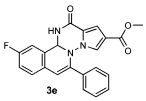
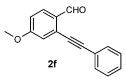
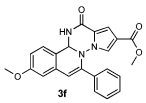
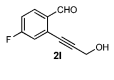
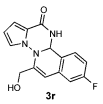
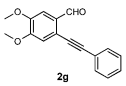
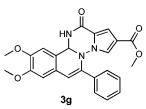
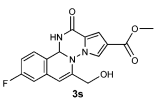
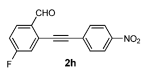
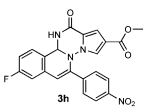
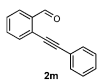
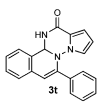
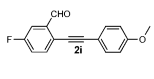
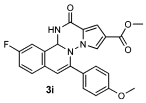
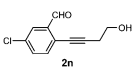
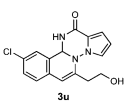
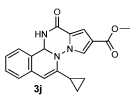
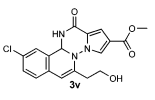
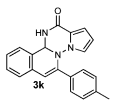
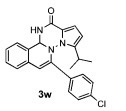
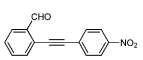
Entry	Catalyst	Additive	Solvent	Temp./°C	Yield of **3a**[b]	**4a**[c]
1	AuCl	4 Å MS	DCE	r.t.	0	59
2	AuCl	—	DCE	80–90	30	20
3	$Cu(OTf)_2$	—	DCE	80–90	31	15
4	$Cu(OTf)_2$	—	DMF	80–90	65	0
5	$CuCl_2 \cdot H_2O$	—	DMF	80–90	72	0
6	$CuBr_2$	—	DMF	80–90	83	0
7	CuCl	—	DMF	80–90	n.d.	30
8	$FeCl_3$	—	DMF	80–90	n.d.	40
9	$Cu(NO_3)_2 \cdot 3H_2O$	—	DMF	80–90	n.d.	46
10[d]	$CuCl_2 \cdot H_2O$	Phen	DMF	80–90	n.d.	28
11[d]	$CuCl_2 \cdot H_2O$	Phen + DBU	DMF	80–90	n.d.	24
12	—	—	DMF	80–90	0	73
13	$CuBr_2$	—	DMF	80–90	61[e]	Trace
14	$CuBr_2$	—	DMF	80–90	83[f]	0

[a] Reaction condition: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (0.02 mmol), solvent (3 ml), 4 h. [b] Yield isolated by column chromatograph. [c] Yield isolated by column chromatograph. [d] Phen (0.04 mmol), DBU (0.4 mmol) was added. [e] Reaction time for 2 h. [f] Reaction time for 7 h. r.t.: room temperature. Phen: 1,10-phenanthroline. DBU:1,8-diazabicyclo[5.4.0]undec-7-ene. n.d. = not detected.

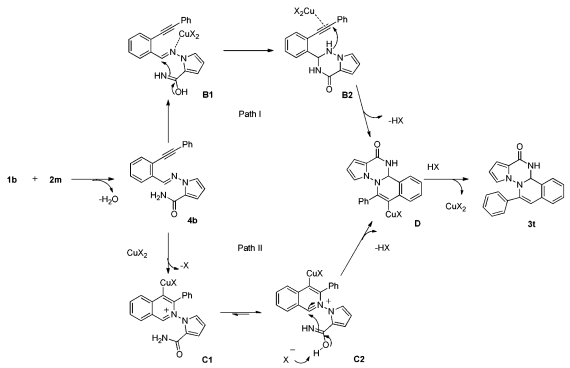
Table 2 Synthesis of substituted 4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one compounds[a]



1 2 3

Entry	1	2	3	Yield[b] (%)	Entry	1	2	3	Yield[b] (%)
1				83	13	**1b**	**2d**		81
2	**1a**			79	14	**1b**	**2b**		92
3	**1a**			56	15	**1b**	**2i**		73
4	**1a**			75	16	**1b**	**2h**		85
5	**1a**			64	17	**1b**	**2j**		72
6	**1a**			78	18	**1b**			84
7	**1a**			—[c]	19	**1a**	**2l**		71
8	**1a**			60	20	**1b**			64
9	**1a**			75	21	**1b**			94
10	**1a**			77	22	**1a**	**2n**		75
11	**1a**	**2c**		81	23		**2a**		71
12				67[d] 40[e]					

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $CuBr_2$ (0.02 mmol), DMF (3 ml), 80 °C, 4 h. [b] Isolated yield. [c] An inseparable mixture of unidentified products was obtained. [d] An inseparable mixture of **3l** and its brominated product in a ratio of 83 : 17 detected by LC-MS. [e] The pure compound **3l** was obtained in the presence of $Cu(OTf)_2$.



Scheme 3 A possible mechanism for the Cu(II)-catalysed cyclization of **1b** with **2m** as an example.

on the R could also give moderate to excellent yields (56–92%, Table 2, entries 2, 3, 6, 9, 11, 14, and 15). The similar results were also observed when R_2 was electron-withdrawing group fluoride or electron-donating group methoxyl except **2g** (Table 2, entries 5, 6, 8, and 9). We proposed that the two electron-donating groups of **2g** reduced the electrophilicity at the remote end of the alkyne, which thereby reduced the efficiency of the desired transformation by a 6-*endo*-dig cyclization approach (Table 2, entry 7). To our delight, the reaction went smoothly when R was alkyl or substituted alkyl. For example, alkyne **2j** bearing a cyclopropyl group provided the target product **3j** in 77% yield (Table 2, entry 10). Alkyne **2l** and **2n**, containing the aliphatic chain with hydroxyl group, were also suitable substrates for this reaction with excellent yields (71–94%, Table 2, entries 18, 19, 21, 22). We also investigated the electron effects of substituents on *N*-amino pyrrole-2-carboxyamide. The results showed that the electron-withdrawing group ($-CO_2CH_3$) gave much lower yields than that of un-substituted substrates (Table 2, entry 2 *vs.* 14, 3 *vs.* 11, 4 *vs.* 13, 8 *vs.* 16, 18 *vs.* 19, and 21 *vs.* 22) and the electron-donating group (-isopropyl) was also tolerated in this reaction (Table 2, entry 23).

On the basis of all the above results, the mechanism hypothesis, by taking the reaction of **1b** and **2m** as an example, has been proposed and shown in Scheme 3. At first, Condensation between **1b** and **2m** would generate imine **4b**. Imine **4b** can be converted to the final product **3t** through a cascade process proposed in two approaches. In path **I**, intermediate **B2**, formed by the attack of the nitrogen of the tautomer of amide at the imine, would carry on regiospecific hydroamination reaction, leading to the formation of **D**. In path **II**, copper-coordinated isoquinolinium cation **C1**, formed by nucleophilic attack of imine nitrogen atom at the alkynyl group, would be trapped by the tautomer of pyrrolo-2-amide, with the result of formation of **D**. Finally protonation might then occur to give compound **3t**. Furthermore, the structure of compound **3t** was determined by the X-ray crystallographic analysis (Fig. 2).

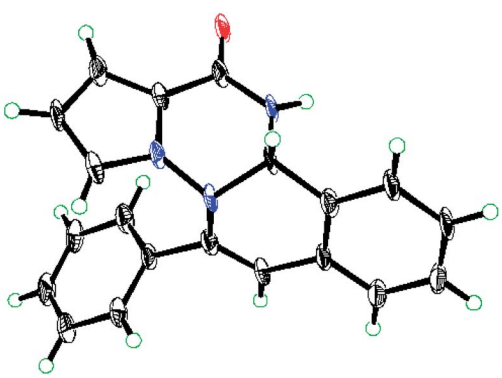


Fig. 2 X-ray crystal structure of **3t**.

Conclusions

In conclusion, we have developed a Cu(II)-catalyzed coupling–cyclization reaction that allowed facile access to an impressive variety of pyrrolo[2,1-*f*][1,2,4]triazine-fused isoquinolines in good to excellent yields. The reaction proceeded with high 6-*endo*-dig regioselectivity, and the product was confirmed by X-ray crystallographic study. This method appeared to be compatible with different substituted starting materials that have different electronic properties, increasing its applicability to various functional groups. Furthermore this reaction is easy to operate and atom-economical, which will make it attractive for the construction of variety of bioactive heterocyclic compounds. Currently biological evaluation of these compounds is under investigation.

Experimental section

Reagents (chemicals) were purchased from commercial sources, and used without further purification. Analytical thin layer chromatography (TLC) used was HSGF 254 (0.15–0.2 mm thickness, Yantai Jiangyou company, China). Nuclear magnetic resonance spectra were recorded on Varian Mercury-300 and/or Varian Mercury-500 spectrometers with TMS as internal standard. Chemical shift were reported in parts per million (ppm, δ) downfield from TMS. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded on a Finnigan/MAT-95 spectrometer. Melting points (m.p.) were measured by Büchi 510 melting point apparatus and were uncorrected.

General procedure for the synthesis of 2f, 2g and 2l

To a stirred solution of 2-bromobenzaldehyde (2 mmol) and terminal aromatic alkynes (2.4 mmol) in Et_3N (10 ml) was added $PdCl_2(PPh_3)$ (0.04 mmol) and CuI (0.02 mmol). The resulted mixture was heated under a nitrogen atmosphere at 50 °C for 4 h and then cooled to room temperature. After the separation of ammonium salt by filtration and removing of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding 2-(arylethyl)benzaldehyde **2f**, **2g** and **2l**.

4-Methoxyl-2-(phenylethynyl)benzaldehyde (2f). White solid. Yield 75%. m.p. 65–68 °C. ^{1}H NMR (300 MHz, CD_3Cl) δ 10.51 (d, J = 0.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.59–7.54 (m, 2H), 7.41–7.36 (m, 3H), 7.09 (d, J = 2.6 Hz, 1H), 6.97 (ddd, J = 8.8, 2.6, 0.8 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.4, 163.8,

131.7, 129.6, 129.5, 129.2, 129.0, 128.6, 122.2, 117.0, 115.6, 96.1, 84.9, 55.7. HRMS (ESI) calcd for $C_{16}H_{12}O_2$ $[M + H]^+$: 237.0916, found: 237.0918.

4,5-Dimethoxy-2-(phenylethynyl)benzaldehyde (2g). White solid. Yield 86%. m.p. 90–94 °C. ^{1}H NMR (300 MHz, CD_3Cl) δ 10.50 (s, 1H), 7.56 (dd, J = 6.7, 3.1 Hz, 2H), 7.43 (s, 1H), 7.41–7.34 (m, 3H), 7.06 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 153.7, 149.7, 131.6, 130.2, 128.9, 128.5, 122.5, 121.6, 114.3, 108.2, 95.0, 84.8, 56.4, 56.2. HRMS (ESI) calcd for $C_{17}H_{15}O_3$ $[M + H]^+$: 267.1021, found: 267.1024.

4-Fluoro-2-(3-hydroxyprop-1-yn-1-yl)benzaldehyde (2l). Yellow solid. Yield 81%. m.p. 72–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (d, J = 0.8 Hz, 1H), 7.93 (dd, J = 8.7, 5.8 Hz, 1H), 7.25–7.10 (m, 2H), 4.57 (d, J = 4.4 Hz, 2H), 2.13 (t, J = 6.7 Hz, 1H, OH). ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.0, 165.6 (d, $^1J_{C,F}$ = 253 Hz), 132.8 (d, $^4J_{C,F}$ = 2.6 Hz), 130.3 (d, $^3J_{C,F}$ = 10.2 Hz), 128.5 (d, $^3J_{C,F}$ = 10.9 Hz), 120.0 (d, $^2J_{C,F}$ = 23.4 Hz), 116.8 (d, $^2J_{C,F}$ = 22.1 Hz), 95.5, 80.2 (d, $^4J_{C,F}$ = 2.8 Hz), 51.5. HRMS (ESI) calcd for $C_{10}H_8FO_2$ $[M + H]^+$: 179.0508, found: 179.0509.

General procedure for the AuCl-catalyzed reaction for synthesis of 4a and 4b

To a DCE (3 ml) solution of **1a** (0.2 mmol) and **2a** (0.24 mmol) in 10 ml two-neck flask was added AuCl (10 mmol%) and some molecular sieves under a nitrogen atmosphere. The mixture was stirred at room temperature for 0.5–1 hour. The white precipitate was collected by filtration, washed by water and ether, and then dried *in vacuo* to obtain white solid **4a**.

(*E*)-Methyl 5-carbamoyl-1-(2-((4-chlorophenyl)ethynyl) benzylidene)amino-1*H*-pyrrole-3-carboxylate (4a). White solid. m.p. 265–270 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.36–8.34 (m, 1H), 8.08–8.04 (m, 1H), 7.86–7.81 (m, 1H), 7.78–7.73 (m, 1H), 7.70–7.55(m, 5H), 7.56–7.50 (m, 2H), 7.17–7.13 (m, 1H), 3.76 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.0, 160.7, 155.7, 134.5, 133.8, 133.7, 133.4, 132.5, 130.0, 129.4, 128.3, 127.6, 123.6, 122.2, 121.2, 115.0, 114.0, 94.7, 87.9, 51.8. IR (KBr): ν 3409.53, 3139.54, 1708.62, 1679.69, 1490.70, 1238.08, 761.74, 516.83 cm^{-1}. LCMS (ESI): m/z 406.2 $[M + H]^+$, 428.1 $[M + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{17}ClN_3O_3$ $[M + H]^+$ 406.0958, found 406.0965.

(*E*)-1-((2-(Phenylethynyl)benzylidene)amino)-1*H*-pyrrole-2-carboxamide (4b). White solid. m.p. 190–194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.05–8.00 (m, 1H), 7.83–7.80 (m, 1H), 7.79–7.76 (m, 1H), 7.74–7.70 (m, 1H), 7.66–7.61 (m, 2H), 7.60–7.54 (m, 2H), 7.47–7.41 (m, 4H), 6.83 (dd, J = 4.0, 1.8 Hz, 1H), 6.29 (dd, J = 4.0, 3.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.2, 150.7, 133.9, 133.509, 132.1, 131.9, 129.9, 129.8, 129.3, 127.3, 127.0, 123.6, 122.3, 117.1, 115.7, 109.0, 95.9, 86.7. IR (KBr): ν 3401.82, 3160.76, 1658.48, 1641.13, 1454.06, 1255.43, 755.96 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{16}N_3O$ $[M + H]^+$ 314.1293, found 314.1306.

General procedure for the Cu(II)-catalyzed annulation reaction

In a 10 ml reaction tube, *N*-amino-1*H*-pyrrole-2-carboxyamide (0.2 mmol), 2-alkynylbenzaldehyde (0.24 mmol), $CuBr_2$ (0.02 mmol) were mixed and stirred at room temperature for 5 min. Then the system was vigorously stirred at 80–90 °C for 4 h. After completion of the reaction, the mixture was poured into water, and then extracted with ethyl acetate (10 ml × 3). The combined organic layer was washed by saturated brine, and then concentrated *in vacuo* to afford the crude product. The pure product was obtained after purification of the residue by silica gel column chromatography (eluted with petroleum ether–ethyl acetate 3 : 1).

Methyl 12-(4-chlorophenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one-8-carboxylate (3a). White solid. m.p. 283–287 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.48–7.45 (m, 1H), 7.41(d, J = 7.0 Hz, 2H), 7.33–7.26 (m, 4H), 7.07 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 1.2 Hz, 1H), 6.36 (s, 1H), 6.05 (s, 1H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 157.8, 142.7, 134.2, 132.9, 130.9, 130.7, 130.4, 128.6, 128.1, 127.7, 127.7, 126.7, 125.6, 125.5, 112.8, 111.0, 108.79, 69.36, 51.73. IR (KBr): ν 3137.62, 3058.55, 1725.98, 1654.62, 1560.13, 759.82 cm^{-1}. LCMS (ESI): m/z 406.2 $[M + H]^+$, 428.1 $[M + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{17}ClN_3O_3$ $[M + H]^+$ 406.0958, found 406.0965.

Methyl 12-(4-methoxylphenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo-[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3b). Green solid. m.p. 245–250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.43–7.35 (m, 3H), 7.32–7.24 (m, 2H), 6.95–6.89 (m, 3H), 6.82–6.76 (m, 2H), 6.34 (s, 1H), 5.97 (s, 1H), 3.69 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 159.9, 157.9, 143.7, 131.3, 130.3, 130.0, 128.0, 127.7, 127.3, 126.5, 126.2, 125.6, 125.3, 113.9, 112.6, 110.8, 108.1, 69.4, 55.6, 51.6. IR (KBr): ν 3399.89, 3139.54, 1718.26, 1664.27, 1560.13, 1508.06, 759.82 cm^{-1}. LCMS (ESI): m/z 402.2 $[M + H]^+$, 424.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{23}H_{20}N_3O_4$ $[M + H]^+$: 402.1454, found 402.1471.

Methyl 12-*p*-tolyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3c). White solid. m.p. > 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.44–7.36 (m, 3H), 7.32–7.25 (m, 2H), 7.05 (d, J = 7.5 Hz, 2H), 6.92–6.87 (m, 3H), 6.34 (s, 1H), 5.97 (s, 1H), 3.63 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 157.9, 143.9, 138.8, 131.2, 130.4, 129.0, 128.5, 128.0, 127.7, 127.4, 126.6, 125.6, 125.4, 112.6, 110.9, 108.2, 69.4, 51.7, 21.2. IR (KBr): ν 3426.89, 3164.61, 2921.63, 1724.05, 1658.48, 759.82 cm^{-1}. LCMS (ESI): m/z 386.2 $[M + H]^+$, 408.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{23}H_{20}N_3O_3$ $[M + H]^+$: 386.1505, found 386.1490.

Methyl 12-(4-carboxylmethylphenyl)-4b*H*-isoquino[2,1-*a*]-pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3d). Yellow solid. m.p. 240–245 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.49–7.41 (m, 1H), 7.35–7.31 (m, 2H), 7.27–7.21 (m, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.96–6.94 (m, 1H), 6.22–6.19 (s, 1H), 5.93 (s, 1H), 5.82 (s, 1H), 3.90 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.6, 157.8, 142.8, 137.7, 130.9, 130.8, 130.6, 129.5, 128.5, 127.9, 126.9, 126.6, 125.9, 125.7, 124.4, 114.0, 113.1, 108.6, 70.1, 52.3, 51.5. IR (KBr): ν 3145.33, 1714.41, 1656.55, 1562.06, 759.82 cm^{-1}. LCMS (ESI): m/z 430.2 $[M + H]^+$, 452.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{24}H_{20}N_3O_5$ $[M + H]^+$: 430.1403, found 430.1399.

Methyl 3-fluoro-12-phenyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one-8-carboxylate (3e). Yellow solid. m.p. 270–274 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H), 7.38–7.20 (m, 7H), 7.02 (d, J = 7.2 Hz, 2H), 6.88 (d, J = 1.6 Hz, 1H),

6.36 (s, 1H), 6.04 (s, 1H), 3.61 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.6, 161.5 (d, $^1J_{C,F}$ = 245 Hz), 157.8, 143.2, 132.9, 129.6 (d, $^2J_{C,F}$ = 17.9 Hz), 129.3, 129.1 (d, $^3J_{C,F}$ = 7.4 Hz), 128.8, 128.4, 128.3, 127.6 (d, $^3J_{C,F}$ = 7.4 Hz), 127.5, 127.4, 127.2, 124.3, 117.7 (d, $^2J_{C,F}$ = 22.2 Hz), 113.9 (d, $^2J_{C,F}$ = 20.0 Hz), 113.0, 69.7 (d, $^4J_{C,F}$ = 1.4 Hz), 51.5. IR (KBr): ν 3409.53, 3149.19, 1712.48, 1654.62, 1562.06, 757.89 cm^{-1}. LCMS (ESI): *m*/*z* 390.2 $[M + H]^+$: 412.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{17}N_3O_3F$ $[M + H]^+$: 390.1254, found 390.1236.

Methyl 2-methoxy-12-phenyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one-8-carboxylate (3f). White solid. m.p. 302–305 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.36–7.17 (m, 5H), 7.04–6.96 (m, 2H), 6.89–6.84 (m, 3H), 6.29 (s, 1H), 5.96 (s, 1H), 3.77 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.49, 161.70, 158.76, 145.14, 134.88, 133.30, 130.27, 130.19, 129.56, 129.37, 128.52, 126.36, 120.12, 113.95, 113.46, 111.65, 111.38, 109.15, 70.00, 56.64, 52.56. IR (KBr): ν 3399.89, 3139.54, 1718.26, 1664.27, 1560.13, 1508.06, 759.82 cm^{-1}. LCMS (ESI): *m*/*z* 402.2 $[M + H]^+$, 424.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{23}H_{20}N_3O_4$ $[M + H]^+$: 402.1454, found 402.1471.

Methyl 2-fluoro-12-(4-nitrophenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3h). Yellow solid. m.p. > 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 1.7 Hz, 1H), 7.52–7.46 (m, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.23–7.16 (m, 2H), 6.91 (d, J = 1.7 Hz, 1H), 6.44 (s, 1H), 6.16 (s, 1H), 3.62 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.5, 163.4 (d, $^1J_{C,F}$ = 244.8 Hz), 157.7, 148.1, 143.1, 140.2, 132.9 (d, $^3J_{C,F}$ = 9.4 Hz), 130.5 (d, $^3J_{C,F}$ = 9.2 Hz), 130.4, 127.7, 125.4, 123.6, 123.1 (d, $^4J_{C,F}$ = 3.2 Hz), 114.7 (d, $^2J_{C,F}$ = 22.4 Hz), 113.1, 112.3 (d, $^2J_{C,F}$ = 23.0 Hz), 111.4, 108.8, 68.8, 51.7. IR (KBr): ν 3392.17, 3201.25, 1662.34, 1635.34, 1521.56, 1348.00, 750.17 cm^{-1}. LCMS (ESI): *m*/*z* 435.2 $[M + H]^+$, 457.1 $[M + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{15}FN_4O_5Na$ $[M + Na]^+$: 457.0924, found 457.0930.

Methyl 3-fluoro-12-(4-methoxylphenyl)-4b*H*-isoquino[2,1-*a*]-pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3i). White solid. m.p. 261–265 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.39 (s, 1H), 7.35–7.25 (m, 3H), 6.94–6.89 (m, 3H), 6.81–6.76 (m, 2H), 6.34 (s, 1H), 5.98 (s, 1H), 3.69 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6, 160.6 (d, $^1J_{C,F}$ = 245 Hz), 159.9, 157.8, 143.1, 130.1 × 2, 128.4 (d, $^3J_{C,F}$ = 8.3 Hz), 128.0 (d, $^4J_{C,F}$ = 3.2 Hz), 127.8, 127.4 (d, $^3J_{C,F}$ = 7.9 Hz), 126.1, 125.5, 117.2 (d, $^2J_{C,F}$ = 20.9 Hz), 115.1 (d, $^2J_{C,F}$ = 23.3 Hz), 113.9, 112.7, 111.0, 107.2, 68.9, 55.6, 51.7. IR (KBr): ν 3401.82, 3139.54, 1712.48, 1652.70, 1562.06, 1509.99, 833.10, 759.82 cm^{-1}. LCMS (ESI): *m*/*z* 420.2 $[M + H]^+$, 442.1 $[M + Na]^+$. HRMS (ESI) calcd for $C_{23}H_{19}FN_3O_3$ $[M + H]^+$: 420.1360, found 420.1345.

Methyl 12-cyclopropyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one-8-carboxylate (3j). White solid. m.p. 255–260 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 1.7 Hz, 1H), 7.42–7.33 (m, 2H), 7.25–7.21 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.11 (d, J = 1.3 Hz, 1H), 5.72 (d, J = 1.2 Hz, 1H), 5.63 (s, 1H), 3.85 (s, 3H), 1.02–0.92 (m, 1H), 0.79–0.59 (m, 2H), 0.55–0.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 157.6, 145.4, 131.0, 130.6, 127.7, 127.0, 126.4, 125.5, 125.2, 124.5, 114.1, 112.7, 103.8, 70.1, 51.6, 11.4, 6.7, 5.1. IR (KBr): ν 3421.10, 3176.18, 3131.83, 1708.62, 1656.55, 1562.06, 763.67 cm^{-1}. LCMS (ESI): *m*/*z* 336.2 $[M + H]^+$, 358.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{19}H_{18}N_3O_3$ $[M + H]^+$ 336.1348, found 336.1364.

12-*p*-Tolyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3k). White solid. m.p. 222–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (ddd, J = 8.6, 7.6, 4.0 Hz, 1H), 7.29 (dd, J = 4.0, 0.9 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.7 Hz, 2H), 6.90 (dd, J = 4.3, 1.6 Hz, 1H), 6.87–6.81 (m, 2H), 6.35 (dd, J = 2.8, 1.6 Hz, 1H), 6.23 (d, J = 1.7 Hz, 1H), 5.86–5.81 (m, 2H), 5.70 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 144.6, 138.8, 131.4, 131.0, 130.4, 128.7, 128.3, 127.1, 126.5, 125.9, 125.4, 123.8, 123.5, 112.1, 107.2, 106.4, 70.2, 21.3. IR (KBr): ν 3419.17, 3172.33, 1731.76, 1654.62, 763.67, 738.60 cm^{-1}. LCMS (ESI): *m*/*z* 328.2, $[M + H]^+$, 350.2, $[M + Na]^+$. HRMS (ESI) calcd for $C_{21}H_{18}N_3O$ $[M + H]^+$, 328.1450, found 328.1430.

12-(4-Nitrophenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]-triazin-6(5*H*)-one (3l). Yellow solid. m.p. 302–306 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–7.99 (m, 2H), 7.46 (ddd, J = 7.6, 6.8, 2.1 Hz, 1H), 7.40–7.22 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 6.91 (dd, J = 4.3, 1.6 Hz, 1H), 6.35 (dd, J = 2.8, 1.6 Hz, 1H), 6.24 (d, J = 1.5 Hz, 1H), 5.93 (s, 1H), 5.86 (dd, J = 4.3, 2.8 Hz, 1H), 5.67 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.5, 147.9, 142.6, 141.1, 130.7, 130.3, 130.2, 128.1, 127.9, 127.1, 125.7, 124.3, 123.9, 123.4, 111.2, 109.1, 106.6, 69.6. IR (KBr): ν 3397.96, 3178.11, 1666.20, 1348.00, 727.03 cm^{-1}. LCMS (ESI): *m*/*z* 359.2 $[M + H]^+$, 381.2 $[M + Na]^+$. HRMS (ESI) calcd for $C_{20}H_{14}N_4NaO_3$ $[M + Na]^+$,381.0964, found 381.0981.

12-(4-Carboxylmethylphenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo-[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3m). White solid. m.p. >300 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 2H), 7.48–7.40 (m, 1H), 7.37–7.19 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.89 (dd, J = 4.2, 1.7 Hz, 1H), 6.32 (dd, J = 2.8, 1.6 Hz, 1H), 6.23 (s, 1H), 5.90 (s, 1H), 5.82 (dd, J = 4.3, 2.7 Hz, 1H), 5.62 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.2, 158.5, 143.6, 139.2, 130.9, 130.3, 130.1, 129.1, 128.1, 127.6, 127.0, 125.5, 124.3, 123.9, 110.9, 108.3, 106.4, 69.5, 52.7. IR (KBr): ν 3423.03, 3174.26, 1720.19, 1652.70, 771.39, 738.60 cm^{-1}. LCMS (ESI): *m*/*z* 372.2 $[M + H]^+$, 394.2$[M + Na]^+$. HRMS (ESI) calcd for $C_{22}H_{17}N_3O_3Na$ $[M + Na]^+$, 394.1168, found 394.1171.

12-(4-Methoxylphenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one (3n). Yellow solid. m.p. 240–246 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.38 (m, 1H), 7.32–7.27 (m, 2H), 7.20 (d, J = 7.5 Hz, 1H), 6.93–6.84 (m, 3H), 6.73–6.64 (m, 2H), 6.36–6.33 (m, 1H), 6.22 (t, J = 2.0 Hz, 1H), 5.88–5.83 (m, 2H), 5.55 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 158.6, 144.2, 131.4, 130.4, 129.7, 127.0, 126.5, 126.2, 125.8, 125.4, 123.8, 123.4, 113.3, 112.1, 107.2, 106.4, 70.1, 55.2. IR (KBr): ν 3137.62, 3064.33, 1658.48, 1550.49, 1509.99, 736.67 cm^{-1}. LCMS (ESI): *m*/*z* 344.2, $[M + H]^+$, 366.2, $[M + Na]^+$. HRMS (ESI) calcd for $C_{21}H_{18}N_3O_2$ $[M + H]^+$, 344.1399, found 344.1411.

3-Fluoro-12-(4-methoxylphenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo-[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3o). White solid. m.p. 240–245 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.16 (m, 1H), 7.12 (td, J = 8.5, 2.6 Hz, 1H), 7.04 (dd, J = 8.1, 2.6 Hz, 1H), 6.89 (dd, J = 4.3, 1.6 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.34 (dd, J = 2.8, 1.6 Hz, 1H), 6.19 (s, 1H), 5.85 (dd, J = 4.3, 2.8 Hz, 1H), 5.83 (s, 1H), 5.62 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (125

MHz, DMSO-d_6) δ 160.5 (d, $^1J_{C,F} = 243.2$ Hz), 159.4, 158.1, 143.3, 129.4, 128.3 (d, $^3J_{C,F} = 7.2$ Hz), 127.8 (d, $^4J_{C,F} = 2.5$ Hz), 127.7 (d, $^3J_{C,F} = 6.4$ Hz), 126.2, 123.8, 123.6, 116.5 (d, $^2J_{C,F} = 21.8$ Hz), 114.7 (d, $^2J_{C,F} = 23.5$ Hz), 113.3, 110.3, 106.1, 105.8, 68.69, 55.06. IR (KBr): ν 3423.03, 3176.18, 1735.62, 1658.48, 1511.92, 734.75 cm^{-1}. LCMS (ESI): m/z 362.2 [M + H]$^+$, 384.2 [M + Na]$^+$. HRMS (ESI) calcd for $C_{21}H_{17}FN_3O_2$ [M + H]$^+$ 362.1305, found 362.1311.

2-Fluoro-12-(4-nitrophenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one (3p). Yellow solid. m.p. 296–300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.08 (d, $J = 8.5$ Hz, 2H), 7.52–7.45 (m, 1H), 7.26 (d, $J = 8.7$ Hz, 2H), 7.20–7.16 (m, 2H), 6.79 (s, 1H), 6.66–6.62 (m, 1H), 6.38 (s, 1H), 6.10 (s, 1H), 5.87–5.81 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4 (d, $^1J_{C,F} = 244.6$ Hz), 158.4, 148.0, 143.8, 140.7, 133.3 (d, $^3J_{C,F} = 9.3$ Hz), 130.5(d, $^3J_{C,F} = 8.8$ Hz), 130.1, 124.2, 124.0, 123.5, 123.3(d, $^4J_{C,F} = 3.2$ Hz), 114.4 (d, $^2J_{C,F} = 22.4$ Hz), 112.1(d, $^2J_{C,F} = 22.7$ Hz), 111.3, 108.2, 106.7, 68.9. IR (KBr): ν 3396.03, 3201.25, 1664.27, 1635.34, 1521.56, 1348.00, 750.17 cm^{-1}. LCMS (ESI) m/z 377.2 [M + H]$^+$, 399.2 [M + Na]$^+$. HRMS: calcd for $C_{20}H_{14}N_4O_3F$ [M + H]$^+$: 377.1050, found 377.1045.

12-Cyclopropyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3q). White solid. m.p. 196–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.33 (m, 1H), 7.22 (d, $J = 4.0$ Hz, 2H), 7.12 (d, $J = 7.7$ Hz, 1H), 7.06 (dd, $J = 2.8$, 1.6 Hz, 1H), 6.97 (dd, $J = 4.2$, 1.6 Hz, 1H), 6.20 (dd, $J = 4.2$, 2.8 Hz, 1H), 6.13 (d, $J = 1.5$ Hz, 1H), 5.68 (d, $J = 1.3$ Hz, 1H), 5.40 (s, 1H), 0.98–0.86 (m, 1H), 0.77–0.57 (m, 2H), 0.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 146.5, 131.3, 130.3, 126.6, 126.3, 125.8, 125.0, 124.3, 123.4, 111.9, 106.6, 102.8, 70.2, 11.3, 7.1, 5.0. IR (KBr): ν 3133.76, 2923.56, 1650.77, 757.89, 730.89 cm^{-1}. LCMS (ESI): m/z 278.2 [M + H]$^+$, 300.2 [M + Na]$^+$. HRMS (ESI) calcd for $C_{17}H_{15}N_3ONa$ [M + Na]$^+$, 300.1113, found 300.1131.

2-Fluoro-12-hydroxymethyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3r). White solid. m.p. 256–260 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, $J = 8.3$, 5.3 Hz, 1H), 7.00 (dd, $J = 2.8$, 1.5 Hz, 1H), 6.92–6.80 (m, 3H), 6.15 (dd, $J = 4.3$, 2.8 Hz, 1H), 5.99 (d, $J = 6.2$ Hz, 2H), 3.80 (d, $J = 14.8$ Hz, 1H), 3.60 (d, $J = 14.9$ Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.4 (d, $^1J_{C,F} = 243.9$ Hz), 158.1, 146.5, 133.6(d, $^3J_{C,F} = 9.3$ Hz), 130.1 (d, $^3J_{C,F} = 9.1$ Hz), 124.1, 123.9, 123.1 (d, $^4J_{C,F} = 3.2$ Hz), 113.1 (d, $^2J_{C,F} = 22.1$ Hz), 111.3 (d, $^2J_{C,F} = 22.7$ Hz), 110.8, 106.6, 102.3, 68.9, 58.1. IR (KBr): ν 3351.68, 3183.90, 2919.70, 1643.05, 1619.91, 740.53 cm^{-1}. LCMS (ESI): m/z 286.2 [M + H]$^+$, 308.1 [M + Na]$^+$. HRMS (ESI) calcd for $C_{15}H_{13}N_3O_2F$ [M + H]$^+$ 286.0992, found 286.1015.

Methyl 2-fluoro-12-hydroxylmethyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3s). Yellow solid. m.p. 300–304 °C. ^{1}H NMR (300 MHz, CD_3Cl) δ 7.69 (d, $J = 1.7$ Hz, 1H), 7.35–7.32 (m, 2H), 7.31–7.27 (m, 1H), 7.02–6.91 (m, 2H), 6.09 (m, 2H), 3.85 (m, 4H), 3.83–3.76 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.8, 163.4 (d, $^1J_{C,F} = 244.3$), 157.5, 145.1, 133.4 (d, $^3J_{C,F} = 9.4$ Hz), 130.2 (d, $^3J_{C,F} = 9.2$ Hz), 127.7, 125.3, 122.8 (d, $^4J_{C,F} = 3.2$ Hz), 113.5 (d, $^2J_{C,F} = 22.4$ Hz), 113.2, 111.5 (d, $^2J_{C,F} = 22.8$ Hz), 110.9, 103.5, 68.6, 58.5, 51.8. IR (KBr): ν 3482.81, 3183.90, 2919.70, 1700.91, 1666.20, 1560.13, 763.67 cm^{-1}. LCMS (ESI): m/z 344.2 [M + H]$^+$, 366.2 [M + Na]$^+$. HRMS (ESI) calcd for $C_{17}H_{15}N_3O_4F$ [M + H]$^+$ 344.1047, found 344.1029.

12-Phenyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3t). White solid. m.p. 240–245 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.38 (m, 1H), 7.32–7.27 (m, 3H), 7.24–7.14 (m, 3H), 7.01–6.96 (d, $J = 7.3$ Hz, 2H), 6.89 (dd, $J = 4.3$, 1.6 Hz, 1H), 6.35–6.30 (m, 1H), 6.23 (d, $J = 1.2$ Hz, 1H), 5.88 (s, 1H), 5.81 (dd, $J = 4.3$, 2.8 Hz, 1H), 5.60–5.52 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 144.5, 133.8, 131.2, 130.5, 128.8, 128.5, 128.0, 127.2, 126.5, 125.9, 125.5, 123.7, 123.5, 112.2, 107.3, 106.4, 70.1. IR (KBr): ν 3430.74, 3166.54, 1650.77, 736.67 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{16}N_3O$ [M + H]$^+$ 314.1293, found 314.1306.

3-Chloro-12-hydroxylethyl-4b*H*-isoquino[2,1-*a*]pyrrolo[2,1-*f*]-[1,2,4]triazin-6(5*H*)-one (3u). Yellow solid. m.p. 220–224 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.45–7.32 (m, 3H), 7.18 (d, $J = 8.2$ Hz, 1H), 6.72 (d, $J = 4.0$ Hz, 1H), 6.20–6.16 (m, 2H), 5.86 (s, 1H), 4.65–4.60 (m, 1H), 3.42–3.34 (m, 1H), 3.28–3.20 (m, 1H), 2.16–2.09 (m, 1H), 1.95–1.82 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.0, 144.1, 131.1, 130.9, 130.7, 128.9, 128.5, 127.0, 125.1, 124.8, 111.7, 107.6, 104.6, 69.6, 59.8, 34.2. IR (KBr): ν 3143.40, 2921.63, 1654.62, 1554.34, 1328.71, 728.96 cm^{-1}. LCMS (ESI): m/z 316.1 [M + H]$^+$, 338.1 [M + Na]$^+$. HRMS (ESI) calcd for $C_{16}H_{14}N_3O_2NaCl$, [M + Na]$^+$ 338.0672, found 338.0670.

Methyl 3-chloro-12-hydroxylethyl-4b*H*-isoquino[2,1-*a*]pyrrolo-[2,1-*f*][1,2,4]triazin-6(5*H*)-one-8-carboxylate (3v). White solid. m.p. 282–286 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40 (s, 1H), 8.07–8.05 (m, 1H), 7.45–7.37 (m, 2H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 1.7$ Hz, 1H), 6.24 (s, 1H), 5.91 (s, 1H), 4.66 (t, $J = 5.1$ Hz, 1H), 3.76 (s, 3H), 3.42–3.22 (m, 2H), 2.28–2.14 (m, 1H), 1.94–1.80 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.6, 158.2, 158.2, 143.2, 131.1, 130.9, 128.8, 128.6, 128.5, 127.2, 126.2, 114.1, 111.8, 105.0, 69.3, 59.6, 52.6, 34.0. IR (KBr): ν 3382.53, 3259.11, 1695.12, 1666.20, 1301.72, 767.53 cm^{-1}. LCMS (ESI): m/z 374.2 [M + H]$^+$, 396.1, [M + Na]$^+$. HRMS (ESI) calcd for $C_{18}H_{16}N_3O_4NaCl$ [M + Na]$^+$ 396.0727, found 396.0740.

9-Isopropyl-12-(4-chlorophenyl)-4b*H*-isoquino[2,1-*a*]pyrrolo-[2,1-*f*][1,2,4]triazin-6(5*H*)-one (3w). White solid. m.p. 278–282 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.38 (m, 1H), 7.37–7.20 (m, 3H), 7.15 (d, $J = 8.2$ Hz, 2H), 6.96 (d, $J = 4.4$ Hz, 1H), 6.79 (d, $J = 8.3$ Hz, 2H), 6.15 (s, 1H), 5.91 (s, 1H), 5.73 (d, $J = 4.4$ Hz, 1H), 5.55 (s, 1H), 2.48–2.36 (m, 1H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.57 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.92, 143.55, 143.28, 135.04, 132.66, 131.29, 130.45, 129.87, 128.40, 127.38, 126.50, 126.23, 125.56, 122.43, 112.66, 108.23, 102.89, 70.31, 25.07, 23.64, 19.87. IR (KBr) ν 3237.62, 3058.55, 1725.98, 1654.62, 1560.13, 1382.15, 1368.40, 920.78, 758.82 cm^{-1}. LCMS (ESI): m/z 390.2 [M + H]$^+$, 412.1 [M + Na]$^+$. HRMS (ESI) calcd for $C_{23}H_{21}ClN_3O$ [M + H]$^+$ 390.1373, found 390.1384.

Acknowledgements

This work was financially supported by the Chinese Academy of Sciences ('Interdisciplinary Cooperation Team' Program for Science and Technology Innovation), the National Natural Science Foundation of China (21072205, 81202398), and SKLDR/SIMM (SIMM1105KF-02).

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