A Convenient One-Pot Synthesis of Triazolopyridine and Related Heterocycle Fused-Triazole Analogs Through Copper Catalyzed Oxidative Cyclization Strategy

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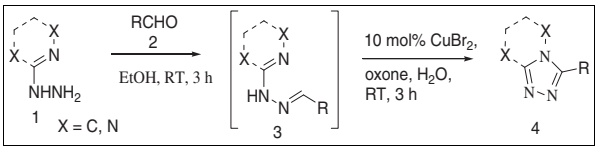

One-pot synthesis of heterocycle fused-triazole analogs from the corresponding aldehydes and heteroarylhydrazines is demonstrated. Transformation of hydrazones to the desired systems was achieved by employing the oxidative cyclization with catalytic $CuBr_2$ and oxone. This reaction condition is mild and selective, and a wide range of functional groups were able to sustain. An array of biologically important triazolopyridines, triazolopyridazines, triazolopyrimidines, and triazoloquinolines were obtained in fairly good yield.

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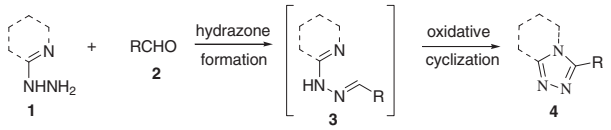
INTRODUCTION

1,2,4-Triazole represents an important class of heterocyclic unit found to have wide range of applications in chemistry and biology [1]. Particularly, heterocycle fused-triazoles received a long standing interest due to their medicinal relevance. [1,2,4]Triazolo[4,3-*a*]pyridine, a hybrid 1,2,4-triazole and pyridine, is an important prototype of this family, and one of the well studied systems of this kind in literature [2]. This motif embedded compounds are found to display biological activities such as antibacterial, antifungal, anti-inflammatory, antiproliferative, antithrombotic, anticonvulsant, herbicidal, and anxiolytic activity [3]. Like triazolopyridines, triazolopyridazines, and the diazine congeners, triazolopyrimidines as well as triazoloquinolines are other important frameworks that belong to heterocycle fused-triazoles wherein 1,2,4-triazole is fused with pyridazines, pyrimidines, and quinolines, respectively. [1,2,4]Triazolo[4,3-*b*]pyridazine is shown to be a weak yet selective muscarinic acetylcholine receptor antagonist [4]. Also, it can act as a highly selective and potent Pim-1 kinase inhibitor where the selectivity is derived from an unorthodox binding mode to the unique hinge region of Pim-1, and further, this class of analogs is identified as subtype selective ligands for the benzodiazepine binding site of GABA-A receptors [5]. Interestingly, [1,2,4]triazolo[1,5-*c*] pyrimidine is found to display a range of bioactivities like analgesic, anticancer, antiviral and adenosine A_1 receptor antagonistic activity [6a]. In addition to that, it acts as potent inhibitor of kinases and Shiga toxin trafficking [6b,6c]. Likewise, [1,2,4]triazolo[4,3-*a*]quinoline exhibits potent antibacterial activity [7]. Owing to their broad spectrum of biological activities, heterocycle fused-triazoles have gained considerable interest among the researchers and these systems can be routinely synthesized by constructing the 1,2,4-triazole motif by adopting either dehydrative cyclization of acyl hydrazides [8] or oxidative cyclization of heteroaryl hydrazones [9–11]. Although the former method was used successfully for the efficient preparation of numerous heterocyclic compounds, the latter is the most common, attractive and widely exploited method. To execute oxidative cyclization of heteroaryl hydrazones, hazardous reagents such as Br_2, $POCl_3$, and $Pb(OAc)_4$ [9] were used in the past. Recently, chloramines-T [10a], LiI [6a], $PhI(OAc)_2$ [7,10b], and $PhI(OCOCF_3)_2$ [10c] are being employed for cyclization. In addition to the synthetic methodologies involving PS-PPh_3/CCl_3CN under microwave heating, electrochemical methods are also developed [11a,11b]. Very recently, a solvent free approach has also surfaced [11c].

However, the earlier synthetic procedures have some constraints such as the employment of hazardous materials or metal reagents and also their moisture sensitive nature. Further, the requirement of isolating the intermediate hydrazone prior to oxidative cyclization invariably adds a step in the synthesis. Furthermore, the stoichiometric amount of reagent is required to carry out the oxidative cyclization. Thus, it is highly desired to find a suitable reagent that should be catalytic, nontoxic, and also has the capability of performing the reaction in one pot.

In recent years, transition metal catalysis emerged as a powerful tool to form numerous C–C and C–heteroatom

Scheme 1. Synthesis of heterocycle fused triazole.



bonds efficiently. Among the various metal catalyzed reactions, there is a growing interest in copper catalyzed reactions as they are less toxic and inexpensive. In practical point of view, copper salts are not only less moisture sensitive and hence less difficult to store but also easy to handle, and they can be readily be obtained by commercial sources. A single report describes the synthesis of heterocycle fused-triazole using $CuCl_2$, but stoichiometric amount of copper was needed [12]. However, catalytic version based oxidative cyclization is a more attractive approach to heterocycle fused triazoles. Notably, although numerous specific fused triazole synthesis were reported, reports dealing with the combined synthesis of triazolopyridines, triazolopyridazines, triazolopyrimidines, and triazoloquinolines have been less documented in literature [12]. In this context, we disclose the synthesis of heterocycle fused triazoles using catalytic amount of copper catalyst.

The general scheme wherein the treatment of heterocyclic hydrazine **1** with aldehyde **2** to produce aldehyde derived hydrazone **3**, which on oxidative cyclization leads to heterocycle fused triazole **4**, is given in Scheme 1.

Table 1

Reagent and oxidant sources used in the synthesis of triazolopyridine.

Entry	Reagent[a]	Oxidant[b]	Temp. (°C)	Time (h)	Yield (%)[c]
1	$Pd(OAc)_2$	—	80	12	—
2	$Pd(OAc)_2$	Ag_2CO_3	80	12	10
3	$RuCl_3{\cdot}H_2O$	—	80	12	—
4	$RuCl_3{\cdot}H_2O$	Ag_2CO_3	80	12	—
5	$CuBr_2$	—	80	12	10
6	$CuCl_2$	DDQ	80	12	26
7	$CuBr_2$	DDQ	80	6	42
8	$CuBr_2$	Ag_2CO_3	80	12	32
9	$CuBr_2$	$K_2S_2O_8$	80	5	35
10	$CuBr_2$	BQ	80	3	38
11	$CuBr_2$	Oxone	80	3	68
12	$CuBr_2$	Oxone	RT	3	90
13	$CuBr_2$[d]	Oxone	RT	3	72
14	$CuBr_2$[e]	Oxone	RT	7	82
15	—	Oxone	80	12	7
16	$CuCl_2$	Oxone	80	12	40
17	$Pd(OAc)_2$	Oxone	RT	12	18
18	$RuCl_3{\cdot}H_2O$	Oxone	RT	12	12

Reactions were carried out in EtOH:water (4:1).
[a]0.1 equiv. of reagent was used.
[b]1 equiv. of oxidant was used.
[c]Isolated yield.
[d]0.2 equiv. of reagent was used.
[e]0.05 equiv. of reagent was used.

At the outset, we focused our attention on triazolopyridines to optimize the reaction conditions. Initially, a mixture of 2-pyridyl hydrazine **1a** and benzaldehyde **2a** was stirred in ethanol at room temperature for 3 h to afford the hydrazone of aldehyde **3a** whose formation and conversion was confirmed by TLC. Without isolating the hydrazone **3a**, a direct oxidative cyclization was planned by screening under various reagents and oxidant sources to obtain **4a** (Table 1). Palladium diacetate without oxidant showed no desired cyclization whereas in the presence of silver carbonate provided triazolopyridine **4a** in low yield. Ruthenium trichloride hydrate with or without oxidant did not afford **4a**. With 0.1 equivalent of cupric bromide, **4a** was obtained in poor yield. $CuCl_2$ with DDQ as an oxidant also gave low yield. Various oxidants such as Ag_2CO_3, $K_2S_2O_8$, BQ, and DDQ with catalytic $CuBr_2$ showed gradual increase in the yield. The best yield was obtained with 0.1 equivalent of cupric bromide and 1 equivalent of oxone (entry 12–15). In order to find the efficiency of this oxidant, experiments were conducted using $CuCl_2$, $Pd(OAc)_2$ and $RuCl_3{\cdot}H_2O$ with oxone as well as oxone without metal catalyst provided very low yield.

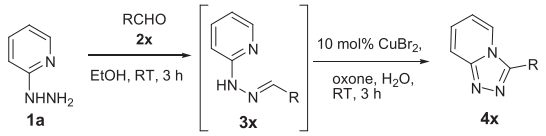
After identification of the optimized condition, **1a** was treated with various aldehydes **2** to produce triazolopyridines **4x** (Table 2). Halo substituted aryl aldehydes furnished the desired compounds without affecting the halo units **4b–4d** (entry 2–4). It is noteworthy that in general, bromo and chloro substituents are labile to copper condition but remained unreactive in the present condition. Multi substituted aryl aldehydes also underwent the cyclization smoothly. Olefin unit was preserved when an aldehyde containing olefin was used **4f–4g** (entry 6 and 7). 3-Cyanobenzaldehyde gave the desired product in high yield (91%). The same was the case with heterocyclic aryl aldehydes **4i–4m** (entry 9–11). Alicyclic aldehydes provided the products **4n–4o** in moderate yield (entry 12).

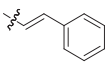
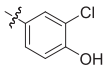
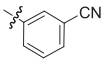
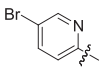
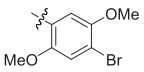
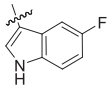
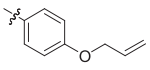
Having demonstrated the protocol for the synthesis of triazolopyridines, attention was directed toward the synthesis of triazolopyridazines by taking pyridazine derived hydrazine **1b** as the starting material (Table 3). Hydrazone formation was realized by following the routine procedure, and those derivatives were further subjected to oxidative cyclization to give **5x**. Aryl aldehydes having bromo, methoxy, allyl, and cyano substituents furnished the corresponding products **5a–5f** in good yield (entry 1–6). It is to be noted that the electronic influence of substituents in the aryl has played insignificant role as the yields were almost comparable. Further, the reactive chloro unit in the pyridazine moiety was remaining intact during the reaction condition. Heterocyclic aryl aldehydes were found to undergo smooth cyclization to form **5g–5k** in good yield (entry 7–9). Cyclopropane carboxaldehyde and *n*-heptanal were able to form the triazolopyridazines **5l** and **5m**, respectively (entry 10).

A similar protocol was employed for the synthesis of triazolopyrimidines **6x** as shown in Table 4. Aryl

Table 2

Synthesis of triazolopyridines.



Entry	R	Yield	Entry	R	Yield
1		**4a**, 90%	7		**4g**, 80%
2		**4b**, 87%	8		**4h**, 91%
3		**4c**, 89%	9		**4i**, 76%
4		**4d**, 85%	10	R = 2-furyl; R = 2-thiophenyl; R = 3-thiophenyl;	**4j**, 70% **4k**, 84% **4l**, 86%
5		**4e**, 84%	11		**4m**, 85%
6		**4f**, 87%	12	R = cyclohexyl; R = cyclopropyl;	**4n**, 78% **4o**, 74%

aldehydes as well as alicyclic aldehydes provided the corresponding products **6a–6d** although in moderate yield.

Finally, triazoloquinolines **7x** were obtained from the hydrazine **1d** and aldehyde derivative **2x** (Table 5). A range of aryl, heteroaryl, and aliphatic aldehydes underwent the oxidative cyclization to form the products **7a–7k** in good yield.

CONCLUSION

In conclusion, we have developed a convenient one-pot synthesis of heterocycle fused-triazoles from the readily available aldehydes and heterocyclic hydrazines. Oxidative cyclization of the aldehyde derived hydrazone with 10 mol % of $CuBr_2$ and oxone is the key step in the synthesis of the desired analogs under mild condition because the hydrazone formation and oxidative cyclization have taken place at room temperature while the literature procedures reveal that such cyclizations were carried out normally at high temperatures. Further, the oxidative cyclization is also selective as the halo substituents remained unaffected. Employing this protocol, a focused library involving the synthesis of triazolopyridine, triazolopyridazine, triazolopyrimidine, and triazoloquinoline derivatives has been established.

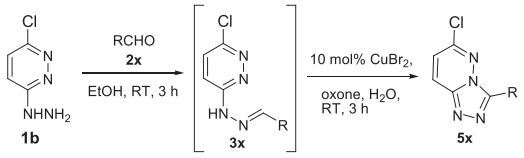
EXPERIMENTAL

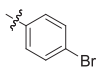
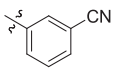
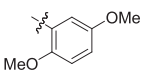
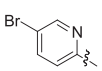
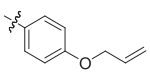
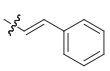
General methods. All the reagents were purchased commercially and used without further purification. Solvents were used without drying. ^1H and ^{13}C NMR spectra were recorded on 300 or 400 MHz Brucker spectrometers in $CDCl_3/CD_3OD$/DMSO-d_6. The chemical shifts were reported in δ ppm relative to TMS. IR Spectra were recorded on Nicolet 6700 instrument using a universal ATR sampling unit. Mass Spectra were obtained on LC-MS Agilent 1100 series instrument, and UPLC was recorded on Acquity ultra performance LC instrument. Melting point was measured in BÜCKI-B545 instrument.

General experimental procedure for preparation of triazoles. To a solution of hydrazine (1.8 mmol) in ethanol (8 mL) was added the aldehyde (1.8 mmol) at room temperature, and the mixture was stirred for 3 h. Then water (2 mL) was added to the reaction mixture followed by the slow addition of oxone (1.8 mmol) and cupric bromide (0.18 mmol). The reaction

Table 3

Synthesis of triazolopyridazines.



Entry	R	Yield	Entry	R	Yield
1		**5a**, 80%	6		**5f**, 80%
2		**5b**, 87%	7		**5g**, 80%
3		**5c**, 80%	8		**5h**, 90%
4		**5d**, 92%	9	R = 2-furyl; R = 2-thiophenyl; R = 3-thiophenyl;	**5i**, 79% **5j**, 78% **5k**, 75%
5		**5e**, 85%	10	R = cyclopropyl; R = *n*-hexyl;	**5l**, 75% **5m**, 87%

mixture was stirred at RT for another 3 h. Water (5 mL) was added to the reaction mixture, which was then extracted with dichloromethane (2 × 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. It was concentrated under reduced pressure, and the residue obtained was purified either silica gel column chromatography or crystallization with EtOAc to give the triazoles in good yield.

A similar procedure was followed for all other examples shown in Tables 2–5. The triazoles obtained were either purified by column chromatography or crystallization with EtOAc.

Characterization of the triazolo analogs synthesized

3-Phenyl-[1,2,4]triazolo[4,3-a]pyridine (4a). mp 173–175°C (lit[10c]: 172–174°C). IR (neat) 1629, 1496, 1061, 750, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34–8.30 (m, 1H), 7.84–7.82 (m, 3H), 7.60–7.52 (m, 3H), 7.29 (t, J = 6.60 Hz, 1H), 6.87 (t, J = 6.72 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5 (C), 146.8 (C), 130.2 (CH), 129.3 (CH), 128.2 (CH), 127.1 (CH), 126.6 (C), 122.6 (CH), 116.8 (CH), 114.3 (CH). UPLC: $(M+H)^+$ 196.2. *Anal.* Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.63; H, 4.73; N, 21.57.

4-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-2-chlorophenol (4b). mp 258–259°C. IR (neat) 1637, 1308, 815, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.82 (s, 1H), 8.53–8.51 (m, 1H), 7.85–7.82 (m, 2H), 7.67 (d, J = 8.36 Hz, 1H), 7.41 (t, J = 7.28 Hz, 1H), 7.18 (d, J = 8.41 Hz, 1H), 7.0 (t, J = 6.72 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.1, 130.1, 128.7, 128.3, 124.5, 118.8, 117.6, 116.0, 114.8. LCMS: $(M+H)^+$ 246.0.

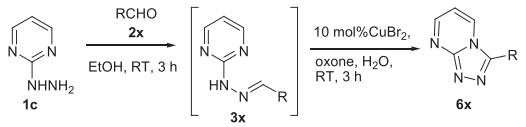
3-(4-Bromophenyl)-[1,2,4]triazolo[4,3-a]pyridine (4c). mp 191–193°C. IR (neat) 3076, 1633, 1495, 1456, 1398, 1364, 1062, 1002, 981, 815, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J = 6.96 Hz, 1H), 7.88–7.80 (m, 5H), 7.46–7.41 (m, 1H), 7.02 (t, J = 6.69 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (C), 145.8 (C), 132.6 (2CH), 129.6 (2CH), 127.3 (CH), 125.5 (C), 124.6 (CH), 122.5 (C), 116.8 (CH), 114.6 (CH). UPLC: $(M+H)^+$ 274.2. *Anal.* Calcd for $C_{12}H_8BrN_3$: C, 52.58; H, 2.94; N, 15.33. Found: C, 52.28; H, 2.84; N, 15.13.

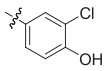
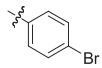
3-(4-Bromo-2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-a] pyridine (4d). mp 185–187°C. IR (neat) 1638, 1480, 1217, 1020, 859, 752 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.12–8.11 (m, 1H), 7.89–7.87 (m, 1H), 7.56 (s, 1H), 7.49 (t, J = 6.64 Hz, 1H), 7.30 (s, 1H), 7.02 (t, J = 6.72 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.3, 149.7, 129.8, 125.8, 117.2, 115.4, 114.7, 114.4, 114.2, 56.8, 56.5. UPLC: $(M+H)^+$ 334.3. *Anal.* Calcd for $C_{14}H_{12}BrN_3O_2$: C, 50.32; H, 3.62; N, 12.57. Found: C, 50.22; H, 3.32; N, 12.67.

3-(1-Phenylethyl)-[1,2,4]triazolo[4,3-a]pyridine (4e). mp 124–126°C. IR (neat) 2975, 2922, 1632, 1488, 1263, 1023, 730, 693 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.13 (d, J = 6.88 Hz, 1H), 7.74 (d, J = 9.24 Hz, 1H), 7.32–7.22

Table 4

Synthesis of triazolopyrimidines.



Entry	R	Yield	Entry	R	Yield
1		**6a**, 70%	3		**6c**, 60%
2		**6b**, 75%	4		**6d**, 65%

(m,5H), 7.20 (t, $J = 2.04$ Hz, 1H), 6.87 (t, $J = 6.72$ Hz, 1H), 4.79 (q, $J = 7.12$ Hz, 1H), 1.79 (d, $J = 7.08$ Hz, 3H ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.4, 129.3, 127.8, 127.6, 127.4, 123.8, 115.9, 113.8, 35.7, 21.3. UPLC: $(M + H)^+$ 224.6 *Anal.* Calcd for $C_{14}H13N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.55; H, 5.65; N, 18.56.

3-(4-(Allyloxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridine (4f). IR (neat) 3083, 1608, 1501, 1466, 1372, 1245, 1175, 988, 836, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 7.89 (br s, 1H), 7.77 (d, $J = 8.12$ Hz, 1H), 7.31 (s, 1H), 7.13 (d, $J = 6.9$ Hz, 1H), 6.87 (t, $J = 6.28$ Hz, 1H), 6.15–6.07 (m, 1H), 5.51–5.46 (m, 2H), 5.36 (d, $J = 10.48$ Hz, 1H), 4.67–4.65 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 133.4, 129.6, 127.5, 123.9, 119.0, 117.7, 115.7, 115.4, 114.2, 68.3. LCMS: $(M + H)^+$ 252.0.

(E)-3-Styryl-[1,2,4]triazolo[4,3-a]pyridine (4g). mp 167–169°C. (lit[10c]: 169–171°C). IR (neat) 3028, 1632, 1494, 1065, 964, 755, 730, 679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, $J = 6.84$ Hz, 1H), 7.93 (d, $J = 16.06$ Hz, 1H), 7.83 (d, $J = 9.16$ Hz, 1H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.45–7.42 (m, 2H), 7.40–7.36 (m, 1H), 7.32–7.30 (m, 1H), 7.20 (d, $J = 16.06$ Hz, 1H), 6.95 (d, $J = 6.76$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 135.2, 129.1, 128.9 (2C), 127.0 (2C), 126.8, 122.0, 116.9, 114.1, 109.3. UPLC: $(M + H)^+$ 222.3.

3-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)benzonitrile (4h). mp 162–163°C. IR (neat) 2217, 1633, 1495, 1372, 1062, 754 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, $J = 6.92$ Hz, 1H), 8.14 (d, $J = 7.72$ Hz, 1H), 7.99 (t, $J = 7.52$ Hz, 1H), 7.95–7.92 (m, 2H), 7.81 (t, $J = 7.46$ Hz, 1H), 7.51 (m, 1H), 7.07 (t, $J = 6.72$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.2, 143.8, 134.9, 134.3, 131.4, 131.1, 129.7, 129.1, 124.6, 117.8, 116.0, 115.1, 112.5. UPLC: $(M + H)^+$ 221.3. *Anal.* Calcd for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.00; H, 3.46; N, 25.24.

3-(5-Bromopyridin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (4i). mp 170–172°C. IR (neat) 1632, 1490, 1083, 1014, 846, 757, 687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (d, $J = 4.12$ Hz, 1H), 8.78 (s, 1H), 8.47 (d, $J = 8.48$ Hz, 1H), 8.02 (d, $J = 7.80$ Hz, 1H), 7.90 (s, 1H), 7.40 (s, 1H), 7.01 (t, $J = 6.76$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 146.8, 139.8, 128.0, 126.9, 123.8, 120.7, 116.2, 114.6. UPLC: $(M + H)^+$ 275.2.

3-(Furan-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (4j). mp 89–91°C (lit[8c]: 92°C) . IR (neat) 3116, 1635, 1498, 1370, 1011, 891, 745 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (d, $J = 7.0$ Hz, 1H), 8.04 (d, $J = 1.36$ Hz, 1H), 7.88 (d, $J = 9.28$ Hz, 1H), 7.49–7.47 (m, 1H), 7.33 (d, $J = 3.48$ Hz, 1H), 7.13 (t, $J = 6.32$ Hz, 1H), 6.83 (dd, $J = 3.44$, 1.76 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.5 (C), 145.2 (CH), 142.2 (C), 128.7 (CH), 125.0 (CH), 118.2 (C), 116.1 (CH), 115.4 (CH), 112.5 (CH), 111.1 (CH). UPLC: $(M + H)^+$ 186.2.

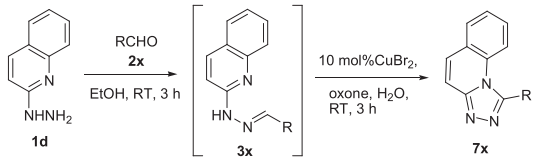
3-(Thiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (4k). mp 164–166°C. (lit[7]: 162–163°C). IR (neat) 3066, 1628, 1494, 723 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (d, $J = 7.04$ Hz, 1H), 7.94–7.91 (m, 2H), 7.88 (dd, $J = 5.12$, 1.00 Hz, 1H), 7.58 (dt, $J = 6.68$, 0.84 Hz, 1H), 7.34 (t, $J = 4.4$ Hz, 1H), 7.20 (dt, $J = 6.78$, 0.76 Hz, 1H; ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.4 (C), 141.9 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 128.0 (C), 127.1 (CH), 124.7 (CH), 116.2 (CH), 115.3 (CH). UPLC: $(M + H)^+$ 202.2. *Anal.* Calcd for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88. Found: C, 59.77; H, 3.33; N, 20.93.

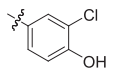
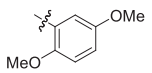
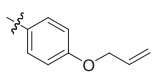
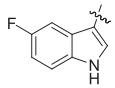
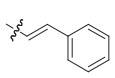
3-(Thiophen-3-yl)-[1,2,4]triazolo[4,3-a]pyridine (4l). mp 170–172°C. IR (neat) 3094, 1628, 1495, 1307, 1063, 824, 742 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ 8.61 (d, $J = 6.18$ Hz, 1H), 8.18–8.17 (m, 1H), 7.81–7.69 (m, 3H), 7.52 (t, $J = 6.78$ Hz, 1H), 7.10 (t, $J = 6.87$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.7 (CH), 127.2 (CH), 127.0 (CH), 126.9 (C), 125.1 (CH), 122.8 (CH), 116.9 (CH), 114.4 (CH). LCMS: $(M + H)^+$ 202.0. *Anal.* Calcd for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; Found: C, 60.00; H, 3.70; N, 20.94.

3-(5-Fluoro-1H-indol-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (4m). mp 256–258°C. IR (neat) 3092, 1638, 1592, 1484, 1158, 806, 737 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.13 (br s, 1H), 8.89–8.8 (m, 1H), 8.42 (d, $J = 2.44$ Hz, 1H), 7.97–7.94 (m, 1H), 7.85 (d, $J = 8.48$ Hz, 1H), 7.57 (dd, $J = 8.88$, 4.48 Hz, 1H), 7.20 (t, $J = 6.68$ Hz, 1H), 7.14 (t, $J = 8.88$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 157.8, 132.7, 130.4, 128.1, 125.7, 115.7, 114.4, 113.4, 111.1, 105.3, 100.7. LCMS: $(M + H)^+$ 253.0.

Table 5

Synthesis of triazoloquinolines.



Entry	R	Yield	Entry	R	Yield
1		**7a**, 90%	5	R = 4-pyridyl**;** R = 5-bromo-2-pyridyl;	**7e**, 83% **7f**, 79%
2		**7b**, 87%	6	R = 2-furyl; R = 3-thiophenyl;	**7g**, 72% **7h**, 70%
3		**7c**, 80%	7		**7i**, 83%
4		**7d**, 81%	8	R = *n*-hexyl; R = cyclopropyl;	**7j**, 78% **7k**, 75%

3-Cyclohexyl-[1,2,4]triazolo[4,3-a]pyridine (4n). IR (neat) 3386, 2929, 1648, 1447, 1161, 1042, 855, 755 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 8.90 (d, J = 6.81 Hz, 1H), 8.15–8.04 (m, 2H), 7.56 (t, J = 6.81 Hz, 1H), 3.46–3.39 (m, 1H), 2.20–2.16 (m, 2H), 1.95–1.90 (m, 2H), 1.85–1.56 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ 138.3 (CH), 126.9 (CH), 119.1 (CH), 112.3 (CH), 34.8 (CH), 31.1 (CH_2), 26.7 (CH_2), 26.5 (CH_2). LCMS: $(M+H)^+$ 202.2.

3-Cyclopropyl-[1,2,4]triazolo[4,3-a]pyridine (4o). IR (neat) 1638, 1501, 1369, 1041, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.54 (d, J = 6.92 Hz, 1H), 7.7 (d, J = 9.2 Hz, 1H), 7.34 (m, 1H), 7.00 (t, J = 6.52 Hz, 1H), 2.42–2.36 (m, 1H), 1.15–1.10 (m, 2H), 1.04–1.00 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.7 (C), 127.8 (CH), 124.0 (CH), 115.7 (CH), 113.7 (CH), 6.9 (CH_2), 4.8 (CH). UPLC: $(M+H)^+$ 160.0.

3-(4-Bromophenyl)-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine (5a). mp 190–192°C. IR (neat) 3044, 1651, 1591, 1522, 1458, 1413, 1325, 1108, 1057, 983, 812, 774 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.55 (d, J = 9.64 Hz, 1H), 8.24 (d, J = 8.48 Hz, 2H), 7.83 (d, J = 8.48 Hz, 2H), 7.57 (d, J = 9.64 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.8 (C), 146.4 (C), 144.6 (C), 132.5 (CH), 129.4 (CH), 127.9 (CH), 125.3 (C), 124.4 (C), 123.3 (CH). UPLC: $(M+H)^+$ 309.1. *Anal.* Calcd for $C_{11}H_6BrClN_4$: C, 42.68; H, 1.95; N, 18.10. Found: C, 42.83; H, 1.89; N, 18.00.

6-Chloro-3-(2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-b] pyridazine (5b). mp 105–107°C. IR (neat) 3358, 2922, 1487, 1226, 1160, 1042, 816, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 9.57 Hz, 1H), 7.21 (d, J = 2.97 Hz, 1H), 7.16–7.03 (m, 3H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 153.4 (C), 152.5 (C), 149.3 (C), 146.9 (C), 127.45 (CH), 123.3 (CH), 118.0 (CH), 117.2 (CH), 115.4 (C), 114.1 (CH), 56.8 (OCH_3), 56.2 (OCH_3). LCMS: $(M+H)^+$ 290.0. *Anal.* Calcd for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 53.95; H, 3.75; N, 19.70.

6-Chloro-3-(1-phenylethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5c). mp 160–162°C. IR (neat) 1524, 1496, 1463, 1324, 1099, 1022, 808, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.43 (dd, J = 9.68, 1.32 Hz, 1H), 7.44 (dd, J = 9.64, 1.32 Hz, 1H), 7.31–7.28 (m, 4H), 7.24–7.20 (m, 1H), 4.77 (q, J = 7.24 Hz, 1H), 1.78 (d, J = 7.20 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.5 (C), 148.8 (C), 142.9 (C), 141.6 (C), 128.6 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 122.6 (CH), 34.9 (CH), 20.3 (CH_3). UPLC: $(M+H)^+$ 259.3. *Anal.* Calcd for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.29; N, 21.66. Found: C, 60.47; H, 4.42; N, 21.72.

(4-(Allyloxy)phenyl)-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine (5d). mp 128–132°C. IR (neat) 1606, 1532, 1459, 1313, 1244, 1180, 1103, 1053, 939, 832, 811 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (d, J = 9.68 Hz, 1H), 8.24 (dd, J = 7.02, 1.8 Hz, 2H), 7.52 (d, J = 9.68 Hz, 1H), 7.2 (d, J = 8.0 Hz, 2H), 6.13–6.03 (m, 1H), 5.44 (dd, J = 17.28, 1.6 Hz, 1H), 5.29 (dd, J = 10.5, 1.4 Hz, 1H), 4.67 (d, J = 5.28 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 149.5, 147.2, 144.1, 133.8, 129.2, 127.8, 122.8, 118.5, 118.3, 115.5, 68.8. UPLC: $(M+H)^+$ 287.5.

(E)-6-Chloro-3-styryl-[1,2,4]triazolo[4,3-b]pyridazine (5e). mp 148–150°C. IR (neat) 3333, 3076, 1635, 1522, 1498, 1450, 1319, 1133, 1048, 964, 813, 753 $cm^{-1.}$ ^1H NMR (300 MHz, CD_3OD): δ 8.27 (d, J = 9.75 Hz, 1H), 8.06 (d, J = 16.50 Hz, 1H), 7.69 (d, J = 6.87 Hz, 1H), 7.49 (d, J = 16.00 Hz, 1H), 7.46–7.38 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.8, 135.9, 135.6, 129.7,

129.4, 127.8, 127.7, 123.1, 110.8. UPLC: $(M+H)^+$ 257.0. *Anal.* Calcd for $C_{13}H_9ClN_4$: C, 42.68; H, 1.95; N, 18.10. Found: C, 42.83; H, 1.89; N, 18.00.

3-(6-Chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)benzonitrile (5f). mp 160–162°C. IR (neat) 3087, 2228, 1521, 1455, 1318, 1105, 1059, 810, 768 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.61–8.59 (m, 2H), 8.07 (d, J = 7.68 Hz, 1H), 7.86 (d, J = 7.84 Hz, 1H), 7.61 (d, J = 9.64 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0, 145.6, 144.7, 134.3, 132.1, 130.9, 130.7, 127.9, 127.3, 123.7, 118.7, 112.6. UPLC: $(M+H)^+$ 256.2. *Anal.* Calcd for $C_{12}H_6ClN_5$: C, 45.80; H, 2.05; N, 23.77. Found: C, 45.70; H, 2.55; N, 23.88.

6-Chloro-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine (5g). mp 220–222°C. IR (neat) 1601, 1521, 1456, 1114, 1063, 845, 824, 747, 676 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 8.82 (br s, 2H), 8.48 (d, J = 5.88 Hz, 2H), 8.43 (d, J = 9.68 Hz, 1H), 7.58 (d, J = 9.72 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.9, 150.2, 145.2, 133.4, 127.9, 123.9, 121.1. LCMS: $(M+H)^+$ 232.0. *Anal.* Calcd for $C_{10}H_6ClN_5$: C, 51.85; H, 2.61; N, 30.23. Found: C, 51.98; H, 2.70, N, 30.30.

3-(5-Bromopyridin-2-yl)-6-chloro-[1,2,4]triazolo[4,3-b]pyridazine (5h). mp 225–227°C. IR (neat) 3021, 2922, 1571, 1514, 1446, 1392, 1317, 1062, 999, 824, 776 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.99 (d, J = 2.2 Hz, 1H), 8.60 (d, J = 9.68 Hz, 1H), 8.36 (dd, J = 8.44, 2.32 Hz, 1H), 8.23 (d, J = 8.44 Hz, 1H), 7.62 (d, J = 9.64 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.3, 150.1, 144.7, 144.3, 140.5, 127.7, 125.7, 123.9, 122.1. LCMS: $(M+H)^+$ 310.2. *Anal.* Calcd for $C_{10}H_5BrClN_5$: C, 38.68; H, 1.62; N, 22.55. Found: C, 38.75; H, 1.57; N, 22.36.

6-Chloro-3-(furan-2-yl)-[1,2,4]triazolo[4,3-b]pyridazine (5i). mp 130–132°C. IR (neat) 3075, 1516, 1323, 1074, 995, 816, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.55 (d, J = 9.64 Hz, 1H), 8.06 (s, 1H), 7.58 (d, J = 9.64 Hz, 1H), 7.41 (d, J = 3.4 Hz, 1H), 6.83–6.82 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.7 (C), 145.3 (CH), 143.2 (C), 140.7 (C), 139.9 (C), 127.2 (CH), 123.0 (CH), 112.5 (CH), 112.1 (CH). *Anal.* Calcd for $C_9H_5ClN_4O$: C, 49.00; H, 2.28; N, 25.40. Found: C, 49.45; H, 2.35; N, 25.23.

6-Chloro-3-(thiophen-2-yl)-[1,2,4]triazolo[4,3-b]pyridazine (5j). mp 155–157°C. IR (neat) 3080, 1519, 1456, 1408, 1314, 1098, 1052, 825 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (d, J = 9.64 Hz, 1H), 8.12 (d, J = 3.56 Hz, 1H), 7.87 (d, J = 5.0 Hz, 1H), 7.56 (d, J = 9.64 Hz, 1H), 7.33 (d, J = 4.80, 3.96 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0, 144.0, 129.8, 129.5, 128.4, 127.8, 126.6, 123.2. UPLC: $(M+H)^+$ 237.2. *Anal.* Calcd for $C_9H_5ClN_4S$: C, 45.67; H, 2.13; N, 23.67. Found: C, 45.80; H, 2.12; N, 23.70.

6-Chloro-3-(thiophen-3-yl)-[1,2,4]triazolo[4,3-b]pyridazine (5k). mp 169–171°C. IR (neat) 1518, 1457, 1341, 1321, 1055, 940, 865, 796, 699 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ 8.65 (dd, J = 2.92, 1.12 Hz, 1H), 8.34 (d, J = 9.68 Hz, 1H), 8.02 (dd, J = 5.14, 1.12 Hz, 1H), 7.70 (dd, J = 5.08, 2.92 Hz, 1H), 7.50 (d, J = 9.64 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.4, 128.7, 128.5, 127.7, 127.2, 126.2, 126.1, 125.9, 122.5. LCMS: $(M+H)^+$ 237.0. *Anal.* Calcd for $C_9H_5ClN_4S$: C, 45.67; H, 2.13; N, 23.67. Found: C, 45.75; H, 2.00; N, 23.34.

6-Chloro-3-cyclopropyl-[1,2,4]triazolo[4,3-b]pyridazine (5l). mp 115–117°C. IR (neat) 3083, 1530, 1320, 1091, 937, 804, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 9.56 Hz, 1H), 7.08 (d, J = 9.48 Hz, 1H), 2.52–2.46 (m, 1H), 1.42–1.38 (m, 2H), 1.28–1.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9 (C), 148.8 (C), 142.9 (C), 127.0 (CH), 122.2 (CH), 7.3 (CH_2), 4.7 (CH). LCMS: $(M+H)^+$ 195.0. *Anal.* Calcd for $C_8H_7ClN_4$: C, 49.37; H, 3.63; N, 28.79. Found: C, 49.55; H, 3.54; N, 28.70.

6-Chloro-3-hexyl-[1,2,4]triazolo[4,3-b]pyridazine (5m). mp 38–40°C. IR (neat) 3079, 2919, 1504, 1464, 1328, 1143, 1074, 824, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, J = 9.64 Hz, 1H), 7.45 (d, J = 9.68 Hz, 1H), 3.05 (t, J = 7.48 Hz, 2H), 1.82–1.75 (m, 2H), 1.39–1.32 (m, 2H), 1.29–1.19 (m, 4H), 0.85 (t, J = 3.40 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.9, 149.1, 143.1, 127.5, 122.6, 31.3, 28.7, 26.2, 23.7, 22.4, 14.3. LCMS: $(M+H)^+$ 239.0.

4-([1,2,4]Triazolo[4,3-a]pyrimidin-3-yl)-2-chlorophenol (6a). mp 271–272°C. IR (neat) 2921, 1611, 1507, 1430, 1305, 848, 778 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.37 (dd, J = 6.75, 1.86 Hz, 1H), 8.83 (d, J = 4.35, 1.92 Hz, 1H), 8.10 (d, J = 2.0 Hz, 2H), 7.99 (d, J = 8.46, 2.10 Hz, 2H), 7.34–7.31 (m, 1H), 7.12 (d, J = 8.49 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7,155.5, 155.4, 155.3, 137.1, 128.3, 127.0, 122.2, 120.2, 117.0, 110.81. LCMS: $(M+H)^+$ 247.0. *Anal.* Calcd for $C_{11}H_7ClN_4O$: C, 53.56; H, 2.86; N, 22.71. Found: C, 53.90; H, 2.56; N, 22.90.

3-(4-Bromophenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (6b). IR (neat) 3354, 1617, 1594, 1429, 1394, 1066, 1006, 826, 771 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.43 (dd, J = 6.50, 1.48 Hz, 1H), 8.89 (d, J = 2.64 Hz, 1H), 8.15 (d, J = 8.36 Hz, 2H), 7.76 (d, J = 8.40 Hz, 2H), 7.38 (t, J = 5.48 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.6 (C), 155.7 (CH), 155.5 (C), 137.3 (CH), 132.1 (CH), 129.0 (C), 128.8 (CH), 124.2 (C), 111.2 (CH). LCMS: $(M+H)^+$ 274.8.

3-Cyclohexyl-[1,2,4]triazolo[4,3-a]pyrimidine (6c). mp 118–120°C. IR (neat) 3376, 2923, 1610, 1505, 1461, 1346, 1383, 1220, 779 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.32 (dd, J = 6.78, 1.88 Hz, 1H), 8.80 (m, 1H), 7.28 (m, 1H), 2.89–2.87 (m, 1H), 2.05–2.01 (m, 2H), 1.81–1.71 (m, 2H), 1.70–1.55 (m, 4H), 1.45–1.23 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.7 (C), 155.4 (C), 155.3 (CH), 137.4 (CH), 110.7 (CH), 38.0 (CH), 31.7 (CH_2), 26.0 (CH_2), 25.9 (CH_2). *Anal.* Calcd for $C_{11}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.43; H, 7.09; N, 27.87.

3-Cyclopropyl-[1,2,4]triazolo[4,3-a]pyrimidine (6d). IR (neat) 3394, 3014, 1612, 1513, 1488, 1381, 1191, 1034, 897, 779 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.25 (dd, J = 6.72, 1.92 Hz, 1H), 8.76 (dd, J = 4.32, 1.92 Hz, 1H), 7.24 (dd, J = 6.72, 4.36 Hz, 1H), 2.17–2.12 (m, 1H), 1.09–1.08 (m, 2H), 1.07–1.06 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.9 (C), 160.0 (C), 155.1 (CH), 137.0 (CH) , 110.5 (CH), 9.9 (CH), 8.1 (CH_2). LCMS: $(M+H)^+$ 274.8.

4-([1,2,4]Triazolo[4,3-a]quinolin-1-yl)-2-chlorophenol (7a). mp 276–282°C. IR (neat) 2976, 2922, 1620, 1534, 1456, 1296, 1188, 1054, 801, 750 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.00–7.98 (m, 1H), 7.83–7.79 (m, 1H), 7.73–7.71 (m, 2H), 7.53–7.45 (m, 4H), 7.2 (d, J = 7.76 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.4, 132.0, 130.4, 130.3, 130.0,129.7, 126.6, 124.7, 121.5, 120.7, 117.5, 116.4, 115.0. LCMS: $(M+H)^+$ 296.0. *Anal.* Calcd for $C_{16}H_{10}ClN_3O$: C, 64.98; H, 3.41; N, 14.21. Found: C, 65.05; H, 3.72; N, 14.56.

1-(2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-a]quinoline (7b). mp 137–139°C. IR (neat) 1618, 1482, 1220, 1038, 802, 750 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.0 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 9.6 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.55–7.48 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.28–7.20 (m, 3H), 3.78 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 153.7, 152.2, 132.1, 130.3, 129.8,126.6, 124.3, 119.5, 117.9, 115.9, 115.0, 113.4,

56.3, 56.2. LCMS: $(M+H)^+$ 306.0. *Anal.* Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.65; H, 4.90; N, 13.69.

1-(4-(Allyloxy)phenyl)-[1,2,4]triazolo[4,3-a]quinoline (7c). mp 91–93°C. IR (neat) 3045, 1611, 1530, 1446, 1398, 1246, 817, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01–7.99 (m, 1H), 7.91 (d, J = 9.56 Hz, 1H), 7.73 (d, J = 9.52 Hz, 1H),7.65–7.62 (m, 2H), 7.54–7.49 (m, 1H), 7.47–7.43 (m, 2H), 7.23–7.19 (m, 2H), 6.17–6.07 (m, 1H), 5.50–5.44 (m, 1H), 5.32 (dd, J = 10.52, 1.52 Hz, 1H), 4.71 (dt, J = 5.20, 1.32 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 133.9, 132.0, 131.9, 130.2, 130.0, 129.5, 126.5, 124.7, 122.1, 118.3, 116.4, 115.7, 115.1, 68.8. LCMS: $(M+H)^+$ 302.0.

(E)-1-Styryl-[1,2,4]triazolo[4,3-a]quinoline (7d). mp 157–159°C. IR (neat) 3056, 1613, 1443, 1400, 972, 800, 749, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.33 (d, J = 8.37 Hz, 1H), 7.86–7.81 (m, 2H), 7.71–7.67 (m, 4H), 7.59–7.54 (m, 2H), 7.49–7.38 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.8, 148.7, 137.4, 136.1, 132.2, 130.5, 130.2, 129.9, 129.6, 129.3, 128.1, 126.7, 124.9, 117.8, 115.1, 115.0. UPLC: $(M+H)^+$ 272.2. *Anal.* Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.41; H, 4.67; N, 15.55.

1-(Pyridin-4-yl)-[1,2,4]triazolo[4,3-a]quinoline (7e). mp 204–206°C. IR (neat) 3039, 2921, 1596, 1407, 1217, 1064, 825, 750 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.89 (br s, 2H), 8.05 (dd, J = 7.58, 1.80 Hz, 1H), 7.89 (d, J = 9.50 Hz, 1H) 7.82 (d, J = 5.12 Hz, 2H), 7.80 (d, J = 9.56 Hz, 1H), 7.55 (m, 2H), 7.44 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9, 150.0, 146.9, 138.0, 131.58, 130.9, 130.2, 129.9, 126.9, 124.9, 124.7, 116.8, 114.9. UPLC: $(M+H)^+$ 247.5. *Anal.* Calcd for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 73.20; H, 4.45; N, 22.89.

1-(5-Bromopyridin-2-yl)-[1,2,4]triazolo[4,3-a]quinoline (7f). mp 175–177°C. IR (neat) 3068, 1615, 1401, 1082, 1004, 810, 746 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 2.16 Hz, 1H), 8.40 (dd, J = 8.3, 2.36 Hz, 1H), 8.03–7.99 (m, 2H), 7.89 (d, J = 9.52 Hz, 1H), 7.79 (d, J = 9.48 Hz, 1H), 7.62–7.59 (m, 1H), 7.56–7.53 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 151.0, 150.1, 147.8, 147.7, 141.1, 131.4, 131.1, 129.8, 129.7, 128.03, 127.0, 124.7, 122.4, 118.2, 114.8. LCMS: $(M+H)^+$ 327.0. *Anal.* Calcd for $C_{15}H_9BrN_4$: C, 55.41; H, 2.79; N, 17.23. Found: 55.57; H, 2.98; N, 17.09.

1-(Furan-2-yl)-[1,2,4]triazolo[4,3-a]quinoline (7g). mp 114–116°C. IR (neat) 3112, 1615, 1444, 1399, 1167, 1067, 1011, 806, 782 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 8.03 (d, J = 6.44 Hz, 1H), 7.93 (s, 1H), 7.81–7.84 (m, 1H), 7.61–7.57 (m, 1H), 7.17 (s, 1H), 7.08 (d, J = 7.52 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.6, 140.7, 131.0, 130.1, 129.7, 129.4, 129.0, 126.4, 126.2, 124.1, 115.8, 115.1, 114.4, 112.1. UPLC: $(M+H)^+$ 236.5.

1-(Thiophen-3-yl)-[1,2,4]triazolo[4,3-a]quinoline (7h). mp 170–172°C. IR (neat) 3098, 1612, 1441, 1402, 1056, 801, 744 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (dd, J = 2.90, 1.20 Hz, 1H), 8.02 (m, 1H), 7.93 (m, 1H) 7.84 (d, J = 9.48 Hz, 1H), 7.75 (d, J = 9.44 Hz, 1H), 7.51–7.57 (m, 3H), 7.43 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 131.93, 130.47, 130.43, 129.75, 129.69, 129.52, 129.12, 128.60, 124.67, 116.28, 114.96. UPLC: $(M+H)^+$ 252.5.

1-(5-Fluoro-1H-indol-2-yl)-[1,2,4]triazolo[4,3-a]quinoline (7i). mp 270–272°C. IR (neat) 3149, 1620, 1579, 1451, 1402, 1162, 806, 752 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H), 8.00–7.98 (m, 2H), 7.82 (d, J = 9.40 Hz, 1H), 7.53 (d, J = 9.48 Hz, 1H), 7.62 (d, J = 8.54 Hz, 1H), 7.59 (dd, J = 8.88, 4.52 Hz, 1H), 7.48 (t, J = 7.28 Hz, 1H), 7.35 (td, J = 8.56, 1.32 Hz, 1H), 7.08 (td, J = 9.20, 2.44 Hz, 1H), 6.98 (dd, J = 9.72, 2.36 Hz, 1H), ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.0, 133.3, 132.7, 130.2, 130.0, 129.7, 129.5, 127.3, 126.4, 124.8, 116.4, 115.4, 114.1, 111.1, 104.7, 104.2. LCMS: $(M+H)^+$ 303.0. *Anal.* Calcd for $C_{18}H_{11}FN_4$: C, 71.51; H, 3.67; N, 18.53. Found: C, 71.76; H, 3.77; N, 18.67.

1-Hexyl-[1,2,4]triazolo[4,3-a]quinoline (7j). IR (neat) 2928, 2853, 1615, 1465, 1410, 814, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.48 Hz, 1H), 7.83 (d, J = 7.84 Hz, 1H), 7.73–7.69 (m, 1H), 7.68–7.64 (m, 1H), 7.58–7.51 (m, 2H), 3.48 (t, J = 7.72 Hz, 2H), 2.11–2.03 (m, 2H), 1.64–1.56 (m, 2H), 1.46–1.37 (m, 4H), 0.85 (t, J = 3.40 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 132.3, 130.1, 129.8, 128.3, 126.3, 124.6, 117.0, 115.1, 31.5, 28.9, 28.8, 26.5, 22.5, 14.4. LCMS: $(M+H)^+$ 254.2.

1-Cyclopropyl-[1,2,4]triazolo[4,3-a]quinoline (7k). mp 85–87°C. IR (neat) 3380, 1616, 1411, 1119, 808, 760 cm^{-1}. ^1HNMR (400 MHz, $CDCl_3$): δ 8.83 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 7.56 Hz, 1H), 7.77–7.73 (m, 2H), 7.57 (t, J = 7.52 Hz, 2H), 2.52–2.48 (m, 1H), 1.45–1.39 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 132.1, 129.5, 129.3, 129.2, 125.9, 124.1, 116.8, 114.6, 9.4, 6.9. LCMS: $(M+H)^+$ 210.2.0. *Anal.* Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.56; H, 5.24; N, 20.13.

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CONFLICT OF INTEREST

The authors disclose that there is no academic and financial conflict of interest in this work.

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