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ARTICLE TYPE

Regioselective one-pot three-component synthesis of quinoline based 1,2,4-triazolo[1,5-a]quinoline derivatives

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A one-pot three-component approach for the synthesis of 2-(piperidin-1-yl) quinoline based 1,2,4-triazolo[1,5-a]quinoline derivatives (**4a-l**) has been described by the reaction of aldehyde (**1a-f**), methyl 2-cyanoacetate (**2**) and enaminones (**3a-b**). Regioselectivity of reaction attained by different catalyst and higher regioselectivity is achieved by L-proline. This new procedure provides an efficient method to construct fused tricyclic heterocycles containing 1,2,4-triazole analogues. In this regards, we have using least amount of amphoteric catalyst like L-proline, ammonium acetate and mixture of pyrolidine with acetic acid to obtain 1,4-dihydroquinoline derivative **5a** as a by product, where as mild reaction condition, high yield (75-85%) and higher regioselectivity toward desired products **4a-l** are the salient features of this protocol. The structures of the title compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

1. Introduction

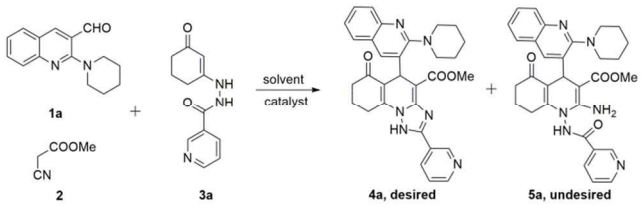
Quinoline is an imperative group of compounds achieved from both nature and synthetic origin that acquire miscellaneous pharmaceutical and biological activities, often depending on the substituent they bear in the parent benzopyridine moiety. The quinoline scaffolds are known due to their biomedical potential, including antibacterial, anti-inflammatory, antiasthmathic and antihypertensive agents and also in tyrosine kinase inhibitors.[1-4]

Fused 1,2,4-triazoles are used as peptidomimetic derivatives and as hydrogen bond acceptors[5, 6] or as amide bond isostere for the design of receptor ligands with the intention of enlarge their pharmacokinetic properties.[7] Compounds containing the triazolopyridine substructure have been shown to possess cardiovascular,[8] JAK2 inhibitors,[9] antibacterial, antithrombotic, anti-inflammatory, antiproliferative, and herbicidal agents.[10-14]

From the literature survey, we found that none of one have reported the synthesis of 1,2,4-triazolo[1,5-*a*]quinoline. But, a few synthetic pathways to the 1,2,4-triazolo[4,3-*a*]quinoline system have been developed.[11, 15-18] Substituted 1,2,4-triazolo[4,3-*a*]quinoline was first found to have anticonvulsant,[15, 16, 19] antibacterial[11] activity. So, our aim to design 1,2,4-triazolo[1,5-*a*]quinoline consists of a triazole ring fused with a quinoline.

Multicomponent reactions[20, 21] (MCRs) have become the most efficient and powerful tools for the rapid generation of modern drug discovery with diversity in predefined functionality of chemical biology. Chemo and stereoselectivities[22, 23] of MCRs have been widely accepted as a significant challenging task for synthetic organic chemists.

In the present work, it is intended to explore synthesis of 1,2,4-triazolo[1,5-*a*]quinoline accepting facile synthetic approaches and utilizing easily accessible starting chemicals. In this work, we describe a regioselective synthesis for 1,2,4-triazolo[1,5-*a*]quinoline using the aldehyde (**1a-f**), methyl 2-cyanoacetate (**2**) and enaminones (**3a-b**). To determine the most excellent reaction conditions, we studied the influence of catalysts on regioselectivity of reaction. The reaction of 2-(piperidin-1-yl) quinoline-3-carbaldehyde **1a**, methyl 2-cyanoacetate **2** and *N*'-(3-oxocyclohex-1-enyl) nicotinohydrazide **3a** were as a selected model reaction for all catalytic studies (**Scheme 1**) as well as for the desired products (**4a-l**) and the results are summarized in **Table 1**.



Scheme 1. Model reaction for screening of catalysts to optimize reaction condition.

2. Result and discussion

In the context of our continuing efforts on developing multicomponent synthesis of polyhydroquinoline,[24-27] we are interested in regioselective synthesis of 1,2,4-triazolo[1,5-*a*]quinoline. However, practical and general approaches to this type of fused quinoline are rare in the literature. Herein we report a much improved and new synthesis of 1,2,4-triazolo[1,5-*a*]quinoline over a polyhydroquinoline using aldehyde, methyl 2-cyanoacetate and enaminones in the presence of L-proline as a catalyst and ethanol as solvent.(**Scheme 2**).

We began our studies by screening different catalysts for their

ability to catalyze the intramolecular cyclization to form 1,2,4-triazolo[1,5-*a*]quinoline over polyhydroquinoline. Using only 0.2 equivalent of each catalyst afforded 1,2,4-triazolo[1,5-a]quinoline in poor to high yields after different time interval (**Scheme 1**). In order to evaluate the regioselectivity of reaction, the model reaction were performed with various catalyst and the regioselectivity were found in decreasing order L-proline > pyrolidine + acetic acid > ammonium acetate > triethylamine (TEA) > piperidine > pyrolidine > NaOH > dimethylaminopyridine (DMAP) > acetic acid (**Table 1**).

Table 1. The influence of different catalysts on the model reaction using ethanol as a solvent.

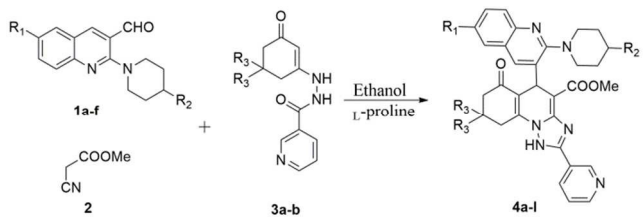
Entry[a]	Catalyst	Time[b]	Yield of **4a**[c](%)	Yield of **5a**[c](%)
1	piperidine	5 h	30	55
2	TEA	5 h	40	43
3	DMAP	6 h	13	60
4	NaOH	6 h	20	62
5	ammonium acetate	4 h	55	33
6	**L-proline**	**2 h**	**80**	**10**
7	pyrolidine	6 h	26	55
8	pyrolidine + acetic acid	3 h	65	23
9	acetic acid	4 h	-	-

[a] Reaction of 2-(piperidin-1-yl)quinoline-3-carbaldehyde **1a** (1 mmol), methyl 2-cyanoacetate **2** with *N*'-(3-oxocyclohex-1-enyl)nicotinehydrazide **3a** (1 mmol) in the presence of 0.2 mmol of catalyst

[b] Reaction progress monitored by TLC

[c] Isolated yield by column chromatography

For optimized of reaction condition initially the reaction in ethanol as solvent in presence of piperidine as catalyst to afford desired product **4a** in lower yield as compared to undesired product **5a** (entry 1). Then we were tried TEA as catalyst to generate a new tricyclic molecule, in this case also we obtained lower yield (entry 2). Further investigation of various basic catalyst like DMAP, NaOH and pyrolidine, in this cases we found very low yield of desired product **4a** (entry 3,4,7). When acetic acid employ as a catalyst no product formation was observed (entry 9). After using different basic and acetic acid as catalyst, we observed that not much improvement in regioselectivity of reaction as well as in yield of desired product. Then we go for amphoteric catalysts like ammonium acetate (entry 5), L-proline (entry 6) and mixture of pyrolidine with acetic acid (entry 8), herein case to obtained high yield with the greater enhancement of regioselectivity scrutinise. The results are summarized in **Table 1**.



Scheme 2. Regioselective synthesis of substituted 1,2,4-triazolo[1,5-a]quinoline.

From these results, L-proline was selected as catalyst for the regioselective synthesis of 1,2,4-triazolo[1,5-a]quinoline. We find out the high yield of desired product with high regioselectivity of reaction by using L-proline as compared to other catalysts. In our study, the nature of catalyst was found to have profound influence on the reaction; basic catalysts such as piperidine, TEA, DMAP, NaOH and pyrolidine promoted the regioselectivity of reaction relatively lower compare to amphoteric catalysts like L-proline, ammonium acetate and pyrolidine + acetic acid.

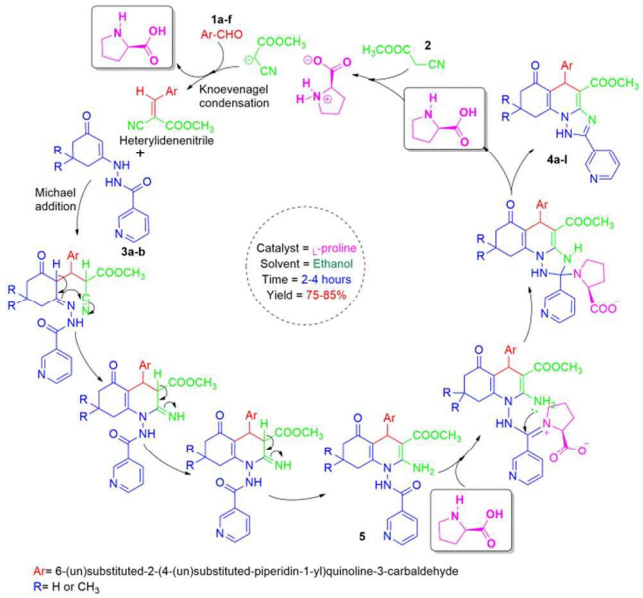
Table 2. The synthetic results for the products **4a.**

Entry[a]	R_1	R_2	R_3	Product	Time (h)	Yields[b] (%)
1	H	H	H	4a	2.0	80
2	H	H	CH_3	4b	2.0	85
3	H	CH_3	H	4c	2.5	82
4	H	CH_3	CH_3	4d	2.0	80
5	CH_3	H	H	4e	2.5	78
6	CH_3	H	CH_3	4f	3.0	81
7	CH_3	CH_3	H	4g	3.0	84
8	CH_3	CH_3	CH_3	4h	4.0	79
9	OCH_3	H	H	4i	2.5	80
10	OCH_3	H	CH_3	4j	3.0	77
11	OCH_3	CH_3	H	4k	3.5	78
12	OCH_3	CH_3	CH_3	4l	4.0	75

[a] Reagents and conditions: **1a-f** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), L-proline (0.2 mmol), ethanol (10 mL), reflux.

[b] Isolated yields by column chromatography

From the above concept, we prepared a variety of 6-(un)substituted-2-(4-(un)substituted-piperidin-1-yl)quinoline-3-carbaldehyde **1a–f** by a base mediated reaction of corresponding substituted 2-chloro-3-formyl-quinoline with piperidine or 4-methyl piperidine[28, 29] and obtained N'-(5,5-(un)substituted-3-oxocyclohex-1-en-1-yl)nicotinohydrazide **3a–b** by reacting the corresponding 1,3-cyclohexadione or 5,5-dimethylcyclohexane-1,3-dione with a nicotinohydrazide.[30] Further we have studied reactions of **1a–f**, **2** and **3a-b** using L-proline as the catalyst in ethanol to gain the corresponding 1,2,4-triazolo[1,5-a]quinoline **4a-l** (**Scheme 2**) in high yield (75–85%) as shown in **Table 2**.

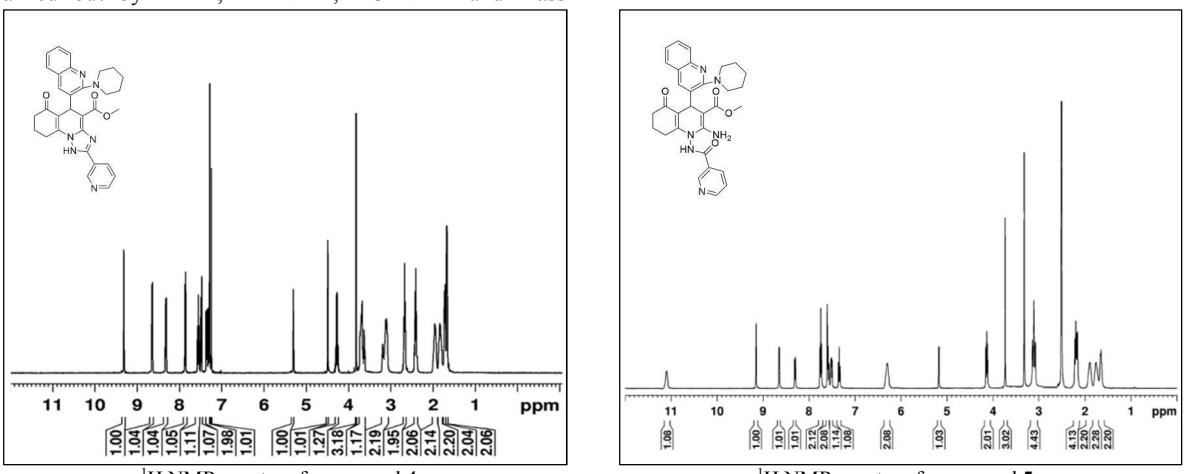


Scheme 3. Plausible mechanistic pathway for the synthesis of 1,2,4-triazolo[1,5-a]quinoline.

A plausible mechanism for the reaction is outlined in **Scheme 3**. The reaction occurs *via in situ* initial formation of the

heterylidenenitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between 6-(un)substituted-2-(4-(un)substituted-piperidin-1-yl)quinoline-3-carbaldehyde **1a–f** and malononitrile **2** by loss of water molecule, Michael addition of *N'*-(5,5-(un)substituted-3-oxocyclohex-1-en-1-yl)nicotinohydrazide **3a-b** to the ylidenic bond to form an acyclic intermediate which undergoes cyclization by nucleophilic attack of the –NH group on the electron deficient cyano carbon, followed by tautomerisation to the intermediate products polyhydroquinoline. We realized polyhydroquinoline intermediate undergo intra-molecular keto-amine cyclization reaction to give 1,2,4-triazolo[1,5-a]quinoline derivative **4a-l**.

The structural elucidations of the synthesized compounds **4a-l** were carried out by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. In model reaction the compounds **4a** and **5a** were isolated on the basis of ^{1}H NMR and mass spectrometry. In ESI-mass spectrum gave a molecular ion at m/z 535 indicated the formation of the desired product **4a** and molecular ion at m/z 553 indicated the formation of the undesired product **5a**, the difference of 18 in mass indicate the loss of water molecule from **5a** and generate a new molecule **4a**. In 1H NMR spectra of **5** show two peaks of –NH_2 and –CONH at 6.29 and 11.15 δ ppm respectively but in **4a**, NH_2 and CONH peak was not observed. The ^{1}H NMR spectrum of the compound **4a** displayed one more proton at 4.49 δ ppm that indicates the cyclic -NH proton. (**Figure 1**)



^{1}H NMR spectra of compound **4a** ^{1}H NMR spectra of compound **5a**

Figure 1. ^{1}H NMR spectra of compound **4a** and **5a.**

3. Conclusion

We have developed a novel and efficient method for the regioselective synthesis of [1,2,4]triazolo[1,5-*a*]quinoline derivatives **4a-l** *via* three-component cyclocondensation of aldehydes **1a-f**, methyl 2-cyanoacetate **2** and enaminones **3a-b** followed by intramolecular cyclization using L-proline as the catalyst. The method utilizes readily available reactant, inexpensive catalyst and affords regioselectivity of fused tricyclic heterocycles in high yields.

4. Experimental section

4.1. Chemistry

All reactions were performed with commercially available reagents. They were used without further purification. The solvents used were of analytical grade. All reactions were monitored by thin-layer chromatography (TLC) on aluminium plates coated with silica gel 60 F254, 0.25 mm thickness (Merck). Detection of the components was made by exposure to iodine vapours or UV light. Melting points were taken in melting point apparatus μThermoCal10 (Analab Scientific Pvt. Ltd, India) and are uncorrected. The IR spectra were recorded on a FTIR MB 3000 spectrophotometer (ABB Bomem Inc., Canada/Agaram Industries, Chennai) using Zn-Se Optics (490-8500 cm-1). Mass spectra were recorded on Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan) purchased under PURSE program of DST at Sardar Patel University, Vallabh Vidyanagar. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using residual solvent signal as an internal standard at 400 MHz and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm). Splitting patterns were designated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet and m, multiplet. The elemental analysis was carried out by using Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ± 0.4% of the theoretical compositions. Yields are optimized by column chromatography purification.

4.2. General procedure for the synthesis of methyl 2'-amino-6-(un)substituted-7',7'-(un)substituted-2-(4-(un)substituted piperidin-1-yl)-1'-(nicotinamido)-5'-oxo-1',4',5',6',7',8'-hexahydro-[3,4'-biquinoline]-3'-carboxylate (4a-l)

A 50 mL round bottom flask, fitted with a reflux condenser, was charged with a mixture of aldehyde **1a-f** (1 mmol), methyl 2-cayno acetate (1 mmol) **2**, substituted enaminones **3a-b** (1 mmol), and catalyst L-proline (0.2 mmol) in ethanol (10 mL). The mixture was heated under reflux for 2-3 h and the progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and reaction mixture was concentrated under reduced pressure to obtain solid mass. The crude product was purified by column

chromatography. The physicochemical and spectroscopic characterization data of the synthesized compounds **4a-l** are given below.

4.2.1. methyl-5-(2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4a***

Yield 80%; white solid; m.p. 240°C; IR (ν_{max}, cm^{-1}): 3290, 3046, 1701, 1656; ^1H NMR (400 MHz, $CDCl_3$): 1.67-1.95 (m, 8H), 2.40 (t, 2H, *J* = 6.4 Hz), 2.65-2.69 (m, 2H), 3.11(d, 2H, *J* = 8.4 Hz), 3.63-3.72 (m, 1H), 3.82 (s, 3H), 4.27 (dd, 1H, *J* = 2.0 Hz, *J* = 7.2 Hz), 4.49 (s, 1H), 5.32 (s, 1H), 7.24-7.57 (m, 5H), 7.86 (d, 1H, *J* = 8.4 Hz), 8.32 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 8.64 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 9.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.3, 21.0, 24.2, 26.0, 34.7, 36.8, 45.3, 52.7, 53.7, 119.1, 124.5, 125.4, 125.6, 125.9, 127.2, 127.5, 128.1, 129.9, 133.9, 134.5, 146.3, 147.5, 150.8, 151.3, 160.8, 161.8, 168.5, 168.9, 196.7; ESI-MS (m/z): Calcd. for $C_{31}H_{30}N_6O_3$ 534.61, found 535.15 (M^+).

4.2.2. methyl-8,8-dimethyl-5-(2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4b***

Yield 85%; white solid; m.p. 246°C; IR (ν_{max}, cm^{-1}): 3290, 3045, 1703, 1655; ^1H NMR (400 MHz, $CDCl_3$): 1.32 (s, 3H), 1.37 (s, 3H), 1.67-1.95 (m, 8H), 2.53 (s, 2H), 3.04-3.15 (m, 2H), 3.67-3.75 (m, 1H), 3.80 (s, 3H), 4.26 (dd, 1H, *J* = 7.2 Hz, *J* = 14.4 Hz), 4.48 (s, 1H), 5.30 (s, 1H), 7.25-7.37 (m, 2H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 7.6 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.33 (d, 1H, *J* = 6.4 Hz), 8.65(s, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 21.1, 22.5, 26.2, 29.5, 33.3, 34.6, 37.3, 45.2, 50.4, 53.6, 118.8, 124.4, 125.5, 125.8, 126.2, 127.4, 128.3, 129.8, 133.8, 134.3, 146.0, 147.3, 149.5, 151.4, 160.5, 162.0, 168.5, 169.2, 196.6; ESI-MS (m/z): Calcd. 562.66, found 562.65 (M^+).

4.2.3. methyl-5-(2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4c***

Yield 82%; white solid; m.p. 251°C; IR (ν_{max}, cm^{-1}): 3284, 2991, 1702, 1653; ^1H NMR (400 MHz, $CDCl_3$): 1.05 (d, 3H, *J* = 12.0 Hz), 1.26-1.94 (m, 4H), 2.44-2.78 (m, 5H), 3.13-3.68 (m, 4H), 3.82 (s, 3H), 4.05 (d, 1H, *J* = 12.8 Hz), 4.25-4.30 (m, 1H), 4.48 (s, 1H), 5.30 (s, 1H), 7.24-7.37 (m, 3H), 7.47-7.57 (m, 2H), 7.86 (d, 1H, *J* = 8.4 Hz), 8.30-8.33 (m, 1H), 8.64-8.65 (m, 1H), 9.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.4, 21.1, 24.1, 26.5, 30.4, 33.7, 37.0, 45.2, 50.5, 53.6, 117.7, 124.1, 125.8, 126.2, 127.3, 127.8, 128.1, 129.8, 134.3, 134.8, 146.0, 147.2, 148.4, 151.5, 160.7, 161.6, 168.6, 169.2, 196.6; ESI-MS (m/z): Calcd. 548.63, found 549.30 (M^+).

4.2.4. methyl-8,8-dimethyl-5-(2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4d***

Yield 80%; white solid; m.p. 235°C; IR (ν_{max}, cm^{-1}): 3290, 3049, 1701, 1655; ^1H NMR (400 MHz, $CDCl_3$): 1.06 (d, 3H, *J* = 12.0 Hz), 1.27 (s, 3H), 1.35 (s, 3H), 1.46-1.49 (m, 1H), 1.59-1.66 (m, 2H), 1.86-1.94 (m, 2H), 2.52 (s, 2H), 2.77 (t, 1H, *J* = 11.2 Hz), 3.06 (d, 1H, *J* = 18.0 Hz), 3.34-3.48 (m, 2H), 3.80 (s, 3H), 4.05 (d, 1H, *J* = 12.4 Hz), 4.26 (dd, 1H, *J* = 6.8 Hz, *J* = 14.4 Hz), 4.46 (s, 1H), 5.28 (s, 1H), 7.25-7.36 (m, 3H), 7.45 (d, 1H, *J* = 8.0 Hz), 7.52-7.56 (m, 1H), 7.85 (d, 1H, *J* = 8.0 Hz), 8.32 (d, 1H, *J* = 8.0 Hz), 8.64 (dd, 1H, *J* = 1.2 Hz, *J* = 4.8 Hz), 9.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.5, 22.4, 26.7, 29.4, 30.8, 33.5, 34.4, 37.4, 45.3, 50.2, 53.7, 118.4, 124.5, 125.5, 125.8, 127.1, 127.5, 127.9, 130.0, 134.0, 134.5, 146.4, 147.5, 148.8, 151.5, 160.9, 161.7, 168.6, 169.1, 196.6; ESI-MS (m/z): Calcd. 576.69, found 576.55 (M^+).

4.2.5. methyl-5-(6-methyl-2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4e***

Yield 78%; white solid; m.p. 233°C; IR (ν_{max}, cm^{-1}): 3291, 3052, 1701, 1656; ^1H NMR (400 MHz, $CDCl_3$): 1.69-1.94 (m, 6H), 2.42 (s, 3H), 2.64-2.68 (m, 2H), 3.05-3.19 (m, 4H), 3.50 (d, 1H, *J* = 4.4 Hz), 3.60-3.69 (m, 3H), 3.80 (s, 3H), 4.49 (s, 1H), 5.31 (s, 1H), 7.16 (s, 1H), 7.26-7.40 (m, 3H), 7.76 (d, 1H, *J* = 8.8 Hz), 8.31-8.34 (m, 1H), 8.65 (dd, 1H, *J* = 1.6 Hz, *J* = 5.2 Hz), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 21.4, 24.5, 26.4, 30.5, 33.4, 36.8, 45.4, 50.2, 53.8, 117.1, 124.5, 125.7, 126.4, 127.0, 127.8, 128.4, 129.6, 134.1, 134.7, 146.1, 147.2, 148.3, 151.4, 160.8, 161.9, 168.4, 169.0, 196.4; ESI-MS (m/z): Calcd. 548.63, found 548.77 (M^+).

4.2.6. methyl-8,8-dimethyl-5-(6-methyl-2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4f***

Yield 81%; white solid; m.p. 241°C; IR (ν_{max}, cm^{-1}): 3281, 2991, 1703, 1652; ^1H NMR (400 MHz, $CDCl_3$): 1.32 (s, 3H), 1.43 (s, 3H), 1.69-1.91 (m, 6H), 2.43 (s, 3H), 2.47 (s, 2H), 3.04-3.12 (m, 4H), 3.46 (d, 1H, *J* = 18.4 Hz), 3.65-3.69 (m, 1H), 3.78 (s, 3H), 4.46 (s, 1H), 5.29 (s, 1H), 7.12-7.19 (m, 2H), 7.34-7.39 (m, 2H), 7.74 (d, 1H, *J* = 19.6 Hz), 8.32-8.35 (m, 1H), 8.65 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.7, 21.1, 22.6, 26.4, 29.0, 31.1, 33.3, 34.6, 37.8, 45.6, 50.5, 53.5, 118.0, 124.1, 125.3, 125.9, 127.5, 127.8, 128.1, 129.9, 134.3, 134.5, 146.0, 147.1, 148.5, 151.2, 160.7, 161.5, 168.4, 169.5, 196.8; ESI-MS (m/z): Calcd. 576.69, found 576.55 (M^+).

4.2.7. methyl-5-(6-methyl-2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4g***

Yield 84%; white solid; m.p. 228°C; IR (ν_{max}, cm^{-1}): 3215, 3053, 1700, 1655; ^1H NMR (400 MHz, $CDCl_3$): 1.07 (d, 3H, *J* = 12.0 Hz), 1.60-1.93 (m, 7H), 2.39 (s, 3H), 2.64-2.78 (m, 3H), 3.16 (dd, 1H, *J* = 5.6 Hz, *J* = 18.4 Hz), 3.36-3.39 (m, 2H), 3.60-3.67 (m, 1H), 3.82 (s, 3H), 4.00 (d, 1H, *J* = 12.4 Hz), 4.49 (s, 1H), 5.29 (s, 1H), 7.17-7.39 (m, 4H), 7.75 (d, 1H, *J* = 8.8 Hz), 8.31-8.34 (m, 1H), 8.65 (dd, 1H, *J* = 1.2 Hz, *J* = 4.8 Hz), 9.31 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.6, 21.3, 25.5, 27.0, 29.2, 33.1, 34.2, 38.3, 46.1, 51.0, 53.1, 123.5, 124.9, 126.4, 128.6, 129.1, 129.5, 130.5, 133.2, 133.8, 134.9, 138.1, 144.0, 144.9, 148.5, 148.7, 153.4, 163.1, 169.2, 171.5, 197.0; ESI-MS (m/z): Calcd. 562.66, found 563.20 (M^+).

4.2.8. methyl-8,8-dimethyl-5-(6-methyl-2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4h***

Yield 79%; white solid; m.p. 244°C; IR (ν_{max}, cm^{-1}): 3291, 3052, 1701, 1657; ^1H NMR (400 MHz, $CDCl_3$): 1.07 (d, 3H, *J* = 6.0 Hz), 1.32 (s, 3H), 1.41 (s, 3H), 1.43-1.50 (m, 1H), 1.66 (s, 2H), 1.86-1.93 (m, 2H), 2.39 (s, 3H), 2.52 (s, 2H), 2.74-2.80 (m, 1H), 3.04-3.12 (m, 1H), 3.33-3.48 (m, 2H), 3.81 (s, 3H), 4.01 (d, 1H, *J* = 13.6 Hz), 4.26 (dd, 1H, *J* = 7.2 Hz, *J* = 14.4 Hz), 4.46 (s, 1H), 5.27 (s, 1H), 7.18-7.39 (m, 4H), 7.75 (d, 1H, *J* = 8.4 Hz), 8.33 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 8.65 (d, 1H, *J* = 4.8 Hz), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.5, 21.2, 22.6, 24.2, 26.5, 29.6, 33.5, 34.4, 37.5, 45.4, 50.3, 53.7, 124.6, 125.6, 127.3, 128.0, 128.9, 129.8, 130.7, 133.0, 133.9, 134.9, 136.5, 142.9,

144.5, 147.5, 148.7, 151.5, 162.4, 168.9, 169.1, 196.6; ESI-MS (m/z): Calcd. 590.71, found 590.80 (M^+).

4.2.9. methyl-5-(6-methoxy-2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4i***

Yield 80%; white solid; m.p. 239°C; IR (ν_{max}, cm^{-1}): 3284, 2997, 1701, 1652; ^1H NMR (400 MHz, $CDCl_3$): 1.68-1.93 (m, 6H), 2.42 (dd, 2H, *J* = 6.4 Hz, *J* = 12.4 Hz), 2.68 (dd, 2H, *J* = 5.2 Hz, *J* = 7.6 Hz), 3.02-3.20 (m, 3H), 3.62-3.68 (m, 3H), 3.82 (s, 6H), 4.50 (s, 1H), 5.32 (s, 1H), 6.78 (d, 1H, *J* = 2.8 Hz), 7.15 (s, 1H), 7.20-7.38 (m, 2H), 7.77 (d, 1H, *J* = 9.2 Hz), 8.32-8.35 (m, 1H), 8.65 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.3, 21.0, 24.2, 24.6, 26.1, 34.5, 36.8, 45.4, 52.8, 53.7, 55.8, 106.4, 119.1, 119.2, 121.8, 124.5, 125.7, 126.9, 127.6, 127.9, 129.0, 133.5, 133.9, 142.0, 147.5, 150.6, 150.7, 151.1, 151.3, 151.5, 156.8, 160.0, 160.8, 168.5, 169.0, 196.7; ESI-MS (m/z): Calcd. 564.63, found 565.00 (M^+).

4.2.10. methyl-8,8-dimethyl-5-(6-methoxy-2-(piperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4j***

Yield 77%; white solid; m.p. 235°C; IR (ν_{max}, cm^{-1}): 3215, 3052, 1704, 1655; ^1H NMR (400 MHz, $CDCl_3$): 1.29 (s, 3H), 1.38 (s, 3H), 1.60-1.66 (m, 2H), 1.80 (s, 2H), 1.87 (t, 2H, *J* = 15.2 Hz), 2.53 (s, 2H), 2.78 (t, 1H, *J* = 10.8 Hz), 3.06 (d, 1H, *J* = 18.8 Hz), 3.34-3.48 (m, 2H), 3.81 (s, 6H), 4.04 (d, 1H, *J* = 14.0 Hz), 4.26 (dd, 1H, *J* = 6.8 Hz, *J* = 13.6 Hz), 4.47 (s, 1H), 5.29 (s, 1H), 7.13-7.19 (m, 2H), 7.35-7.40 (m, 2H), 7.75 (d, 1H, *J* = 15.6 Hz), 8.32-8.35 (m, 1H), 8.64 (dd, 1H, *J* = 1.2 Hz, *J* = 4.8 Hz), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.9, 20.9, 22.2, 23.9, 24.5, 26.8, 33.8, 36.8, 46.0, 53.1, 53.8, 55.2, 107.3, 119.0, 119.5, 121.6, 124.3, 125.4, 126.4, 127.8, 129.2, 133.7, 133.9, 142.8, 147.3, 150.1, 150.9, 151.3, 152.0, 152.5, 157.3, 160.1, 161.4, 168.7, 170.6, 195.8; ESI-MS (m/z): Calcd. 592.69, found 592.85 (M^+).

4.2.11. methyl-5-(6-methoxy-2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4k***

Yield 78%; white solid; m.p. 232°C; IR (ν_{max}, cm^{-1}): 3291, 3053, 1700, 1656; ^1H NMR (400 MHz, $CDCl_3$): 1.06 (d, 3H, *J* = 6.0 Hz), 1.43-1.92 (m, 5H), 2.41 (t, 2H, *J* = 6.0 Hz), 2.65-2.77 (m, 2H), 3.14-3.20 (m, 1H), 3.36 (d, 2H, *J* = 6.4 Hz), 3.61-3.69 (m, 1H), 3.82 (s, 6H), 3.95 (d, 1H, *J* = 12.8 Hz), 4.25-4.29 (m, 1H), 4.50 (s, 1H), 5.29 (s, 1H), 6.78 (s, 1H), 7.16-7.37 (m, 3H), 7.76 (d, 1H, *J* = 9.2 Hz), 8.33 (d, 1H, *J* = 8.0 Hz), 8.65 (d, 1H, *J* = 4.8 Hz), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.2, 22.6, 23.4, 26.8, 29.2, 30.6, 33.1, 34.5, 37.2, 45.4, 53.1, 55.4, 117.4, 123.6, 125.4, 126.3, 127.0, 127.9, 128.8, 129.1, 134.5, 134.9, 146.5, 147.5, 148.4, 151.6, 161.3, 162.2, 168.1, 169.2, 196.8; ESI-MS (m/z): Calcd. 578.66, found 578.55 (M^+).

4.2.12. methyl-8,8-dimethyl-5-(6-methoxy-2-(4-methylpiperidin-1-yl)quinolin-3-yl)-6-oxo-2-(pyridin-3-yl)-1,5,6,7,8,9-hexahydro-[1,2,4]triazolo[1,5-a]quinoline-4-carboxylate ***4l***

Yield 75%; white solid; m.p. 243°C; IR (ν_{max}, cm^{-1}): 3284, 2997, 1701, 1653; ^1H NMR (400 MHz, $CDCl_3$): 1.06 (d, 3H, *J* = 6.4 Hz), 1.07 (s, 3H), 1.38 (s, 3H), 1.43-1.66 (m, 3H), 1.79 (s, 2H), 1.85-1.92 (m, 1H), 2.53 (s, 2H), 2.73-2.76 (m, 1H), 3.05-3.10 (m, 1H), 3.35-3.48 (m, 2H), 3.81 (s, 6H), 3.95 (d, 1H, *J* = 12.8 Hz), 4.48 (s, 1H), 5.27 (s, 1H), 6.74 (d, 1H, *J* = 2.8 Hz), 7.16 (s, 1H), 7.19-7.38 (m, 2H), 7.77 (d, 1H, *J* = 8.8 Hz), 8.32-8.35 (m, 1H), 8.65 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.0, 21.1, 22.9, 23.6, 25.7, 29.6, 30.5, 33.3, 34.7, 37.6, 45.8, 53.3, 55.8, 117.6, 123.9, 126.1, 126.8, 127.5, 128.0, 128.5, 131.1, 135.2, 138.3, 148.5, 149.2, 153.4, 162.8, 164.5, 170.0, 172.8, 197.3; ESI-MS (m/z): Calcd. 606.71, found 606.30 (M^+).

4.2.13. methyl 2'-amino-1'-(nicotinamido)-5'-oxo-2-(piperidin-1-yl)-1',4',5',6',7',8'-hexahydro-[3,4'-biquinoline]-3'-carboxylate ***5a***

White solid; m.p. 240°C; IR (ν_{max}, cm^{-1}): 3412, 3369, 2955, 1639; ^1H NMR (400 MHz, DMSO-d_6): 1.65-2.25 (m, 10H), 3.10 (t, 4H, *J* = 12.4 Hz), 3.85 (s, 3H), 4.13 (t, 2H, *J* = 12.0 Hz), 5.15 (s, 1H), 6.29 (s, 2H), 7.34 (t, 1H, *J* = 8.0 Hz), 7.49-7.76 (m, 5H), 8.30 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 8.65 (d, 1H, *J* = 4.4 Hz), 9.15 (s, 1H), 11.15 (s, 1H) ; ESI-MS (m/z): Calcd. for $C_{31}H_{30}N_6O_3$ 553.61, found 553.18 (M^+).

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