Full Paper

Synthesis and Anti-inflammatory Activity Evaluation of Novel 7-Alkoxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinolines

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In this study, a novel series of 7-alkoxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinolines were synthesized by using 6-hydroxy-3,4-dihydro-2(1*H*)-quinolone as the starting material. These compounds were evaluated for anti-inflammatory activity through monitoring their ability to inhibit xylene-induced ear edema in mice. Some of the tested compounds exhibited significant activity, and the compounds **5f** (7-(benzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolin-1-amine) and **5i** (7-(*p*-chlorobenzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolin-1-amine) showed the highest anti-inflammatory activity (52% and 58% inhibition, respectively, at 2 h pre-administration) which were comparable to or even slightly more potent than the reference drug ibuprofen (55%). Furthermore, the structure-activity relationship of these 1,2,4-triazole quinolines was demonstrated.

Keywords: Anti-inflammatory / Quinoline / 1,2,4-Triazole

Received: June 27, 2007; accepted: September 5, 2007

DOI 10.1002/ardp.200700182

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are useful tools in the treatment of acute and chronic inflammation, pain, and fever. However, long-term clinical usage of NSAIDs is associated with significant side effects of gastro-intestinal lesions, bleeding, and nephrotoxicity. Therefore, the discovery of new and safer anti-inflammatory drugs represents a challenging goal for such a research area [1]. As resistance to anti-inflammatory drugs is widespread, there is an increasing need for identification of novel structure leads that may be of use in designing new, potent and less toxic anti-inflammatory agents.

Various derivatives of 1,2,4-triazole have been reported to possess anti-inflammatory activity [2–12]. In our previous studies [13, 14], 7-benzyloxy-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinolines (compound **6**) and 7-benzyloxy-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinoline-1-ones (compound **7**) were synthesized and tested for anticonvulsant activity. Since the two compounds have the 1,2,4-triazole structure, they were assumed to possess anti-inflammatory activity. Then, a third compound **5f** (7-benzyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinoline) was designed and synthesized to test if an amino group at the first position of the 1,2,4-triazole ring could give a better activity. Pharmacological tests on compounds **6**, **7**, and **5f** demonstrated that only compound **5f** showed anti-inflammatory activity. In view of the observations, we designed and synthesized a series of 7-alkyoxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-*a*]quinoline derivatives and investigated the anti-inflammatory activity and structure-activity relationship of these novel compounds.

Results and discussion

Synthesis

Compounds were prepared according to Scheme 1. The starting material 6-hydroxy-3,4-dihydro-2(1*H*)-quinolone

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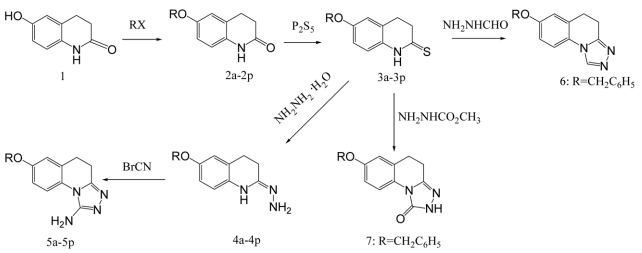
Abbreviations: Non-steroidal anti-inflammatory drugs (NSAIDs)



R:

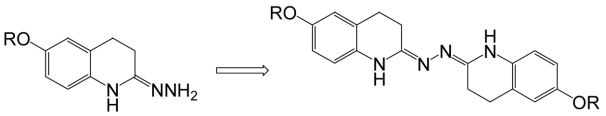
a: -C_3H_7	i: -$CH_2C_6H_4$(*p*-Cl)
b: -C_4H_9	j: -$CH_2C_6H_4$(*o*-F)
c: -C_6H_{13}	k: -$CH_2C_6H_4$(*m*-F)
d: -C_8H_{17}	l: -$CH_2C_6H_4$(*p*-F)
e: -$C_{12}H_{25}$	m: -$CH_2C_6H_4$(*p*-Br)
f: -$CH_2C_6H_5$	n: -$CH_2C_6H_4$(*p*-CH_3)
g: -$CH_2C_6H_4$(*o*-Cl)	o: -$CH_2C_6H_4$(*p*-OCH_3)
h: -$CH_2C_6H_4$(*m*-Cl)	p: -$CH_2C_6H_3$(*2,4*-Cl_2)

Scheme 1. Synthesis of compounds **5a–5p**.

reacted with an appropriate amount of alkyl halide in a solution of sodium hydroxide in absolute methanol or *n*-butanol (for **2o** only) and yielded compounds **2a-2p** [15–17]. Preparing compound **2o** (6-(4-methoxybenzyloxy)-quinoline-2-one), *n*-butanol was used as solvent instead of ethanol and KI was added as catalyst, because the strong electron-donor activity of the *p*-methoxy in the phenyl ring would increase the stability of the positive ion of carbon in the benzyl group and, hence, decrease the rate of nucleophilic substitution; still, only a moderate yield was gained for this compound.

Compounds **3a–3o** were prepared by the reaction of compounds **2a–2o** with phosphorous pentasulfide in acetonitrile in the presence of triethylamine [15]. Since compound **2p** (6-(2,4-dichlorobenzyloxy)quinoline-2-one) did not dissolve in acetonitrile, dioxane was used as solvent and compound **2p** and phosphorous pentasulfide reacted in dioxane with stirring and refluxing for 24 h, which produced **3p** (6-(2,4-dichloro-benzyloxy)-quinoline-2-thione) with a moderate yield.

Compounds **3a–3p** reacted further with hydrazine hydrate in THF to afford **4a–4p**. Briefly, to a solution of hydrazine hydrate in THF, a solution of compounds **3a–3p** in THF was added dropwise at room temperature, and the mixture was stirred at 60°C for 1 h. Then, half of the solvent was removed under reduced pressure, and the product was crystallized in petroleum ether. The precipitate was filtered and washed with petroleum ether, and then kept below 0°C. The compounds obtained were pure enough for the next step. The structures of compounds **4a–4p** may change gradually at room temperature in about 10 h, and the molecular weight indicated the disubstitution of hydrazine with compounds **3a–3p**, as



Scheme 2. Structure change of compounds **4a–4p**.

shown in Scheme 2. But this change could be avoided by keeping compounds **4a–4p** below 0°C.

The target compounds **5a–5p** were obtained by the reaction of **4a–4p** with cyanogene bromide in dioxane [18], in which an appropriate volume (about one fifth of dioxane volume) of aqueous Na_2CO_3 solution was absolutely necessary [19]. The compounds synthesized were characterized by IR, ^{1}H-NMR, MS, and elemental analysis.

Pharmacological evaluations

Phase-I evaluation (Table 1) indicated that most of the newly synthesized compounds **5c–5d** and **5f–5p** showed anti-inflammatory activity at a dose of 200 mg/kg administered orally and 2 h before the inflammatory agent xylene. Among the synthesized compounds, **5f** (7-(benzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolin-1-amine) and **5i** (7-(*p*-chlorobenzyloxy)-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinolin-1-amine) showed the highest ear-inflammation inhibition rate: 52.36% and 58.29%, respectively.

The results of the pharmacological tests were analyzed in the light of the compound structure. For alkyloxy-substituted compounds **5a–5e**, only hexyloxy-substituted compound **5c** and octyloxy-substituted compound **5d** possessed anti-inflammatory activity, suggesting that an appropriate length of the alkyl chain at position C-7, or an lipophilic properties were essential to the anti-inflammatory activity of these compounds. Among the eleven aryl-substituted derivatives **5f–5p**, the electron-donor group on the phenyl ring appeared to contribute more to the anti-inflammatory activity than the electron-acceptor group on the phenyl ring. Comparison of the halogen-substituted derivatives indicated that different halogen atoms contributed to the anti-inflammatory activity in the order of Cl>Br>F; the position of the substituted group on the phenyl ring greatly influenced the anti-inflammatory activity with an activity order of $p > o > m$. Notably, compared with the non-substituted phenyl derivative **5f**, only one derivative **5i** (7-(4-chlorine-benzyloxy-)) showed increased activity.

Based on the results of phase-I screening, two outstanding derivatives, **5f** and **5i**, were chosen to be evaluated in the phase-II screening, where the dose was still 200 mg/kg orally administered, but multiple intervals (0.5 h, 1 h, 2 h, 3 h, 4 h, and 24 h) for xylene application were

Table 1. Anti-inflammatory activity of compounds **5a–5p** administrated orally.

Compound	R	Dose (mg/kg)	Number of mice	Edema mean ± S.D. (mg)	Inhibiton Rate (%)
CMC-Na	–	–	10	12.3 ± 0.20	–
Ibuprofen	–	200	10	5.5 ± 0.19*	55.12
6	$-CH_2C_6H_5$	200	10	12.4 ± 0.34	–
7	$-CH_2C_6H_5$	200	10	12.6 ± 0.68	–
5a	*n*-C_3H_7	200	10	12.4 ± 0.15	–
5b	*n*-C_4H_9	200	10	12.4 ± 0.16	–
5c	*n*-C_6H_{13}	200	10	9.9 ± 0.19*	19.76
5d	*n*-C_8H_{17}	200	10	10.1 ± 0.30*	17.89
5e	*n*-$C_{12}H_{25}$	200	10	12.9 ± 0.24	–
5f	$-CH_2C_6H_5$	200	10	5.9 ± 0.36*	52.36
5g	$-CH_2C_6H_4$(*0*-Cl)	200	10	7.6 ± 0.24*	38.37
5h	$-CH_2C_6H_4$(*m*-Cl)	200	10	11.1 ± 0.46*	9.59
5i	$-CH_2C_6H_4$(*p*-Cl)	200	10	5.1 ± 0.27*	58.29
5j	$-CH_2C_6H_4$(*0*-F)	200	10	10.7 ± 0.35*	12.68
5k	$-CH_2C_6H_4$(*m*-F)	200	10	11.5 ± 0.21*	6.50
5l	$-CH_2C_6H_4$(*p*-F)	200	10	10 ± 0.29*	18.70
5m	$-CH_2C_6H_4$(*p*-Br)	200	10	8.8 ± 0.25*	28.70
5n	$-CH_2C_6H_4$(*p*-CH_3)	200	10	11.2 ± 0.29*	3.90
5o	$-CH_2C_6H_4$(*p*-OCH_3)	200	10	10.6 ± 0.28*	13.74
5p	$-CH_2C_6H_4$(*2,4*-Cl_2)	200	10	10.7 ± 0.18*	12.68

* $p < 0.01$ compared with theCMC-Na (control) group.

Table 2. Anti-inflammatory activity of compounds **5f** and **5i** administered at different times before the xylene application.

Time (h)	Dose (mg/kg)	Inhibition (%)		
		5f	5i	Ibuprofen
0.5	200	42.76[b)]	31.30	33.82
1	200	46.82	33.50[b)]	42.60
2	200	52.36[a)]	58.29	55.12
3	200	28.46[b)]	34.55	35.61
4	200	26.91[a)]	33.25	31.30
24	200	23.09	22.52	21.87

a) $p < 0.05$.
b) $p < 0.01$ compared with ibuprofen at the corresponding time.

assessed. The results are shown in Table 2. As the interval lengthened, the anti-inflammatory activity of compounds **5f** and **5i** first increased and then declined; the peak activity was observed at the 2 h interval. Comparing **5f** and **5i**, compound **5f** showed stronger activity than compound **5i** at all time points except the 2 h-point. Compared with the reference drug ibuprofen, compound **5f** showed a significantly higher activity at 0.5 h after administration but comparable (1 h, 24 h) or lower (2–4 h) activity at other time points, indicating its quick absorption and potential for acute anti-inflammatory action. Compound **5i** showed similar activity level as the reference drug at all time points except at 1 h time point, when it had lower activity than ibuprofen.

Table 3. Anti-inflammatory activity of compounds **5f** and **5i** at different doses.

Time (h)	Dose (mg/kg)	Inhibition (%)		
		5f	5i	Ibuprofen
2	200	52.36[a)]	58.29	55.12
2	100	33.33	49.51[b)]	33.41
2	50	22.03	24.63	25.12

a) $p < 0.05$.
b) $p < 0.01$ compared with ibuprofen at the corresponding dose.

In the phase-III testing, the ear-inflammation inhibition rate of compounds **5f**, **5i**, and the reference drug ibuprofen (at lower doses 100 mg/kg and 50 mg/kg and administered 2 h before xylene application) were evaluated and compared (Table 3). Compound **5f** showed similar effects as ibuprofen at the two lower doses, while compound **5i** possessed stronger anti-inflammatory activity than ibuprofen at 100 mg/kg.

Conclusions

A new series of anti-inflammatory compounds, 7-alkoxy-1-amino-4,5-dihydro[1,2,4]-triazole[4,3-*a*]quinolines, were synthesized and their anti-inflammatory activity was evaluated by an *in-vivo* test. Two of the compounds, **5f** and **5i**, exhibited anti-inflammatory activity comparable with the reference drug ibuprofen.

This study is supported by a grant from National Natural Science Foundation of China (No. 30460151) and a grant from the Key Projects Fund of Ministry of Education of China (No. 20070422029).

The authors have declared no conflict of interest

Experimental

Chemistry

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FT-IR1730. ^{1}H-NMR spectra were measured on a Bruker-300 (Bruker Bioscience, Billerica, MA, USA) and all chemical shifts were given in ppm relative to tetramethylsilane. Mass spectra were measured on an HP1100LC (Hewlett-Packard, Palo Alto, CA, USA). Microanalyses of C, N and H were performed using a Heraeus CHN Rapid Analyzer (Heraeus, Germany).

*6-Alkoxy-3,4-dihydro-2(1H)-quinolones **2a – 2p***

The starting compound **1** (10 mmol) and appropriate alkyl halide (10 mmol) were added to a solution of sodium hydroxide in absolute methanol with stirring and refluxing for 3 h. The reaction mixture was cooled and then poured into ice water. The white precipitate was collected through filtration and dried in a vacuum to produce the crude products **2a – 2n** and **2p** with a moderate yield and sufficient purity for the next stage. The starting compound **1** (10 mmol), *p*-methoxybenzyl chloride (10 mmol) and KI (5 mmol) were added to a solution of sodium hydroxide in absolute *n*-butanol with stirring and refluxing for 6 h. Next, the solvent was evaporated under reduced pressure; the residue was washed with water to produce a white solid **2o** with a moderate yield.

*6-Alkoxy-3,4-dihydro-1H-quinoline-2-thiones **3a – 3p***

To a stirring mixture of acetonitrile and triethylamine in a three-necked round-bottomed flask in an ice bath, P_2S_5 (1.2 eq), divided into multiple portions, was added one portion at a time after the previous portion had completely dissolved. Then, 6-alkoxy-3,4-dihydro-2(1*H*)-quinolone was added and the solution was refluxed for 3 h under nitrogen. After removing the solvent under reduced pressure, the residue was dissolved in dichloromethane (30 mL), washed with water (3 × 30 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvents gave a crude product, which was purified by silica gel column chromatography with dichloromethane to a light yellow solid **3a – 3o**. Compound **2p** and phosphorous pentasulfide reacted in dioxane with stirring and refluxing for 24 h. The solvent was evaporated under reduced pressure; the residue was washed with water to produce a light yellow solid **3p**.

*6-Alkoxy-3,4-dihydro-2-hydrazine-1H-quinolines **4a – 4p***

A solution of compounds **3a – 3p** (5 mmol) in 30 mL THF was added dropwise to a solution of hydrazine hydrate (25 mmol) in 20 mL THF at room temperature, then the mixture was stirred and heated at 60°C for 1 h. After the reaction, half of the solvent was evaporated under reduced pressure; the products were recrystallized from petroleum ether with a moderate yield, and then kept at 0°C for the next step.

*General procedure for the synthesis of 7-alkoxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinolines **5a – 5p***

In a three-neck round-bottomed flask with thermometer, compounds **4a – 4p** (3 mmol) were dissolved in 60 mL dioxane, and the solution was treated with Na_2CO_3 (3 mmol) in 12 mL H_2O. Then, cyanogene bromide (3 mmol) in 20 mL dioxane was added dropwise to the mixture kept in an ice-bath and then the reaction temperature was kept below 10°C; after stirring for 2 h, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane-methanol 10 : 1).

*7-Propyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline **5a***

Mp. 161 – 163°C; yield 32%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.04 (t, 3H, *J* = 7.4 Hz, -CH_3), 1.76 – 1.85 (m, 2H, -CH_2-), 3.92 (t, 2H, *J* = 6.5 Hz, -OCH_2-), 2.93 – 3.03 (m, 4H, -CH_2-CH_2-), 4.78 (s, 2H, -NH_2), 6.84 – 6.87 (m, 2H, H-6, H-9), 7.64 – 7.68 (m, 1H, H-8). IR (KBr) cm^{-1}: 3410 and 3093 (-NH_2), 1502 (-OCH_2-); MS m/z 245 [M + 1]; Anal. Calcd. for $C_{13}H_{16}N_4O$: C, 63.91; H, 6.60; N, 22.93. Found: C, 63.95; H, 6.67; N, 22.85.

*7-Butyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline **5b***

Mp. 121 – 123°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, *J* = 7.1 Hz, -CH_3), 1.43 – 1.55 (m, 2H, -CH_2-), 1.72 – 1.81 (m, 2H, -CH_2-), 3.94 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.95 – 3.01 (m, 4H, -CH_2-CH_2-), 5.30 (s, 2H, -NH_2), 6.85 – 6.88 (m, 2H, H-6, H-9), 7.69 – 7.71 (m, 1H, H-8). IR (KBr) cm^{-1}: 3340 and 3122 (-NH_2), 1512 (-OCH_2-); MS m/z 259 [M + 1]; Anal. Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 65.12; H, 7.08; N, 21.59.

*7-Hexyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline **5c***

Mp. 86 – 88°C; yield 33%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 7.1 Hz, -CH_3), 1.26 – 1.82 (m, 8H, (-CH_2-)$_4$), 3.96 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.94-3.03 (m, 4H, -CH_2-CH_2-), 4.45 (s, 2H, -NH_2), 6.85 – 6.89 (m, 2H, H-6, H-9), 7.64 – 7.67 (m, 1H, H-8). IR (KBr) cm^{-1}: 3336 and 3119 (-NH_2), 1508 (-OCH_2-); MS m/z 287 [M + 1]; Anal. Calcd. for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.15; H, 7.78; N, 19.50.

*7-Octyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline **5d***

Mp. 109 – 111°C; yield 37%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, *J* = 7.2 Hz, -CH_3), 1.26 – 1.84 (m, 12H, (-CH_2-)$_6$), 3.96 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.94 – 3.02 (m, 4H, -CH_2-CH_2-), 4.67 (s, 2H, -NH_2), 6.85 – 6.88 (m, 2H, H-6, H-9), 7.64 – 7.67 (m, 1H, H-8). IR (KBr) cm^{-1}: 3345 and 3105 (-NH_2), 1515 (-OCH_2-); MS m/z 315 [M + 1]; Anal. Calcd. for $C_{18}H_{26}N_4O$: C, 68.76; H, 8.33; N, 17.82. Found: C, 68.82; H,8.37; N, 17.76.

*7-Dodecyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline **5e***

Mp. 114 – 116°C; yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, *J* = 7.4 Hz, -CH_3), 1.27 – 1.82 (m, 20H, (-CH_2-)$_{10}$), 3.97 (t, 2H, *J* = 6.4 Hz, -OCH_2-), 2.94 – 3.03 (m, 4H, -CH_2-CH_2-), 4.48 (s, 2H, -NH_2), 6.85 – 6.88 (m, 2H, H-6, H-9), 7.64 – 7.67 (m, 1H, H-8). IR (KBr) cm^{-1}: 3350 and 3086 (-NH_2), 1523 (-OCH_2-); MS m/z 371 [M + 1]; Anal.

Calcd. for $C_{22}H_{34}N_4O$: C, 71.31; H, 9.25; N, 15.12. Found: C, 71.35; H,9.28; N, 15.04.

7-Benzyloxy-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5f***

Mp. 156–158°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.00–3.06 (m, 4H, -CH_2-CH_2-), 4.42 (s, 2H, -NH_2), 5.10 (s, 2H, -OCH_2-), 6.93–6.99 (m, 2H, H-6, H-9), 7.36–7.44 (m, 5H, Ar-H), 7.66–7.69 (m, 1H, H-8). IR (KBr) cm^{-1}: 3340 and 3126 (-NH_2), 1511 (-OCH_2-); MS m/z 293 [M + 1]; Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17. Found: C, 69.90; H, 5.56; N, 19.10.

7-(2-Chlorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5g***

Mp. 168–170°C; yield 29%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.96–3.04 (m, 4H, -CH_2-CH_2-), 4.51 (s, 2H, -NH_2), 5.19 (s, 2H, -OCH_2-), 6.95–7.00 (m, 2H, H-6, H-9), 7.30–7.54 (m, 4H, Ar-H), 7.68–7.71 (m, 1H, H-8). IR (KBr) cm^{-1}: 3349 and 3108 (-NH_2), 1521 (-OCH_2-); MS m/z 327 [M + 1], 329 [M + 3]; Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.50; H, 4.68; N, 17.11.

7-(3-Chlorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5h***

Mp. 162–164°C; yield 33%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94–3.02 (m, 4H, -CH_2-CH_2-), 4.71 (s, 2H, -NH_2), 5.05 (s, 2H, -OCH_2-), 6.90–6.95 (m, 2H, H-6, H-9), 7.27–7.44 (m, 4H, Ar-H), 7.67–7.70 (m, 1H, H-8). IR (KBr) cm^{-1}: 3280 and 3103 (-NH_2), 1662 (-OCH_2-); MS m/z 327 [M + 1], 329 [M + 3]; Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.49; H, 4.70; N, 17.10.

7-(4-Chlorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5i***

Mp. 166–168°C; yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94–3.04 (m, 4H, -CH_2-CH_2-), 4.60 (s, 2H, -NH_2), 5.06 (s, 2H, -OCH_2-), 6.90–6.96 (m, 2H, H-6, H-9), 7.35–7.38 (m, 4H, Ar-H), 7.66–7.69 (m, 1H, H-8). IR (KBr) cm^{-1}: 3339 and 3124 (-NH_2), 1516 (-OCH_2-); MS m/z 327 [M + 1], 329 [M + 3]; Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.52; H, 4.72; N, 17.13.

7-(2-Fluorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5j***

Mp. 148–150°C; yield 37%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.89–3.03 (m, 4H, -CH_2-CH_2-), 4.79 (s, 2H, -NH_2), 5.14 (s, 2H, -OCH_2-), 6.93–6.97 (m, 2H, H-6, H-9), 7.07–7.51 (m, 4H, Ar-H), 7.67–7.70 (m, 1H, H-8). IR (KBr) cm^{-1}: 3336 and 3089 (-NH_2), 1512 (-OCH_2-); MS m/z 312 [M + 1]; Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.88; H, 4.90; N, 17.99.

7-(3-Fluorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5k***

Mp. 158–160°C; yield 34%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.87–3.01 (m, 4H, -CH_2-CH_2-), 4.87 (s, 2H, -NH_2), 5.18 (s, 2H, -OCH_2-), 6.76–6.79 (m, 2H, H-6, H-9), 7.04–7.37 (m, 4H, Ar-H), 7.72–7.75 (m, 1H, H-8). IR (KBr) cm^{-1}: 3305 and 3120 (-NH_2), 1504 (-OCH_2-); MS m/z 312 [M + 1]; Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.89; H, 4.92; N, 17.96.

7-(4-Fluorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5l***

Mp. 160–162°C; yield 38%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.95–3.03 (m, 4H, -CH_2-CH_2-), 4.72 (s, 2H, -NH_2), 5.04 (s, 2H, -OCH_2-), 6.91–6.96 (m, 2H, H-6, H-9), 7.06–7.43 (m, 4H, Ar-H), 7.67–7.70 (m, 1H, H-8). IR (KBr) cm^{-1}: 3335 and 3098(-NH_2), 1518 (-OCH_2-); MS m/z 312 [M + 1]; Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.80; H, 4.87; N, 18.05. Found: C, 65.86; H, 4.92; N, 17.99.

7-(4-Brominebenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5m***

Mp. 160–162°C; yield 31%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.94–3.04 (m, 4H, -CH_2-CH_2-), 4.65 (s, 2H, -NH_2), 5.04 (s, 2H, -OCH_2-), 6.89–6.95 (m, 2H, H-6, H-9), 7.29–7.54 (m, 4H, Ar-H), 7.65–7.68 (m, 1H, H-8). IR (KBr) cm^{-1}: 3340 and 3105 (-NH_2), 1524 (-OCH_2-); MS m/z 371 [M + 1]; Anal. Calcd. for $C_{17}H_{15}BrN_4O$: C, 55.00; H, 4.07; N, 15.09. Found: C, 55.03; H, 4.11; N, 15.03.

7-(4-Methylbenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5n***

Mp. 118–120°C; yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.93–3.03 (m, 4H, -CH_2-CH_2-), 3.75 (s, 3H, -CH_3), 4.80 (s, 2H, -NH_2), 5.04 (s, 2H, -OCH_2-), 6.91–6.96 (m, 2H, H-6, H-9), 7.20–7.33 (m, 4H, Ar-H), 7.64–7.66 (m, 1H, H-8). IR (KBr) cm^{-1}: 3313 and 3136 (-NH_2), 1502 (-OCH_2-); MS m/z 307 [M + 1]; Anal. Calcd. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.63; H, 5.98; N, 18.23.

7-(4-Methoxybenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5o***

Mp. 115–117°C; yield 40%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.95–3.02 (m, 4H, -CH_2-CH_2-), 3.83 (s, 3H, -OCH_3), 4.82 (s, 2H, -NH_2), 5.01 (s, 2H, -OCH_2-), 6.92–6.96 (m, 2H, H-6, H-9), 7.34–7.66 (m, 4H, Ar-H), 7.90–7.94 (m, 1H, H-8). IR (KBr) cm^{-1}: 3329 and 3118 (-NH_2), 1508 (-OCH_2-); MS m/z 323 [M + 1]; Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.11; H, 5.69; N, 17.30.

7-(2,4-Dichlorobenzyloxy)-1-amino-4,5-dihydro[1,2,4]triazole[4,3-a]quinoline ***5p***

Mp. 154–156 C; yield 35%; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.96–3.04 (m, 4H, -CH_2-CH_2-), 4.59 (s, 2H, -NH_2), 5.14 (s, 2H, -OCH_2-), 6.93–6.98 (m, 2H, H-6, H-9), 7.28–7.50 (m, 4H, Ar-H), 7.68–7.71 (m, 1H, H-8). IR (KBr) cm^{-1}: 3309 and 3107 (-NH_2), 1500 (-OCH_2-); MS m/z 361 [M + 1], 363 [M + 3], 365 [M + 5]; Anal. Calcd. for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.91; N, 15.51. Found: C, 56.56; H, 3,94; N, 15.41.

Pharmacology

The anti-inflammatory activity was evaluated by an *in-vivo* inhibition assay monitoring xylene-induced ear edema [19]. All tested compounds were homogenized with 0.5% sodium carboxymethylcellulose (CMC-Na) and administered orally to Kunming mice (20-25 g body weight, 10 animals per group). Control mice received the vehicle only (0.5% sodium carboxymethylcellulose, 0.2 mL/10 g). At a specified later time, 20 μL xylene was applied to the surface of the right ear of each mouse by a micropipette. Mice were sacrificed 30 min later and a cylindrical plug (7 mm diameter) was excised from each of the treated and untreated ears. Edema was quantified by the difference in weight between the two plugs. The anti-inflammatory activity was expressed as percent edema reduction as compared to the CMC-Na adminis-

tered control group. The NSAID drug ibuprofen was tested in parallel as an activity reference. Edema values, expressed as mean ± standard deviation, were compared statistically using Student's t-test. A level of $p < 0.05$ was adopted as the test of significance.

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