European Journal of Medicinal Chemistry 73 (2014) 217–224

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and evaluation of the antidepressant and anticonvulsant activities of triazole-containing quinolinones

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ARTICLE INFO

Article history:
Received 12 July 2013
Received in revised form
11 December 2013
Accepted 12 December 2013
Available online 25 December 2013

Keywords:
Antidepressant
Anticonvulsant
Quinolinone
Triazole
Forced swimming test
Maximal electroshock seizure

ABSTRACT

A series of 1-substituted-6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1*H*)-ones were designed, synthesized, and screened for their antidepressant and anticonvulsant activities. Interestingly, compounds **5i**, **5j**, **5m**, and **5n** led to significant reductions in the immobility time in the forced swimming test at a dose of 50 mg/kg, and exhibited higher levels of efficacy than the reference standard fluoxetine. In addition, compound **5i** exhibited greater efficacy than fluoxetine in the tail suspension test. The results of an open field test further confirmed that compound **5i** provided a good antidepressant effect. In the maximal electroshock seizure screen, compounds **5c** and **5d** showed moderate levels of anticonvulsant activity and protected 100% of the animals at a dose of 100 mg/kg. None of the synthesized compounds showed any neurotoxicity in the rotarod test at a dose of 100 mg/kg.

1. Introduction

Depression and epilepsy are two of the most commonly encountered neurological disorders [1,2], and several reports have recently appeared in the literature concerning the connection between these two disorders [3–6]. It is now effectively well recognized that depression is common among people suffering with epilepsy, and in a community-based study of people with epilepsy, the rate of depression was found to be 37% [7]. In patients typically referred to epilepsy centers (representing a group of people with seizures that are particularly refractory to medication), the rate of depression was found to be 50 percent (Fig. 1) [7]. A large number of patients with epilepsy require some form of antidepressant medication, and this has recently led many experts in the field to question whether the prescribing of antidepressants to this special group could exacerbate the occurrence of seizures. Ojemann et al. [8] performed a retrospective study of the use of the tricyclic antidepressant doxepin in epilepsy patients, and found that whilst the depressive symptoms of the patients had been reduced by 89%, the frequency of their seizures had increased by 79%. These results therefore suggested the existence of a negative relationship between these two effects. In contrast, favale et al. [9] used fluoxetine (20 mg/day) to treat 17 epilepsy patients with symptoms of depression, and reported the complete remission of seizures in six patients. Furthermore, the other patients also experienced a 30% reduction in the frequency of their seizures. The two antidepressants described in these cases clearly have different effects (i.e., positive and negative) on patients with epilepsy. Research on antidepressants for the treatment of depressive symptoms in patients with epilepsy is currently an area of considerable activity, and the search for novel and increasingly effective drugs with anticonvulsant and antidepressant activities (the same type as fluoxetine) represent an important and challenging area of medicinal chemistry.

There is a growing body of evidence in the literature that suggests that quinolinone derivatives possess a broad range of biologically interesting properties, including anticonvulsant [10–12], anti-cancer [13,14], antifungal and anti-inflammatory [15], antibacterial [16,17], and antidepressant activities [18–20]. Earlier studies by Oshiro et al. [21] have demonstrated that 3,4-dihydro-2(1*H*)-quinolinones (Fig. 2, **I**) have promising antidepressant activities [21]. Several studies in this area have recently confirmed

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0223-5234/$ – see front matter © 2013 Published by Elsevier Masson SAS.
http://dx.doi.org/10.1016/j.ejmech.2013.12.014

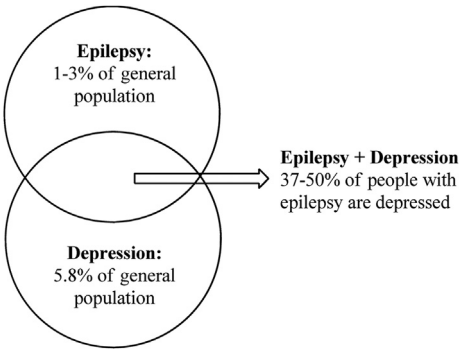


Fig. 1. Epilepsy and depression: estimates of their occurrence.

the antidepressant properties of aripiprazole, which is a 3,4-dihydro-2(1*H*)-quinolinone-containing compound (Fig. 2) that was initially marketed as an antipsychotic agent [22–27]. Triazole is the core structural motif in a variety of different compounds in medicinal chemistry and has been reported to exhibit a broad range of biological properties, including antimicrobial [28,29], enzyme inhibition [30,31], antinociceptive [32], anti-inflammatory [33], antidepressant [34,35], and anticonvulsant activities [36,37]. Our previous work towards the synthesis and evaluation of a series of triazole-containing compounds showed that the addition of a triazole ring to other heterocycles effectively strengthened their anticonvulsant activities (Fig. 2, **II** and **III**) [38–41]. Based on these results, we recently embarked on a program to combine the antidepressant and anticonvulsant activities of 3,4-dihydro-2(1*H*)-quinolinone and triazole through the preparation of a hybrid molecule composed on the two individual units (Fig. 2). Herein, we describe our most recent work towards the design, synthesis, and evaluated of 19 new triazole-containing quinolinones (**5a**–**5s**) for their antidepressant and anticonvulsant activities.

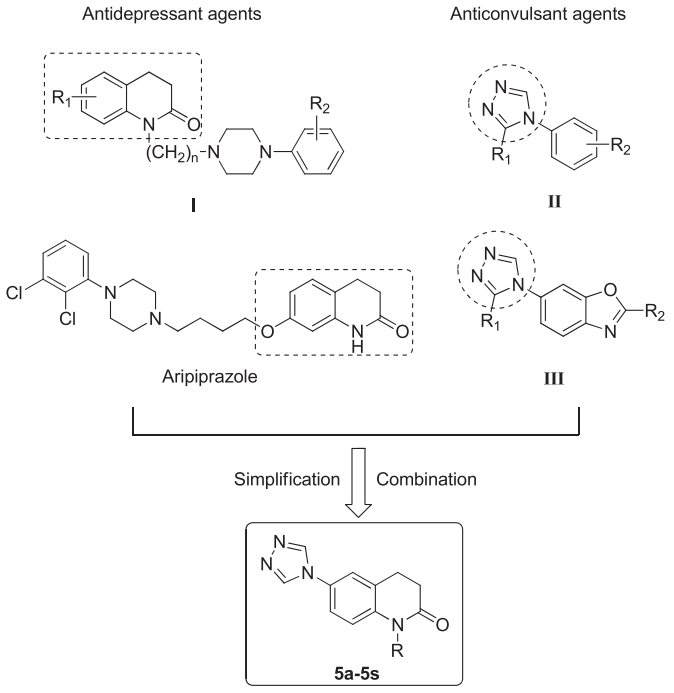


Fig. 2. Design of compounds **5a**–**5s**.

2. Chemistry

All of the target compounds were synthesized according to the route depicted in Scheme 1. Compound **3** was synthesized via the sequential nitration and catalytic hydrogenation of the commercially available 3,4-dihydro-2(1*H*)-quinolinone according to methods previously described in the literature [42]. Compound **3** was then treated with dimethoxy-*N*,*N*-dimethylmethanamine (DMF-DMA) and formylhydrazine in acetonitrile to provide compound **4** [43]. The subsequent alkylation of compound **4** with a variety of different alkylating agents gave the target compounds (**5a**–**s**). The chemical structures of these compounds were characterized by IR, ^{1}H and ^{13}C NMR, and mass spectroscopy. The physical and analytical data are listed in Section 6.

3. Pharmacology

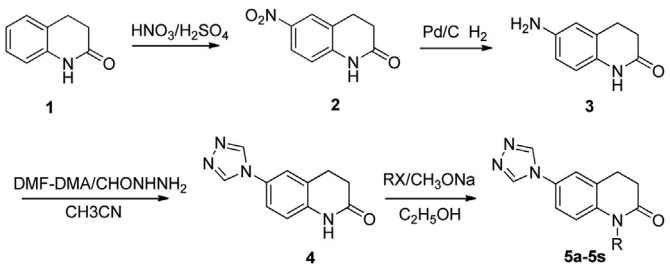
All of the compounds synthesized in the current study were screened for their antidepressant activities using Porsolt's behavioral despair (forced swimming) test [44]. The anticonvulsant activities and neurotoxicities of the compounds were also evaluated. We followed the protocols issued for the phase I tests by the Epilepsy Branch of the Antiepileptic Drug Development (ADD) program at the National Institutes of Health [45,46] with two exceptions. We used a different strain of mice and seizures were elicited in mice with ear stimulation. Compound **5i** was also evaluated using the tail suspension test (TST) [47,48] and the open field test [49] to further confirm its antidepressant activity.

All of the compounds tested in the pharmacology experiments were dissolved in dimethylsulfoxide and administrated intraperitoneally (i.p.) to KunMing mice (22 ± 2 g). The mice were housed collectively in polycarbonate cages in groups of ten, where they were maintained on a 12 h light/dark cycle in a temperature controlled (25 ± 2 °C) laboratory with free access to food and water. Each animal was used only once. All efforts were made to minimize both the suffering of the animals and the number of animals used in the experiments.

4. Results and discussion

4.1. Antidepressant activities

The antidepressant activities of the compounds were investigated in mice using the forced swimming test (FST). The FST was designed by Porsolt et al. [44] as a primary screening test for antidepressants and remains one of the best models of depression because it provides a low-cost, fast and reliable platform for testing potential antidepressants with a strong predictive validity. This animal model is therefore still one of the most widely used tools for the preclinical screening of putative antidepressant agents [50–53]. In the FST, the mice are forced to swim under inescapable conditions, and consequently adopt an immobility behavior



Scheme 1. The synthesis route of compounds **5a**–**5s**.

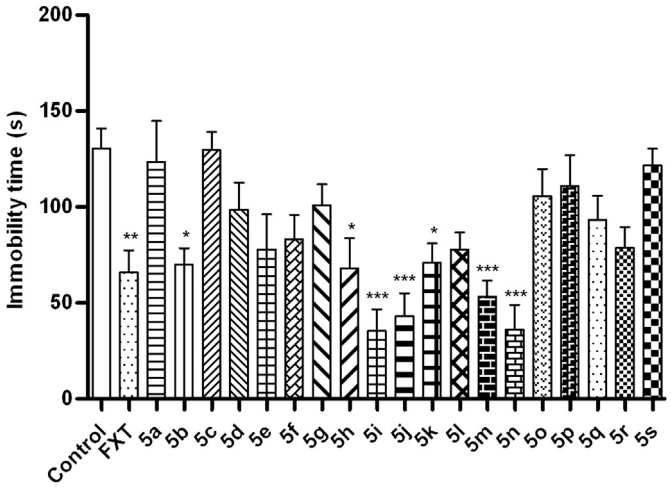


Fig. 3. Effects of treatment of mice with **5a**–**5s** (50 mg/kg) and fluoxetine (FXT, 50 mg/kg) given intraperitoneally (i.p.) on the immobility time in the forced swim test (FST). Results are represented as mean ± SEM with $n = 8$ in each group. Values are significant at $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

following an initial period of agitation/flurry. In this established behavioral model, the ability of a compound to reduce the duration of the immobility behavior is taken as a measure of its antidepressant activity. The antidepressant activities of compounds **5a**–**s** and the reference drug fluoxetine at a dose of 50 mg/kg (i.p.) are shown in Fig. 3. The results of the FST revealed that some of the compounds (including **5b**, **5h**, **5i**, **5j**, **5k**, **5m** and **5n**) displayed potent antidepressant activities. Compounds **5i**, **5j**, **5m**, and **5n** in particular led to significant reductions in the duration of the immobility time compared with the control group with $P < 0.001$. Fluoxetine, which is a selective serotonin reuptake inhibitor, was

Table 1
Antidepressant activities of the compounds **5a**–**5s** in FST.

Compounds	R	Antidepressant activities[a]	
		Duration of immobility (s)[b]	% DID[c]
5a	$-C_3H_7$	123.6 ± 21.13	5.3
5b	$-C_4H_9$	70.0 ± 8.65*	46.4
5c	$-C_5H_{11}$	129.8 ± 9.56	0.5
5d	$-C_6H_{13}$	98.5 ± 14.19	24.5
5e	$-C_7H_{15}$	77.9 ± 18.26	40.3
5f	$-C_8H_{17}$	83.3 ± 12.69	35.8
5g	$-C_{10}H_{21}$	101.0 ± 10.92	22.6
5h	$-CH_2C_6H_5$	68.1 ± 15.85*	47.8
5i	$-CH_2C_6H_4$(*o*-F)	35.6 ± 11.05***	72.7
5j	$-CH_2C_6H_4$(*m*-F)	43.0 ± 12.16***	67.0
5k	$-CH_2C_6H_4$(*p*-F)	71.1 ± 9.90*	45.5
5l	$-CH_2C_6H_4$(*o*-Cl)	77.8 ± 9.02	40.4
5m	$-CH_2C_6H_4$(*m*-Cl)	53.4 ± 8.31***	59.1
5n	$-CH_2C_6H_4$(*p*-Cl)	36.1 ± 12.93***	72.3
5o	$-CH_2C_6H_3$(2,4-2Cl)	105.8 ± 13.93	18.9
5p	$-CH_2C_6H_3$(2,6-2Cl)	111.0 ± 16.04	15.7
5q	$-CH_2C_6H_4$(*m*-CF_3)	93.3 ± 12.74	37.2
5r	$-CH_2C_6H_4$(*p*-CH_3)	78.8 ± 10.61	39.6
5s	$-CH_2C_6H_4$(*p*-OCH_3)	121.6 ± 8.81	6.8
Fluoxetine		65.9 ± 11.77**	49.5
Control		130.5 ± 10.34	–

$^{*}p < 0.05$ as compared to control, $^{**}p < 0.01$ as compared to control, $^{***}p < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

[a] Compounds prepared were administered intraperitoneally at 50 mg/kg, Fluoxetine was administered at 50 mg/kg.

[b] Represent the mean ± SEM. ($n = 8$).

[c] %DID: percentage decrease in immobility duration.

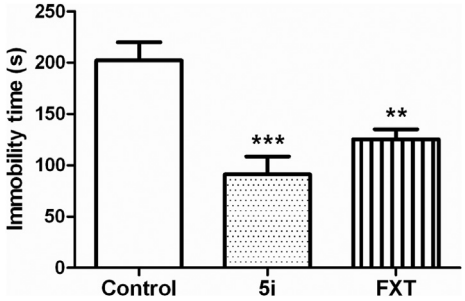


Fig. 4. Effect of treatment of mice with **5i** (at dose of 50 mg/kg) and fluoxetine (FXT, 50 mg/kg) given intraperitoneally (i.p.) on the immobility time in the tail suspension test. Results are represented as mean ± SEM with $n = 8$ in each group. Values are significant at $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

used as the reference drug, and also caused a significant reduction in the immobility time with $P < 0.01$. For a more detailed and comprehensive understanding of the antidepressant activities of the test compounds and fluoxetine, their values for the percentage decrease in the immobility duration (% DID) were calculated using the following formula:

$$\%\mathrm{DID} = [(\mathrm{A} - \mathrm{B})/\mathrm{A}] * 100$$

where A is the duration of immobility (s) in the control group and B is the duration of immobility (s) in the test group.

As shown in Table 1, the majority of the synthesized compounds reduced the duration of immobility and gave high % DID values, although statistical significance values were not obtained for these results. Compounds **5i**, **5j**, **5m**, and **5n** exhibited higher % DID values (in the range of 59.1–72.7) than that of fluoxetine (% DID = 49.5), and appeared to be provide higher levels of antidepressant activity compared with fluoxetine.

Compound **5i** that was found most potent in the FST, and was further evaluated in a TST to effectively confirm its antidepressant activity. The TST is a behavioral despair test that is commonly used to predict the activities of antidepressant agents. In the current study, compound **5i** showed a good activity profile at a dose of 50 mg/kg compared with the standard drug fluoxetine. The results of this test are shown in Fig. 4.

Having confirmed the antidepressant activity of compound **5i**, we proceeded to conduct a dose-dependent study of this compound as doses of 10, 25, and 50 mg/kg using the FST. As shown in Fig. 5, compound **5i** produced an antidepressant effect in a dose-

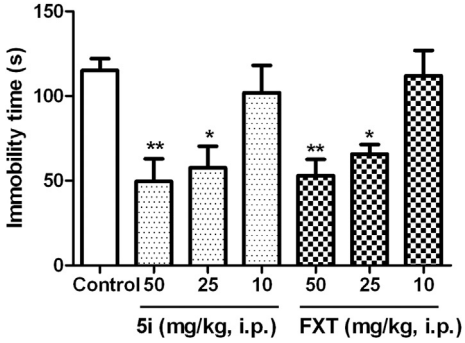


Fig. 5. Effect of treatment of mice with **5i** given intraperitoneally (i.p.) at graded doses on the immobility time in the forced swim test (FST). Results are represented as mean ± SEM with $n = 8$ in each group. Values are significant at $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

dependent manner. Compound **5i** led to a significant reduction in the immobility time in the FST when it was administered at doses of 50 and 25 mg/kg, whereas no significant changes were observed following the administration of a dose of 10 mg/kg.

To determine whether the observed changes in the immobility were associated with changes in the motor activity, compound **5i** was also evaluated for its effect on the locomotor activities of mice using the open-field test, which is a classical animal test used to evaluate the autonomic effects of drugs and the general activities of animals [49]. The results revealed that compound **5i** did not have a significant impact on motor activities (i.e., crossing, rearing, or grooming) in mice (Fig. 6). The results of this study suggested that the antidepressant activity of **5i** observed in the FST did not result from any CNS stimulant properties.

4.2. Anticonvulsant activity

The anticonvulsant activities of the synthesized compounds were also evaluated using the maximal electroshock seizure (MES) test. Compounds **5a**–**s** were administrated intraperitoneally to the mice using doses of 30, 100 and 300 mg/kg, and the observations were taken at time intervals of 0.5 and 4 h. The results are shown in Table 2.

Compounds **5c** and **5d** were found to be the most potent compounds and provided 100% protection at a dose of 100 mg/kg following 0.5 h. Compound **5d** was also active following 4 h, albeit at the higher dose of 300 mg/kg. Compounds **5e**, **5f**, **5o**, and **5q** were also found to be active at a dose of 300 mg/kg in the MES screen. Furthermore, compounds **5f**, **5o** and **5q** also continued to provide protection from seizures following 4 h, indicating that they all have a long duration of anticonvulsant activity. Compound **5i** and compounds **5l**–**m** gave protection against the seizures following 4 h.

4.3. Neurotoxicity

The neurotoxicities of the compounds synthesized in the current study were determined using the minimal motor impairment-rotorod screen. As shown in Table 2, compounds **5g**–**s** did not show any neurotoxic effects at the maximum dose administered (300 mg/kg) following 0.5 and 4 h. The rest of the compounds (**5a**–**e**) did display neurotoxic activities at a dose of 300 mg/kg following 0.5 and 4 h. Pleasingly, however, none of the compounds exhibited neurotoxic activity at the dose (50 mg/kg) used in the FST or TST.

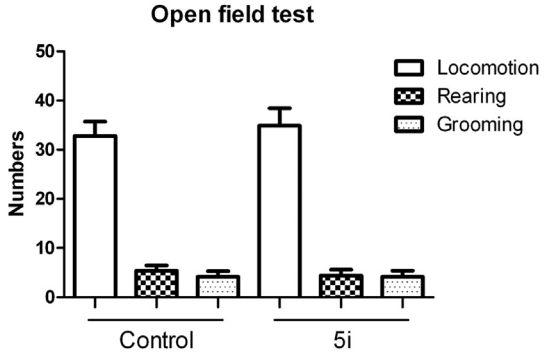
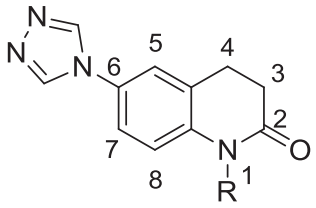


Fig. 6. Effects of treatment of mice with **5i** (50 mg/kg) on the behavioral parameters (locomotion, rearing and grooming) evaluated in the open-field test. Locomotion: number of line crossings; rearing: number of times seen standing on hind legs; grooming: number of modifications. Each column represents means ± SEM. $^{*}P < 0.05$ as compared to control (all comparisons were made by ANOVA followed by bonferroni's test).

Table 2
Preliminary anticonvulsant activity and neurotoxocity of compounds **5a**–**5s** administered intraperitoneally (i.p.) to mice.



Compds.	R	MES[a]		Neurotoxicity	
		0.5 h	4 h	0.5 h	4 h
5a	$-C_3H_7$	–	–	–	300
5b	n-C_4H_9	–	–	–	300
5c	n-C_5H_{11}	100	–	300	300
5d	n-C_6H_{13}	100	300	300	300
5e	n-C_7H_{15}	300	–	300	300
5f	n-C_8H_{17}	300	300	–	300
5g	n-$C_{10}H_{21}$	–	–	–	–
5h	$-CH_2C_6H_5$	–	–	–	–
5i	$-CH_2C_6H_4$(o-F)	–	300	–	–
5j	$-CH_2C_6H_4$(m-F)	–	–	–	–
5k	$-CH_2C_6H_4$(p-F)	–	300	–	–
5l	$-CH_2C_6H_4$(o-Cl)	–	300	–	–
5m	$-CH_2C_6H_4$(m-Cl)	–	300	–	–
5n	$-CH_2C_6H_4$(p-Cl)	–	–	–	–
5o	$-CH_2C_6H_3$(2,4-2Cl)	300	300	–	–
5p	$-CH_2C_6H_3$(2,6-2Cl)	–	–	–	–
5q	$-CH_2C_6H_4$(m-CF_3)	300	300	–	–
5r	$-CH_2C_6H_4$(p-CH_3)	–	–	–	–
5s	$-CH_2C_6H_4$(p-OCH_3)	–	–	–	–
Valproate	–	300	–	–	–
Phenytoin	–	30	100	100	100

[a] 30,100, and 300 mg/kg of doses were administered (i.p.). The figures in the table indicate the minimal dose whereby bioactivity was demonstrated in half or more of the mice. The animals were examined at 0.5 h and 4.0 h after injection. A dash indicates an absence of activity or toxicity at maximum dose administered (300 mg/kg).

In the current study, a series of triazole-containing quinolinones have been designed, synthesized and tested for their antidepressant and anticonvulsant activities. Consideration of the biological activities of the synthesized compounds revealed the following structure–activity relationships (SARs). Compounds **5a**–**5g** contained different alkyl groups attached to the core quinolinone fragment, ranging from a propyl group to a decyl group. Although the length of the alkyl chain on these derivatives did not have a discernible impact on their antidepressant activities, the chain length did appear to have an impact on their anticonvulsant activities. Compounds **5c** and **5d** (bearing an n-pentyl and a hexyl chain, respectively) showed the greatest anticonvulsant activities, indicating that these compounds possessed the optimum level of lipophilicity for the congeners to act on the central nervous system. Compound **5h** was substituted with a benzyl group at the 1-position of the quinolinone core and the subsequent addition of F, Cl, CF_3, CH_3 and OCH_3 groups to different positions of the phenyl ring of the benzyl group of **5h** provided compounds **5i**–**5s**. Pleasingly, the introduction of an F atom (**5i** and **5j**) or a Cl atom (**5m** and **5n**) to the phenyl ring led to an increase in the antidepressant activity compared with **5h**. In contrast, the introduction of two Cl atoms to give compounds **5o** and **5p** resulted in no antidepressant activity in the FST.

The antidepressant activity of the target compounds was desirable, while their anticonvulsant activities kept a certain distance from being satisfactory. Compared with compounds **II** or **III** prepared formerly, the anticonvulsant activities of **5a**–**5s** decreased

significantly. The biggest structural difference among them was the piperidone ring. Therefore, further modifications will be focused on the piperidone part with the aim of increasing the anticonvulsant activity.

5. Conclusion

In conclusion, a series of novel triazole-containing quinolinones has been designed and synthesized and their antidepressant and anticonvulsant activities have been evaluated. In general, the new compounds displayed higher levels of antidepressant efficacy than fluoxetine in the FST and TST, and showed some degree of anticonvulsant activity. Although these compounds could potentially be used as adjuncts of other antidepressants to treat depression in patients with epilepsy, further studies should be conducted to reveal the mechanism of their antidepressant-like effects.

6. Experimental protocols

6.1. Chemistry

Melting points were determined in open capillary-tubes and were uncorrected. Infrared spectra were recorded (in KBr) using a FTIR1730 spectrometer (PerkineElmer, Waltham, MA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded using an AV-300 spectrometer (Bruker, Switzerland), and all chemical shifts were given in parts per million relative to tetramethylsilane. Mass spectra were measured using an HP1100LC spectrometer (Agilent Technologies, Santa Clara, USA). High resolution mass spectra were measured on an MALDI-TOF/TOF mass spectrometer (Bruker Daltonik, Germany). The chemicals were purchased from Aldrich Chemical Corporation (St Louis, USA).

6.1.1. Synthesis of 6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**4**)

Dimethoxy-*N*, *N*-dimethylmethanamine (DMF-DMA) 6.0 g (50 mmol) was added to a solution of formylhydrazine 3.0 g (50 mmol) in acetonitrile (50 ml) in a 100-ml round-bottomed flask equipped with a reflux condenser. The reaction mixture was warmed to 60 °C for 1 h and then 6-amino-3,4-dihydroquinolin-2(1*H*)-one 4.1 g (25 mmol) was added accompanied with acetic acid (5 ml). The reaction temperature was raised to 120 °C for 12 h. After being cooled and concentrated, the precipitate was filtrated, and recrystallized in ethanol to produce the pure compound **4**. Yield 67%; m.p. 294–296 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 2.49 (t, 2H, J = 7.4 Hz, H-3), 2.94 (t, 2H, J = 7.4 Hz, H-4), 6.97 (d, 1H, J = 8.4 Hz, H-8), 7.44 (dd, 1H, J_1 = 2.3 Hz, J_2 = 8.4 Hz, H-7), 7.54 (d, 1H, J = 2.3 Hz, H-5), 9.00 (s, 2H, Triazole-H), 10.29 (s, 1H, CONH). MS *m*/*z* 215.2 ($M + H^+$).

6.1.2. Synthesis of 1-substituted-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-ones (**5a**–**5s**)

Sodium methylate (5 mmol, 0.27 g) and 6-(4*H*-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1*H*)-one (**4**) (5 mmol, 1.1 g) were dissolved in acetonitrile (50 mL) and refluxed for 1 h. Then the appropriate alkyl bromide or benzyl chloride (6 mmol) was added to the mixture. The reaction mixture was heated at reflux temperature for 2–4 h. After removing half of the solvent, 100 mL of water was poured into the flask and the precipitate formed was filtered, which was recrystallized in ethanol (or mix of ether and dichloromethane) to produce a white solid. The yield, melting point and spectral data of each compound were given below.

*6.1.2.1. 1-Propyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5a**).* Yield: 69%, mp: 169–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (t, 3H, J = 7.5 Hz, $-CH_3$), 1.64–1.72 (m, 2H, $-CH_2-$), 2.70 (t, 2H, J = 7.3 Hz, H-3), 2.98 (t, 2H, J = 7.3 Hz, H-4), 3.93 (t, 2H, J = 7.6 Hz, NCH_2-), 7.11 (d, 1H, J = 8.6, H-8), 7.21 (d, 1H, J = 2.5 Hz, H-5), 7.28 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.6 Hz, H-7), 8.44 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.6, 141.6, 140.4, 128.8, 128.3, 122.2, 121.5, 116.1, 43.8, 31.3, 25.5, 20.3, 11.2. IR (KBr) cm^{-1}: 1651 (C═O), 1527 (C═N). MS-EI *m*/*z* 257 ($M + H^+$). ESI-HRMS calcd for $C_{14}H_{17}N_4O^+$ ($[M + H]^+$): 257.1397; found: 257.1395.

*6.1.2.2. 1-Butyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5b**).* Yield: 74%, mp: 154–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97 (t, 3H, J = 7.5 Hz, $-CH_3$), 1.37–1.68 (m, 4H, $-(CH_2)_2-$), 2.70 (t, 2H, J = 6.0 Hz, H-3), 2.98 (t, 2H, J = 6.0 Hz, H-4), 3.97 (t, 2H, J = 7.5 Hz, $N-CH_2-$), 7.11–7.28 (m, 3H, Ph-H), 8.44 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.6, 140.4, 128.8, 128.3, 122.2, 121.5, 116.1, 42.0, 31.3, 29.1, 25.5, 20.1, 13.8. IR (KBr) cm^{-1}: 1651 (C═O), 1526 (C═N). MS-EI *m*/*z* 271 ($M + H^+$). ESI-HRMS calcd for $C_{15}H_{18}N_4O^+$ ($[M + H]^+$): 271.1553; found: 271.1550.

*6.1.2.3. 1-Pentyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5c**).* Yield: 63%, mp: 139–140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92 (t, 3H, J = 6.4 Hz, $-CH_3$), 1.37–1.66 (m, 6H, $-(CH_2)_3-$), 2.71 (t, 2H, J = 7.3 Hz, H-3), 2.99 (t, 2H, J = 7.3 Hz, H-4), 3.97 (t, 2H, J = 7.5 Hz, NCH_2-), 7.10–7.29 (m, 3H, Ph-H), 8.45 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.6, 140.4, 128.8, 128.3, 122.2, 121.5, 116.1, 42.3, 31.3, 29.0, 26.7, 25.5, 22.4, 14.0. IR (KBr) cm^{-1}: 1652 (C═O), 1525 (C═N). MS-EI *m*/*z* 285 ($M + H^+$). ESI-HRMS calcd for $C_{16}H_{21}N_4O^+$ ($[M + H]^+$): 285.1710; found: 285.1711.

*6.1.2.4. 1-Hexyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5d**).* Yield: 57%, mp: 111–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.90 (t, 3H, J = 6.5 Hz, $-CH_3$), 1.16–1.65 (m, 8H, $-(CH_2)_4-$), 2.70 (t, 2H, J = 7.3 Hz, H-3), 2.99 (t, 2H, J = 7.3 Hz, H-4), 3.96 (t, 2H, J = 7.5 Hz, NCH_2-), 7.10–7.28 (m, 3H, Ph-H), 8.45 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.6, 140.3, 128.7, 128.3, 122.2, 121.5, 116.1, 42.3, 31.4, 31.3, 27.0, 26.5, 25.5, 22.5, 14.0. IR (KBr) cm^{-1}: 1659 (C═O), 1528 (C═N) .MS-EI *m*/*z* 299 ($M + H^+$). ESI-HRMS calcd for $C_{17}H_{23}N_4O^+$ ($[M + H]^+$): 299.1866; found: 299.1860.

*6.1.2.5. 1-Heptyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5e**).* Yield: 62%, mp: 134–135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3 H, J = 6.5 Hz, $-CH_3$), 1.28–1.64 (m, 10H, $-(CH_2)_5-$), 2.70 (t, 2H, J = 7.3 Hz, H-3), 2.98 (t, 2H, J = 7.3 Hz, H-4), 3.95 (t, 2H, J = 7.7 Hz, NCH_2-), 7.10–7.20 (m, 3H, Ph-H), 8.44 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.6, 140.4, 128.8, 128.3, 122.2, 121.5, 116.1, 42.3, 31.7, 31.3, 29.0, 27.0, 26.8, 25.5, 22.6, 14.1. IR (KBr) cm^{-1}: 1667 (C═O), 1529 (C═N). MS-EI *m*/*z* 313 ($M + H^+$). ESI-HRMS calcd for $C_{18}H_{25}N_4O^+$ ($[M + H]^+$): 313.2023; found: 313.2016.

*6.1.2.6. 1-Octyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5f**).* Yield: 62%, mp: 126–127 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3 H, J = 6.4 Hz, $-CH_3$), 1.27–1.64 (m, 12H, $-(CH_2)_6-$), 2.70 (t, 2H, J = 7.3 Hz, H-3), 2.98 (t, 2H, J = 7.3 Hz, H-4), 3.95 (t, 2H, J = 7.7 Hz, NCH_2-), 7.11 (d, 1H, J = 8.6, H-8), 7.23 (d, 1H, J = 2.5 Hz, H-5), 7.29 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.6 Hz, H-7), 8.45 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.4, 141.6, 140.4, 128.8, 128.3, 122.2, 121.5, 116.1, 42.3, 31.7, 31.4, 29.3, 29.2, 26.9, 22.6, 22.5, 14.1. IR (KBr) cm^{-1}: 1669 (C═O), 1528 (C═N). MS-EI *m*/*z* 327 ($M + H^+$). ESI-HRMS calcd for $C_{19}H_{27}N_4O^+$ ($[M + H]^+$): 327.2179; found: 327.2182.

*6.1.2.7. 1-Decyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5g**).* Yield: 84%, mp: 130–132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3H, J = 6.5 Hz, $-CH_3$), 1.25–1.64 (m, 16H, $-$

($(CH_2)_8$–), 2.70 (t, 2H, J = 7.3 Hz, H-3), 2.98 (t, 2H, J = 7.3 Hz, H-4), 3.95 (t, 2H, J = 7.7 Hz, N–CH_2–), 7.11 (d, 1H, J = 8.6, H-8), 7.22 (d, 1H, J = 2.5 Hz, H-5), 7.29 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.6 Hz, H-7), 8.45 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5, 141.6, 140.4, 128.7, 128.3, 122.2, 121.5, 116.1, 42.3, 31.8, 31.3, 29.5, 29.5, 29.3, 29.3, 27.0, 26.8, 25.5, 22.6, 14.1. IR (KBr) cm^{-1}: 1671 (C=O), 1529 (C=N). MS-EI m/z 355 (M + H$^+$). ESI-HRMS calcd for $C_{21}H_{31}N_4O^+$ ([M + H]$^+$): 355.2492; found: 355.2496.

*6.1.2.8. 1-Benzyl-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5h**).* Yield: 57%, mp: 224–226 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.86 (t, 2H, J = 7.2 Hz, H-3), 3.08 (t, 2H, J = 7.2 Hz, H-4), 5.22 (s, 2H, NCH_2), 6.99 (d, 1H, J = 8.7, H-8), 7.13 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.7 Hz, H-7), 6.98–7.36 (m, 6H, Ph-H, H-5), 8.40 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.0, 141.6, 140.4, 136.1, 129.0, 128.5, 127.4, 126.3, 122.0, 121.5, 116.9, 113.9, 46.1, 31.3, 25.5. IR (KBr) cm^{-1}: 1669 (C=O), 1525 (C=N). MS-EI m/z 305 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{17}N_4O^+$ ([M + H]$^+$): 305.1397; found: 305.1393.

*6.1.2.9. 1-(2-Fluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5i**).* Yield: 63%, mp: 202–203 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.86 (t, 2H, J = 7.2 Hz, H-3), 3.09 (t, 2H, J = 7.3 Hz, H-4), 5.28 (s, 2H, NCH_2), 6.98–7.28 (m, 7H, Ph-H), 8.40 (s, 2 H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.0, 160.4 (d, $^1J_{c-f}$ = 244 Hz), 141.5, 140.1, 129. 1 (d, $^3J_{c-f}$ = 8.0 Hz), 128.7, 128.6, 127.9 (d, $^3J_{c-f}$ = 3.6 Hz), 124.6, 123.1 (d, $^2J_{c-f}$ = 13.8 Hz), 122.1, 121.5, 116.5, 115.7 (d, $^2J_{c-f}$ = 21.1 Hz), 39.8, 31.3, 25.4. IR (KBr) cm^{-1}: 1668 (C=O), 1530 (C=N). MS-EI m/z 323 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}FN_4O^+$ ([M + H]$^+$): 323.1303; found: 323.1304.

*6.1.2.10. 1-(3-Fluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5j**).* Yield: 58%, mp: 179–180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.87 (t, 2H, J = 7.2 Hz, H-3), 3.09 (t, 2H, J = 7.2 Hz, H-4), 5.22 (s, 2H, NCH_2), 6.94–7.30 (m, 7H, Ph-H), 8.41 (s, 2 H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 163.2 (d, $^1J_{c-f}$ = 244 Hz), 141.5, 140.3, 138.9 (d, $^3J_{c-f}$ = 6.9 Hz), 130.6 (d, $^3J_{c-f}$ = 8.0 Hz), 128.7, 128.5, 122.2, 122.0, 121.6, 116.7, 114.5 (d, $^2J_{c-f}$ = 20.9 Hz), 113.4 (d, $^2J_{c-f}$ = 22.1 Hz), 45.7, 31.2, 25.5. IR (KBr) cm^{-1}: 1666 (C=O), 1530 (C=N). MS-EI m/z 323 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}FN_4O^+$ ([M + H]$^+$): 323.1303; found: 323.1303.

*6.1.2.11. 1-(4-Fluorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5k**).* Yield: 61%, mp: 227–228 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.86 (t, 2H, J = 7.5 Hz, H-3), 3.08 (t, 2H, J = 7.5 Hz, H-4), 5.20 (s, 2H, NCH_2), 7.01–7.28 (m, 7H, Ph-H), 8.40 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 162.2 (d, $^1J_{c-f}$ = 234.9 Hz), 141.5, 140.3, 131.9, 128.7, 128.6, 128.1 (d, $^3J_{c-f}$ = 5.9 Hz), 122.1, 121.5, 116.7, 115.9 (d, $^2J_{c-f}$ = 21.5 Hz), 45.5, 31.3, 25.5. IR (KBr) cm^{-1}: 1668 (C=O), 1532 (C=N). MS-EI m/z 323 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}FN_4O^+$ ([M + H]$^+$): 323.1303; found: 323.1301.

*6.1.2.12. 1-(2-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5l**).* Yield: 60%, mp: 192–194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.89 (t, 2 H, J = 7.2 Hz, H-3), 3.12 (t, 2H, J = 7.2 Hz, H-4), 5.19 (s, 2H, NCH_2), 7.14–7.31 (m, 7H, Ph-H), 8.42 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.5, 140.2, 133.0, 132.7, 129.9, 128.8, 128.7, 128.4, 127.2, 126.7, 122.1, 121.6, 116.7, 44.1, 31.3, 25.4. IR (KBr) cm^{-1}: 1670 (C=O), 1526 (C=N). MS-EI m/z 339 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}ClN_4O^+$ ([M + H]$^+$): 339.1007; found: 339.1006.

*6.1.2.13. 1-(3-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5m**).* Yield: 79%, mp: 218–220 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.87 (t, 2H, J = 7.2 Hz, H-3), 3.10 (t, 2H, J = 7.2 Hz, H-4), 5.20 (s, 2H, NCH_2), 6.94–7.31 (m, 7H, Ph-H), 8.41 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.5, 140.2, 138.4, 134.9, 130.3, 128.8, 128.5, 127.8, 126.5, 124.6, 122.2, 121.6, 116.7, 45.7, 31.2, 25.5. IR (KBr) cm^{-1}: 1671 (C=O), 1528 (C=N). MS-EI m/z 339 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}ClN_4O^+$ ([M + H]$^+$): 339.1007; found: 339.1014.

*6.1.2.14. 1-(4-Chlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5n**).* Yield: 63%, mp: 222–224 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.85 (t, 2H, J = 7.2 Hz, H-3), 3.10 (t, 2H, J = 7.2 Hz, H-4), 5.19 (s, 2 H, NCH_2), 7.14–7.31 (m, 7H, Ph-H), 8.40 (s, 2 H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.5, 140.2, 134.7, 133.3, 129.1, 128.7, 128.6, 127.8, 122.2, 121.5, 116.7, 45.5, 31.2, 25.4. IR (KBr) cm^{-1}: 1674 (C=O), 1526 (C=N). MS-EI m/z 339 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{16}ClN_4O^+$ ([M + H]$^+$): 339.1007; found: 339.1012.

*6.1.2.15. 1-(2,4-Dichlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5o**).* Yield: 64%, mp: 204–205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.88 (t, 2H, J = 7.3 Hz, H-3), 3.12 (t, 2H, J = 7.3 Hz, H-4), 5.25 (s, 2H, NCH_2), 6.79–7.46 (m, 6H, Ph-H), 8.41 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.2, 140.0, 133.8, 133.4, 131.8, 129.7, 128.9, 128.5, 127.8, 127.6, 122.2, 121.7, 116.5, 43.7, 31.2, 25.4. IR (KBr) cm^{-1}: 1676 (C=O), 1528 (C=N). MS-EI m/z 373 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{15}C_{l2}N_4O^+$ ([M + H]$^+$): 373.0617; found: 373.0621.

*6.1.2.16. 1-(2,6-Dichlorobenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5p**).* Yield: 65%, mp: 251–252 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (t, 2H, J = 7.3 Hz, H-3), 3.01 (t, 2H, J = 7.3 Hz, H-4), 5.55 (s, 2H, NCH_2), 7.11–7.29 (m, 6H, Ph-H), 8.39 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.1, 141.4, 139.3, 135.9, 131.1, 130.1, 129.4, 129.2, 128.6, 121.9, 121.0, 117.3, 41.2, 31.9, 25.1. IR (KBr) cm^{-1}: 1677 (C=O), 1529 (C=N). MS-EI m/z 373 (M + H$^+$). ESI-HRMS calcd for $C_{18}H_{15}C_{l2}N_4O^+$ ([M + H]$^+$): 373.0617; found: 373.0614.

*6.1.2.17. 1-(3-(Trifluoromethyl)benzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5q**).* Yield: 58%, mp: 195–196 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.88 (t, 2H, J = 7.2 Hz, H-3), 3.11 (t, 2H, J = 7.2 Hz, H-4), 5.28 (s, 2 H, NCH_2), 6.92–7.56 (m, 7H, Ph-H), 8.41 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.4, 140.2, 137.4, 131.3 (q, $^2J_{c-f}$ = 30.3 Hz) 129.7, 129.5, 128.8, 128.6, 124.4 (q, $^3J_{c-f}$ = 3.8 Hz), 123.2 (q, $^3J_{c-f}$ = 3.9 Hz), 123.9 (q, $^1J_{c-f}$ = 271 Hz), 122.3, 121.6, 116.6, 45.9, 31.2, 25.5. IR (KBr) cm^{-1}: 1681 (C=O), 1530 (C=N). MS-EI m/z 373 (M + H$^+$). ESI-HRMS calcd for $C_{19}H_{16}F_3N_4O^+$ ([M + H]$^+$): 373.1271; found: 373.1276.

*6.1.2.18. 1-(4-Methylbenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5r**).* Yield: 54%, mp: 234–236 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.33 (s, 3H, Ph-CH_3), 2.86 (t, 2H, J = 7.2 Hz, H-3), 3.08 (t, 2H, J = 7.2 Hz, H-4), 5.19 (s, 2H, NCH_2), 7.00–7.27 (m, 7H, Ph-H), 8.39 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 141.5, 140.5, 137.1, 133.1, 129.6, 128.5, 126.3, 122.0, 121.5, 116.9, 109.5, 45.9, 31.3, 25.5, 21.1. IR (KBr) cm^{-1}: 1669 (C=O), 1527 (C=N). MS-EI m/z 319 (M + H$^+$). ESI-HRMS calcd for $C_{19}H_{19}N_4O^+$ ([M + H]$^+$): 319.1553; found: 319.1556.

*6.1.2.19. 1-(4-Methoxybenzyl)-6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-one (**5s**).* Yield: 57%, mp: 200–201 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.85 (t, 2H, J = 7.3 Hz, H-3), 3.06 (t, 2H, J = 7.3 Hz, H-4), 3.78 (s, 3H, –OCH_3), 5.17 (s, 2H, NCH_2), 6.84–7.28 (m, 7H, Ph-H), 8.40 (s, 2H, Triazole-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 158.9, 141.5, 140.5, 128.6, 128.5, 128.2, 127.7, 122.0, 121.4, 116.9, 114.3, 55.3, 45.5, 31.3, 25.5. IR (KBr) cm^{-1}: 1670 (C=O), 1526

(C=N). MS-EI *m/z* 335 ($M + H^+$). ESI-HRMS calcd for $C_{19}H_{19}N_4O_2^+$ ($[M + H]^+$): 335.1503; found: 335.1506.

6.2. Pharmacology

6.2.1. Forced swimming test (FST)

Male Kun-Ming mice were used in the FST. On the test day, mice were assigned to different groups ($n = 8$ for each group). The synthesized compounds and the standard drug fluoxetine were administered as intraperitoneal injections. After 30 min, the mice were dropped one at a time into a Plexiglas cylinder (height 25 cm, diameter 10 cm, containing water to a height of 18 cm at 23–25 °C). A mouse was judged immobile if it floated in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded in the last 4 min of a total period of 6 min. A decrease in the duration of immobility may indicate antidepressant-like effect.

6.2.2. Tail suspension test (TST)

Male mice were individually suspended by the tail above the floor and affixed with adhesive tape placed approximately 1–2 cm from the tip of the tail. The total duration of immobility was recorded in the last 6 min of a total period of 7 min. Mice were determined to be immobile when they were completely motionless and hung passively.

6.2.3. Open-field test

Open-field tests were used to evaluate the exploratory activity of the animal [20]. The investigated compound **5i** was administered (i.p.) 30 min before the experiment. The study was carried out on mice according to Archer's method [27], with slight modifications. Each mouse was placed individually in the center of the open field apparatus, and the locomotor activity was assessed. The open field apparatus was a non-transparent plastic container (80 cm × 60 cm × 30 cm), with the underside divided into 48 units of size 10 cm × 10 cm, without walls. The animals were gently placed in the center of the platform and were allowed to explore their surroundings. Hand-operated counters were used to score locomotion (numbers of crossing lines with all four paws), rearing frequencies (number of times an animal stood on its hind legs), and grooming frequencies (number of modifications) for 3 min. The researchers, who did not know which groups had been treated, scored the behaviors in the open field. The experiments were performed in a dark room, and the apparatus was illuminated by a 60-W bulb giving a yellowish light, positioned 1 m above the center of the apparatus.

6.2.4. Maximal electroshock seizure (MES) test

Seizures were elicited in mice with ear stimulation using a 0.2 s 60-Hz 50-mA alternating current. Protection against the spread of MES-induced seizures was defined as the abolition of the hind limb tonic extension spasm.

6.2.5. Neurotoxicity screening (NT)

The neurotoxicity of the compounds was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod of diameter 3.2 cm that rotates at 10 rpm. Trained animals were given an intraperitoneal injection of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1min in each of the trials.

6.2.6. Statistical analysis

All data are represented as the mean ± S.E.M. Statistical analyses for comparing control and experimental groups were performed using one-way analysis of variance followed by the Dunnet's test using software GraphPad Prism 5. Differences were considered significant if the probability of error was less than 5% ($P < 0.05$).

Acknowledgment

This work was supported by the National Natural Science Foundation of China (No. 81160382) and National Science and Technology Major Project of China (No. 2011ZX09102-003-03).

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