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Synthesis and anticonvulsant activity of 1-(8-(benzyloxy)quinolin-2-yl)-6-substituted-4,6-diazaspiro[2,4]heptane-5,7-diones

Xianran He [a], Min Zhong [b], Tao Zhang [a], Jin Yang [c], Zhongyuan Wu [a], Yuling Xiao [a], Hao Guo [a], Guofu Qiu [a], Xianming Hu [a,*]

[a] State Key Laboratory of Virology, Ministry of Education Laboratory of Combinatorial Biosynthesis and Drug Discovery, Wuhan University School of Pharmaceutical Science, Luojiashan Road, Wuhan 430071, China
[b] Hubei Research Institute of Chemistry, Wuhan 430074, China
[c] Hubei University for Nationalities School of Medicine, Enshi 445000, China

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ABSTRACT

In the present study on the development of new anticonvulsants, 16 new1-(8-(benzyloxy)quinolin-2-yl-6-substituted-4,6-diazaspiro[2,4]heptane-5,7-diones were synthesized and tested for anticonvulsant activity using the maximal electroshock (MES), subcutaneous pentylenetetrazole (*sc*PTZ) screens, which are the most widely employed seizure models for early identification of candidate anticonvulsants. Their neurotoxicity was determined applying the rotorod test. Two compounds **8e** and **8j** showed promising anticonvulsant activities in both models employed for anticonvulsant evaluation. The most active compound **8e** showed the MES-induced seizures with ED_{50} value of 8.6 mg/kg and TD_{50} value of 365.3 mg/kg after intraperitoneally injection to mice, which provided compound **8e** with a protective index (TD_{50}/ED_{50}) of 26.8 in the MES test.

1. Introduction

Epilepsy is a chronic disorder of the brain characterized by recurrent unprovoked seizures that affects about 0.5–1% of the world's population [1,2]. In spite of the large therapeutic arsenal of old and new antiepileptic drugs (AEDs), about 30% of epileptic patients are not seizure-free [3]. Besides, many AEDs such as phenobarbital, phenytoin, carbamazepine, vigabatrin, valproate, felbamate, and lamotrigine, which are effective toward only 60–80% of patients have some undesirable side effects, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism [4–8]. Thus, there is an enormous need for the development of novel AEDs with fewer side effects and more effectives.

Quinoline derivatives, which show several beneficial heterogenous and varied pharmacological properties, for example, antibacterial [9], immunosuppressive [10], analgesic [11], vasorelaxing [12], antiplasmodial [13], anticancer [14] and anticonvulsant [15] activities. On the other hand, many spirohydantoin derivations have been documented as potent anticonvulsants [16–18]. We have previously reported that the structure of cyclopropanespirohydantoin exhibit excellent anticonvulsant activities in various animal seizure models [19–21]. In our previous study, a series of derivatives of 6-methyl-1-substituted-4, 6-diazaspiro[2.4]heptane-5,7-diones were first found to have anticonvulsant activities, among which 6-methyl-1-(4-(methylsulfonyl)phenyl)-4,6-diazaspiro[2.4]heptanes-5,7-dione (Compound **I**) showed the strongest activity with an ED_{50} value of 12.5 mg/kg in the maximal electroshock test (MES) and a TD_{50} value greater than 300 mg/kg (Fig. 1) [19]. Another derivatives in the group of *N*-3-arylamide substituted 5,5-cyclopropanespirohydantoin,1,1-dimethyl-6-(4-(trifluoromethyl) phenyl)4,6-diazaspiro[2.4]heptanes-5,7-dione (Compound **II**) showed ED50 values of 9.2 mg/kg in the maximal electroshock test (MES), protective index (PI = TD_{50}/ED_{50}) values of 45.8 and 6.7 in the MES and the pentylenetetrazole tests respectively (Fig. 1) [20]. As a result, these compounds are potential leads for further design of more active compounds.

Above these facts and in continuation of our research program on design and synthesis of new anticonvulsant agents,

* Corresponding author. Tel.: +86 27 68754621; fax: +86 27 68754629.
E-mail address: hexianran@yahoo.com.cn (X. Hu).

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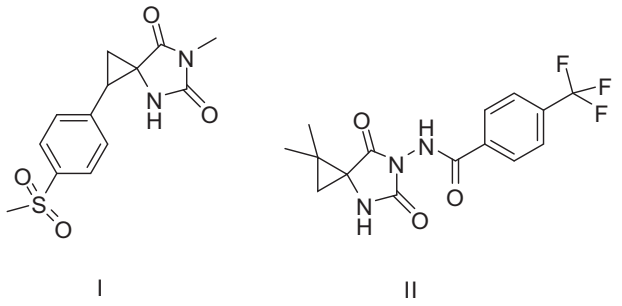


Fig. 1. Structure of compounds **I** and **II**.

we introduced quinoline structure to propane ring of cyclopropanespirohydantoin with different substituents at N-3 position of hydantoin ring in order to develop new potent and safe AEDs. We synthesized and comparatively evaluated the anticonvulsant activity and neurotoxicity of 16 new derivatives of 1-(8-(benzyloxy) quinolin-2-yl)-6-substituted-4,6-diazaspiro[2,4] heptane-5,7-diones. Compounds **8e** and **8j** were quantitatively evaluated for its anticonvulsant activity (ED_{50}) and neurotoxicity (TD_{50}).

2. Chemistry

The synthesis of target compounds **8a**–**p** was accomplished as presented in Scheme 1. We have succeeded in a simple and convenient preparation of compound **1** by reaction of 2-methylquinolin-8-ol with benzyl bromide in anhydrous ethanol in the presence of $NaOC_2H_5$ in 90% yield [22]. Compound **1** was reacted with SeO_2 in anhydrous dioxane to afford the compound **2** in high yield (98%) [23]. Then compound **3** was prepared by condensation of diethyl malonate with Compound **2**. Compound **3** underwent cyclopropane formation with trimethylsulphoxoniumylide (TMSOI) to afford compound **4** [24]. Then monoester compound **5** was obtained after monosaponification in a 1 N NaOH/ethanol (1.1 equiv) solution at room temperature for 12 h [25]. This was then converted to acyl azide by using ethyl chloroformate in the presence of triethylamine (Et_3N) followed by reaction with sodium azide in a one-pot synthesis. α-Carboethoxy isocyanate **6** was successfully generated by a Curtius reaction *in situ* on heating the acyl azide in anhydrous toluene solution at 75 °C. Isocyanate **6** was allowed to react directly with various amines without isolation. The desired α-carboethoxy ureas **7a**–**p** were readily obtained. Finally, compounds **7a**–**p** cyclized on treatment with Na (1.1 equiv) in EtOH and provided **8a**–**p** in good yields (yield ≥90%).

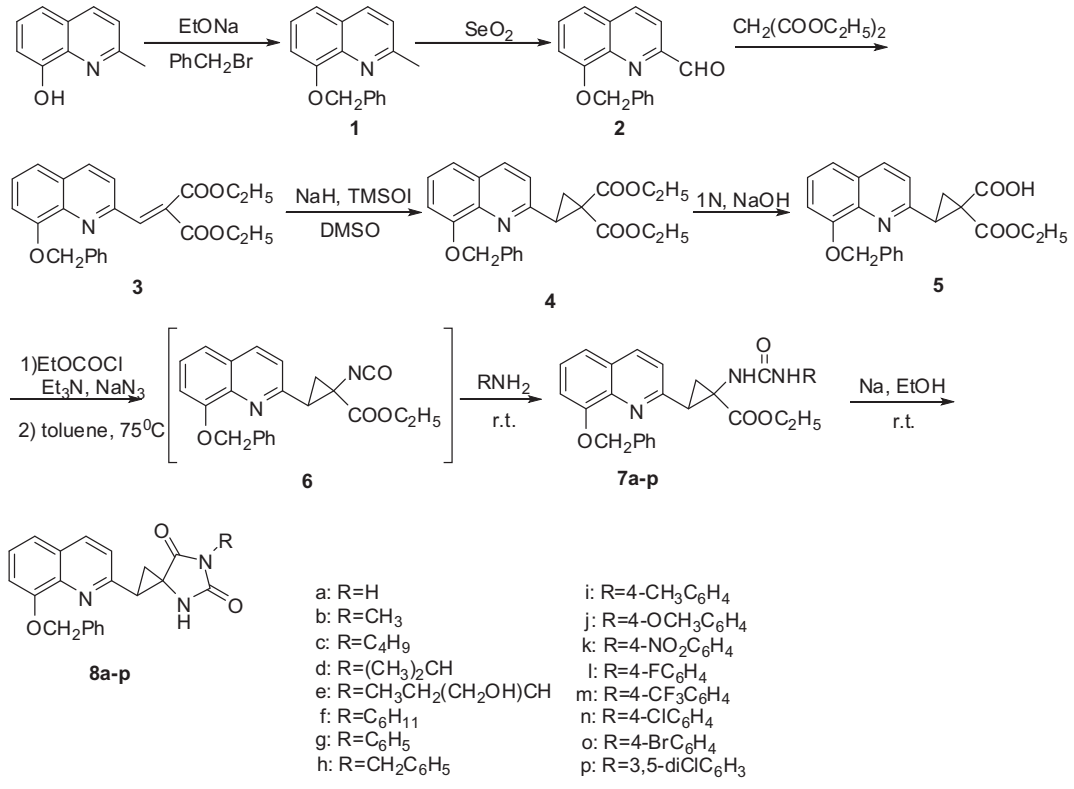
The chemical structures of the compounds synthesized were elucidated on the basis of ^1H NMR, ^{13}C NMR, MS and elemental analysis. The detailed physical and analytical data are listed in Section 5.

All of these compounds were prepared as racemic mixtures and no attempt was made to resolve the enantiomers.

3. Pharmacology results and discussion

The anticonvulsant activity and neurotoxicity of the synthesized compounds were evaluated following the standard procedures proposed by the NIH anticonvulsant drug development (ADD) program, via the anticonvulsant screening project (ASP) [26]. The initial evaluation (Phase I) included the maximal electroshock seizure (MES), the subcutaneous pentylenetetrazole (*sc*PTZ) and neurotoxicity.

The MES test is associated with the electrical induction of the seizure, whereas PTZ test involves a chemical induction to generate the convulsion. Neurotoxicity is primary determined in the minimal motor impairment-rotorod screen. The calculated Log P



Scheme 1. General method for the synthesis of compounds **8a**–**p**.

(Clog p) values were calculated using the software in ACD Labs 8.0 version.

The compounds **8a**–**p** were administrated intraperitoneally (ip) into the mice using dose of 30, 100 and 300 mg/kg and the observations were taken at two different time intervals (0.5 h and 4.0 h). Neurotoxicity was measured by the rotorod test. The results are shown in Table 1.

The initial anticonvulsant evaluation showed that all compounds **8a**–**p**, with different substituents at N-3 of 2-quinolincyclopropanespirohydantoin, were effective in ip MES and/or *sc*PTZ screens.

In the MES test, compounds **8e** and **8j** were active against MES test at dose of 30 mg/kg at 0.5 h. The most active compound was **8e**, which presented 50% of protection at dose of 30 mg/kg at 0.5 h. Interestingly, compound **8e** continued to protect from the seizures at a dose of 30 mg/kg at 4.0 h also. It indicates that **8e** have rapid onset and long duration of anticonvulsant at lower dose. Compound **8j** was active at 4.0 h but at the higher dose of 100 mg/kg.

Compounds that were active at a dose of 100 mg/kg only at 0.5 h in MES screen included **8b** and **8i**, indicating that they have rapid onset and short duration of anticonvulsant activity. Compound **8p** did not show any activity at two time periods in MES screen.

In the *sc*PTZ screen, compounds that showed protection at 0.5 h were **8a**, **8d**, **8e**, **8f**, **8h**, **8j**, **8k** and **8p**. Among these compounds **8d** and **8e** showed anti-*sc*PTZ activity at the dose of 100 mg/kg at time periods 0.5 h. Compounds **8b**, **8c** and **8m** were active only at 4.0 h at a dose of 300 mg/kg indicative of the long duration of action of these compounds.

In the neurotoxicity screen, compounds that did not show any neurotoxicity at the highest dose (300 mg/kg) included **8c**, **8d**, **8e**, **8j** and **8k**. These compounds did not cause any motor impairment at the three doses at the two time periods. Compounds **8g** and **8p** were less neurotoxic than phenytoin and exhibited motor impairment at the dose of 300 mg/kg at 0.5 h and also 4.0 h (**8g**). Compound **8n** and **8o** revealed neurotoxicity at a dose of 100 mg/kg at 0.5 h.

Compounds **8e** and **8j** were selected for quantification of the pharmacological parameters (ED_{50} and TD_{50}). Results of the quantitative test for the compounds, along with the data on the standard drugs (phenytoin, carbamazepine, phenobarbital, and valproate), are reported in Table 2. In the mice ip MES screen, compound **8e** and **8j** showed a higher protective index (PI) than all the standard drugs. In the mice ip *sc*PTZ screen, compound **8e** gave an ED_{50} of 212.3 mg/kg and a TD_{50} of 365.3 mg/kg, resulting in a high protective index (PI), that is, TD_{50}/ED_{50}, of 1.7 when compared to phenobarbital and valproate.

In the present studies, we have synthesized a library of compounds with 2-quinolincyclopropanespirohydantoin as a core fragment and at the position-3 of hydantoin ring we have introduced different substituents. In the preliminary anticonvulsant screen, all of the alkyl- and aryl-substituted 2-quinolincyclopropanespirohydantoins showed better protection against ip MES test but less response toward *sc*PTZ test.

Compounds with long straight chain butyl (**8c**, **8d**) substituents at N-3 have shown less active than alkyl-substituted derivatives (**8b**), the introduction of hydrophilic group at branch of alkyl chain (**8e**) resulted in increased anticonvulsant activity. When the alkyl groups were replaced by a phenyl ring, substitution of an electron-donating group like methoxy and methyl at the *para* position of phenyl ring resulted in increased anticonvulsant activity. For example, the 4-methyl (**8i**) and 4-methoxy (**8j**) substituent derivatives were more potent than 4-nitro (**8k**) and 4-trifuloro (**8m**) derivatives. Compounds **8n**, **8o**, and **8p** did not show apparent activity in MES and *sc*PTZ screen, and the Clog P of these compounds were far from 2.0, which is considered to be the optimum lipophilicity for the congeners that act on the central nervous system [27]. It may be indicated the importance of lipophilicity as well as electronic properties of the substituents on the activity of these compounds.

Table 1
Anticonvulsant activity and neurotoxocity of compounds **8a**–**p** administered intraperitoneally to mice.

Compounds	Intraperitoneal injection in mice[a]						Clog P[b]
	MES[c]		*sc*PTZ[d]		Neurotoxocity[e]		
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h	
8a	300	–	300	–	300	–	1.63 ± 0.41
8b	100	–	–	300	–	300	1.86 ± 0.68
8c	300	–	–	300	–	–	3.45 ± 0.68
8d	300	100	100	–	–	–	2.74 ± 0.68
8e	30	30	100	300	–	–	2.11 ± 0.68
8f	300	300	300	–	–	300	3.92 ± 0.68
8g	–	300	–	–	300	300	4.15 ± 0.61
8h	–	300	300	–	–	300	3.69 ± 0.68
8i	100	–	–	–	–	300	4.61 ± 0.62
8j	30	100	300	–	–	–	3.24 ± 0.64
8k	–	300	300	–	–	–	4.43 ± 0.63
8l	300	–	–	–	–	300	4.44 ± 0.67
8m	300	300	–	300	–	300	5.12 ± 0.66
8n	300	–	–	–	100	300	4.98 ± 0.63
8o	–	300	–	–	100	100	5.16 ± 0.67
8p	–	–	300	–	300	–	6.05 ± 0.72
Phenytoin[f]	30	30	–	–	100	100	2.52 ± 0.38
Ethosuximide[g]	–	–	100	300	–	–	0.38 ± 0.46

[a] 30,100, and 300 mg/kg of doses were administered ip. 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 were administered. A dash indicates an absence of activity at maximum dose administered (300 mg/kg).
[b] Clog P was calculated using software ACD Labs 8.0 version.
[c] Maximal electroshock test.
[d] Subcutaneous pentylenetetrazole test.
[e] Neurotoxocity screening (rotorod test).
[f] Data from Ref. [34].
[g] Data from Ref. [35].

4. Conclusion

In summary, the present studies revealed that number of 1-(8-(benzyloxy)quinolin-2-yl)-6-substituted-4,6-diazaspiro[2,4]heptane-5,7-diones were effective in the MES and/or *sc*PTZ screens. In the neurotoxicity studies some of the active compounds were devoid of toxicity. The most active was 1-(8-(benzyloxy)quinolin-2-yl)-6-(1-hydroxybutan-2-yl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8e**) which showed ED_{50} value of 8.6 mg/kg and a protective index (TD_{50}/ED_{50}) of 26.8 in the MES test in mice. This compound showed greater ED_{50} and lower TD_{50} to standard drugs.

5. Experimental protocols

5.1. Chemistry

All chemicals and solvents were purchased from Aldrich, or Fluka. Solvents and reagents were dried and purified according to the literature methods. Melting points were uncorrected and measured on an XT-4 apparatus. ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker AV400 apparatus in DMSO-d_6 and $CDCl_3$ with TMS as internal standard. The elemental analysis (C, H, N) data were obtained from a VarioEL III (German) elemental analyzer. The mass spectra (MS) were recorded on AMD-604 Mass Spectrometer operating at 70 eV.

Table 2
Phase-II quantitative anticonvulsant evaluation in mice (test drug administered i.p.).

Compound	ED_{50}[a]		TD_{50}[b]	PI[c]	
	MES	*sc*PTZ		MES	*sc*PTZ
8e	8.6 (6.4–12.5)[d]	212.3 (172.4–222.6)	365.3 (353.7–395.5)	26.8	1.7
8j	19.5 (16.3–22.7)	278.6 (221.5–297.2)	432.6 (378.4–464.8)	22.2	1.6
Phenytoin[e]	9.5 (8.1–10.4)	>300	65.5 (52.5–72.9)	6.9	<0.22
Carbamazepinee[e]	8.8 (5.5–14.1)	>100	71.6 (45.9–135)	8.1	<0.22
Phenobarbital[e]	21.8 (21.8–25.5)	13.2 (5.8–15.9)	69 (62.8–72.9)	3.2	5.2
Valproate[e]	272 (247–338)	149 (123–177)	426 (369–450)	1.6	2.9

Number of animals used: 10; solvent used: polyethylene glycol (0.1 mL, i.p.).
[a] Dose in milligrams per kilogram body mass.
[b] Minimal toxicity which was determined by rotorod test 30 min after the test drug was administered.
[c] Protective index (TD_{50}/ED_{50}).
[d] Date in parentheses are the 95% confidence limits.
[e] Date from Ref. [36].

*5.1.1. Synthesis of 8-(benzyloxy)-2-methylquinoline **1***

To a mixture of 2-methylquinolin-8-ol (8.00 g, 50.3 mmol) and Na_2CO_3 (6.30 g, 59.4 mmol) in ethanol (100 ml), a solution of benzyl bromide (10.1 g, 59.4 mmol) in acetone (20 ml) was added. In the dark, the reaction mixture was stirred at r.t. for 12 h. After filtration, the resulting solution was evaporated. Short column chromatography on silica gel with chloroform and recrystallization from PE–ETOAc (6:1) gave **1** (11.22 g, 90%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.81 (s, 3H, CH_3), 5.46 (s, 2H, $PhCH_2O$), 6.98 (d, 1H, J = 7.60 Hz), 7.26–7.52 (m, 6H), 7.54 (d, 2H, J = 7.20 Hz), 8.03 (d, 1H, J = 8.40 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.82, 70.91, 110.83, 118.72, 123.41, 126.45, 126.88, 127.12, 127.95, 128.67, 136.64, 137.27, 139.54, 154.34, 157.36.

*5.1.2. Synthesis of 8-(benzyloxy)quinoline-2-carbaldehyde **2***

8-(Benzyloxy)-2-methylquinoline (9.20 g, 0.035 mmol) was added to a dry flask under nitrogen, followed by dry dioxane (300 ml) and molecular sieves (4 Å, 60 mg). Selenium dioxide (4.65 g, 0.042 mmol) was added and the reaction was stirred at 95 °C for 12 h and then cooled to room temperature. The reaction mixture was filtered through celite to remove the black residue and molecular sieves. The dioxane was removed by rotary evaporation and the yellow oil was re-dissolved in ethyl acetate (500 ml), washed with brine (100 ml), water (100 ml), saturated potassium carbonate solution (100 ml) and dried ($MgSO_4$). Rotary evaporation of the solvent and recrystallization from PE–ETOAc (4:1) give **2** (9.02 g, 98%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2H, $PhCH_2O$), 7.16 (d, 1H, J = 8.40 Hz), 7.32–7.56 (m, 6H), 8.07 (d, 2H, J = 8.44 Hz), 8.28 (d, 1H, J = 8.56 Hz), 10.32 (s, 1H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.32, 111.88, 118.43, 123.32, 126.71, 126.89, 127.54, 128.33, 128.76, 136.54, 138.43, 139.90, 154.33, 155.78, 193.23.

*5.1.3. Synthesis of diethyl 2-((8-(benzyloxy)quinoline-2-yl) methylene)malonate **3***

To a solution of compound **2** (10.0 g, 93.0 mmol) and diethyl malonate (17.94 g, 112.0 mmol), in toluene (200 mL) was added piperidine (7.95 g, 93 mmol) followed by acetic acid (5.61g, 93 mmol).The reaction mixture was heated to reflux for 20 h and the distillate was collected in a Dean–Stark apparatus. It was cooled to room temperature and concentrated in vacuo. The dark brown residue was dissolved in ethyl acetate and washed successively with $NaHCO_3$ (saturated) and NaCl (saturated), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified via a flash chromatography eluting with hexanes–EtOAc (4:1) to give **3** (15.0 g, 65%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, 3H, J = 7.12 Hz, CH_3), 1.25 (t, 3H, J = 7.12 Hz, CH_3), 4.11 (q, 2H, J = 7.12 Hz, CH_2), 4.23 (q, 2H, J = 7.12 Hz, CH_2), 5.27 (s, 1H, $PhCH_2O$), 6.96 (d, 1H, J = 8.42 Hz), 7.21–7.49 (m, 8H), 7.76 (s, 1H, CH=C), 8.03 (d, 1H, J = 8.44 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.99, 14.11, 61.40, 61.76, 71.01, 110.74, 119.71, 123.34, 127.66, 127.95, 128.62, 129.33, 129.76, 136.65, 139.84, 140.63, 150.09, 154.95, 164.11, 166.14.

*5.1.4. Synthesis of diethyl 2-(8-(benzyloxy)quinoline-2-yl) cyclopropane-1,1-dicarboxylate **4***

To a stirred suspension of sodium hydride (2.12 g, 0.044 mol, 57% in oil dispersion) in dry dimethyl sulfoxide (DMSO) (100 ml) under nitrogen was added of trimethylsulfoxonium iodide (TMSI) (9.66 g, 0.044 mol) in a single portion [24]. After frothing ceased, the grey-white suspension was cooled to 15 °C, and to this mixture was added with stirring a solution of 16.22 g (0.04 mol) of **3** in 25 ml of DMSO in one portion. The stirring was continued for 10 min at 15 °C, overnight at room temperature and 4 h at 50–60 °C. After it was cooled and 400 ml of ice-water was added to it, the mixture was extracted with ether, and the combined ether fractions were washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated to give a pale yellow oil. The residue was purified via a chromatography eluting with hexanes–EtOAc (6:1) to give **4** (15.0 g, 65%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, 3H, J = 7.12 Hz, CH_3), 1.28 (t, 3H, J = 7.12 Hz, CH_3), 1.89–1.93 (m, 1H, Cpr–H), 2.68–2.70 (m, 1H, Cpr–H), 3.30–3.35 (m, 1H, Cpr–H), 3.83 (q, 2H, J = 7.12 Hz, CH_2), 4.23 (q, 2H, J = 7.12 Hz, CH_2), 5.34 (s, 1H, $PhCH_2O$), 7.07 (d, 1H, J = 8.48 Hz), 7.25–7.45 (m, 6H), 7.58 (d, 2H, J = 7.56 Hz), 8.04 (d, 1H, J = 8.44 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.45, 13.01, 19.11, 32.45, 35.94, 59.96, 60.79, 70.05, 110.65, 119.08, 121.35, 125.09, 125.71, 125.98, 126.57, 127.39, 134.96, 136.27, 139.00, 153.17, 153.64, 165.41, 168.80.

*5.1.5. Synthesis of 2-(8-(benzyloxy)quinolin-2-yl)-1-(ethoxycarbonyl) cyclopropanecarboxylic acid **5***

To a solution of compound **4** (10 mmol) in anhydrous ethanol (50 ml) was added 1 N sodium hydroxide (25 ml, 1.1 equiv, 25 mmol), and the resulting mixture was stirred art room temperature for 12 h. EtOH was removed under reduced pressure, water was added to the residue, and the mixture was acidified by means of a saturated $KHSO_4$ and extracted with ethyl acetate (3 × 30 ml). The combined extracts were dried over Na_2SO_4 and evaporated to give product **5** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.51 (t, 3H, J = 7.12 Hz, CH_3), 2.02–2.06 (m, 1H, Cpr–H), 2.43–2.46 (m, 1H, Cpr–H), 3.67 (q, 2H, J = 7.12 Hz, CH_2), 3.74–3.80 (m, 1H, Cpr–H), 5.32 (s, 1H, $PhCH_2O$), 7.11 (d, 1H, J = 7.16 Hz), 7.33–7.55 (m, 6H), 7.54 (d, 2H, J = 7.32 Hz), 8.09 (d, 1H, J = 8.48 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.16, 19.02, 31.95, 37.24, 60.15, 69.95, 111.41, 119.90, 122.65, 126.10, 126.98, 127.47, 127.94, 128.26, 136.00, 137.43, 139.19, 153.55, 154.82, 165.97, 170.63.

*5.1.6. General procedure for the synthesis of compounds **7a–p***

Compound **5** (10 mmol) was dissolved in dry THF (30 mL) and cooled to −15 °C. After the addition of EtOCOCl (11 mmol) and Et_3N (12 mmol), the mixture was stirred for 20 min. A solution of NaN_3 (25 mmol) in H_2O was added and stirred for 1 h at −10 °C. The solution was then diluted with H_2O and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give crude acyl azide. This crude acyl azide could be further purified by a flash column chromatography (PE–EtOAc, 4:1, $R_f = 0.7$). Purified acyl azide was dissolved in toluene (30 mL) and the resulting solution was heated to 75 °C under stirring. After gas evolution had stopped toluene was removed under reduced pressure to afford α-carboethoxy isocyanate **6** as clear oil. This α-carboethoxy isocyanate **6** was directly used in the next step without further purification. Arylhydrazide (10 mmol) was added to a stirred suspension of isocyanate **6** in appropriate solvent (40 mL) at r.t. The solvent was removed under reduced pressure when the reaction was completed (detected by TLC) and the products **7** were purified by a column chromatography.

*5.1.6.1. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-ureidocyclopropanecarboxylate (**7a**).* Mp: 151–153 °C, yield = 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.51 (t, 3H, J = 7.12 Hz, CH_3), 2.28–2.32 (m, 1H, Cpr–CH), 2.58–2.61 (m, 1H, Cpr–CH), 3.53 (q, 2H, J = 7.12 Hz, CH_2), 3.71–3.76 (m, 1H, Cpr–CH), 5.01–5.13 (m, 1H, NH_2), 5.39 (s, 2H, $PhCH_2O$), 5.66 (br s, 1H, NH), 7.07–7.09 (m, 1H), 7.30–7.44 (m, 6H), 7.56 (d, 2H, J = 7.40 Hz), 8.04 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.07, 18.34, 33.41, 38.37, 60.41, 69.98, 111.35, 119.86, 122.49, 126.16, 127.10, 127.52, 127.89, 128.28, 135.89, 137.40, 139.25, 153.58, 154.99, 159.83, 172.02. MS m/z 406.4 ($M^+ + 1$). Anal. Calcd. For $C_{23}H_{23}N_3O_4$: C 68.13, H 5.72, N 10.36. Found: C 68.21, H 5.81, N 10.47.

*5.1.6.2. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-methylureido) cyclopropanecarboxylate (**7b**).* Mp: 134–136 °C, yield = 83%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.50 (t, 3H, J = 7.16 Hz, CH_3), 2.30–2.33 (m, 1H, Cpr–CH), 2.52–2.55 (m, 1H, Cpr–CH), 2.90 (s, 3H, NCH_3), 3.51 (q, 2H, J = 7.16 Hz, CH_2), 3.71–3.75 (m, 1H, Cpr–CH), 4.56 (br s, 1H, NH), 5.34 (br s, 1H, NH), 5.40 (s, 2H, $PhCH_2O$), 7.06–7.08 (m, 1H), 7.30–7.43 (m, 6H,), 7.55 (d, 2H, J = 7.40 Hz), 8.04 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 12.14, 19.05, 25.72, 33.87, 37.49, 59.92, 70.01, 110.32, 118.94, 121.69, 125.40, 126.06, 126.72, 127.35, 127.48, 135.04, 136.26, 139.00, 153.15, 154.18, 158.63, 171.06. MS m/z 420.2 ($M^+ + 1$). Anal. Calcd. For $C_{24}H_{25}N_3O_4$: C 68.72, H 6.01, N 10.02. Found: C 68.81, H 6.07, N 10.07.

*5.1.6.3. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-butylureido)cyclopropanecarboxylate (**7c**).* Mp: 143–145 °C, yield = 78%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.51 (t, 3H, J = 7.16 Hz, CH_3), 0.95 (t, 3H, J = 7.32 Hz, CH_3), 1.25–1.43 (m, 2H, CH_2), 1.53–1.58 (m, 2H, CH_2), 2.28–2.31 (m, 1H, Cpr–CH), 2.51–2.54 (m, 1H, Cpr–CH), 3.29–3.40 (m, 2H, CH_2), 3.53 (q, 2H, J = 7.16 Hz, CH_2), 3.71–3.76 (m, 1H, Cpr–CH), 4.62 (br s, 1H, NH), 4.99 (br s, 1H, NH), 5.39 (s, 2H, $PhCH_2O$), 7.07–7.09 (m, 1H), 7.29–7.44 (m, 6H), 7.56 (d, 1H, J = 7.48 Hz), 8.04 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 12.48, 13.16, 19.55, 29.03, 30.79, 34.26, 37.68, 39.13, 60.23, 70.33, 110.52, 119.27, 122.05, 125.72, 126.42, 127.07, 127.65, 127.83, 135.36, 136.54, 139.27, 153.46, 154.57, 157.18, 170.38. MS m/z 462.3 ($M^+ + 1$). Anal. Calcd. For $C_{27}H_{31}N_3O_4$: C 70.26, H 6.77, N 9.10. Found: C 70.33, H 6.57, N 9.17.

*5.1.6.4. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-isopropylureido) cyclopropanecarboxylate (**7d**).* Mp: 123–125 °C, yield = 80%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.52 (t, 3H, J = 7.12 Hz, CH_3), 1.22 (dd, 6H, J_1 = 16.04 Hz, J_2 = 6.60 Hz, 2× CH_3), 2.26–2.29 (m, 1H, Cpr–CH), 2.50–2.52 (m, 1H, Cpr–CH), 3.46–3.50 (m, 1H, Cpr–CH), 3.72 (q, 2H, J = 7.12 Hz, CH_2), 4.13 (m, 1H, Cpr–CH), 5.52 (br s, 1H, NH), 5.38 (s, 2H, $PhCH_2O$), 5.86 (br s, 1H, NH), 7.07–7.09 (m, 1H), 7.29–7.43 (m, 6H), 7.56 (d, 1H, J = 7.44 Hz), 8.03 (d, 1H, J = 8.48 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.14, 20.11, 22.58, 22.77, 34.94, 38.17, 41.87, 60.86, 70.93, 111.06, 119.92, 122.72, 126.40, 127.09, 127.75, 128.30, 128.49, 136.03, 137.16, 139.87, 154.08, 155.28, 161.95, 170.99. MS m/z 448.5 ($M^+ + 1$). Anal. Calcd. For$C_{26}H_{29}N_3O_4$: C 69.78, H 6.53, N 9.39. Found: C 69.88, H 6.47, N 9.27.

*5.1.6.5. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(1-hydroxybutan-2-yl)ureido)cyclopropanecarboxylate (**7e**).* Mp: 148–150 °C, yield = 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.52 (t, 3H, J = 7.12 Hz, CH_3), 1.02 (t, 3H, J = 7.44 Hz, CH_3), 1.55–1.71 (m, 2H, CH_2), 2.25–2.28 (m, 1H, Cpr–CH), 2.52–2.55 (m, 1H, Cpr–CH), 3.32 (br s, 1H, OH), 3.52–3.54 (m, 2H, CH_2), 3.58–3.63 (m, 1H, CH), 3.70–3.75 (m, 2H, CH_2), 3.90–3.95 (m, 1H, Cpr–CH), 5.33 (br s, 1H, NH), 5.38 (s, 2H, $PhCH_2O$), 5.89 (br s, 1H, NH), 7.08–7.09 (m, 1H), 7.30–7.44 (m, 6H), 7.55 (d, 1H, J = 7.40 Hz), 8.05 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.13, 13.81, 20.24, 19.69, 31.47, 34.89, 38.41, 39.80, 60.89, 71.02, 111.27, 119.95, 122.71, 126.37, 127.05, 127.71, 128.32, 128.48, 136.00, 137.25, 139.99, 154.16, 155.23, 160.83, 171.08. MS m/z 478.4 ($M^+ + 1$). Anal. Calcd. For $C_{27}H_{31}N_3O_5$: C 67.91, H 6.54, N 8.80. Found: C 67.85, H 6.44, N 8.63.

*5.1.6.6. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-cyclohexylureido) cyclopropanecarboxylate (**7f**).* Mp: 163–165 °C, yield = 80%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.41 (t, 3H, J = 7.12 Hz, CH_3), 1.22–1.88 (m, 10H), 2.28–2.31 (m, 1H, Cpr–CH), 2.51–2.54 (m, 1H, Cpr–CH), 3.53 (q, 2H, J = 7.12 Hz, CH_2), 3.71–3.76 (m, 1H, Cpr–CH), 3.73–3.82 (m, 1H), 4.89 (br s, 1H, NH), 5.22 (br s, 1H, NH), 5.29 (s, 2H, $PhCH_2O$), 7.07–7.09 (m, 1H), 7.29–7.44 (m, 6H), 7.92 (d, 1H, J = 7.48 Hz), 8.38 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 12.12, 19.15, 23.66, 24.64, 31.69, 31.91, 33.93, 37.22, 47.54, 52.44, 59.82, 69.99, 110.19, 118.93, 121.67, 125.34, 126.04, 126.68, 127.27, 127.45, 134.95, 136.19, 138.92, 153.11, 154.27, 159.74, 169.98. MS m/z 488.6 ($M^+ + 1$). Anal. Calcd. For $C_{29}H_{33}N_3O_4$: C 71.44, H 6.82, N 8.62. Found: C 71.51, H 6.79, N 8.55.

*5.1.6.7. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-phenylureido)cyclopropanecarboxylate (**7g**).* Mp: 117–120 °C, yield = 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.40 (t, 3H, J = 7.16 Hz, CH_3), 2.31–2.34 (m, 1H, Cpr–CH), 2.51–2.53 (m, 1H, Cpr–CH), 3.47 (q, 2H, J = 7.16 Hz, CH_2), 3.62–3.68 (m, 1H, Cpr–CH), 5.27 (s, 2H, $PhCH_2O$), 6.01 (br s, 1H, NH), 6.62 (br s, 1H, NH), 6.96–7.01 (m, 2H), 7.19–7.29 (m, 7H), 7.33 (d, 1H, J = 8.44 Hz), 7.46 (d, 2H, J = 7.44 Hz), 7.53 (d, 2H, J = 8.00 Hz), 7.93 (d, 1H, J = 8.44 Hz). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 12.06, 19.48, 34.15, 38.51, 60.19, 69.90, 110.13, 118.88, 119.04, 121.60, 123.05, 125.51, 126.05, 126.71, 127.30, 127.45, 127.85, 135.12, 136.08, 137.16, 138.87, 153.06, 153.75, 158.06, 171.23. MS m/z 482.6 ($M^+ + 1$). Anal. Calcd. For $C_{29}H_{27}N_3O_4$: C 72.33, H 5.65, N 8.73. Found: C 72.45, H 5.54, N 8.66.

*5.1.6.8. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-benzylureido)cyclopropanecarboxylate (**7h**).* Mp: 101–103 °C, yield = 88%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.33 (t, 3H, J = 7.16 Hz, CH_3), 2.21–2.25 (m, 1H, Cpr–CH), 2.43–2.46 (m, 1H, Cpr–CH), 3.39 (q, 2H, J = 7.16 Hz, CH_2), 3.52–3.60 (m, 1H, Cpr–CH), 4.42 (s, 2H, $PhCH_2$), 5.23 (s, 2H, $PhCH_2O$), 6.44 (br s, 1H, NH), 6.91–6.95 (m, 1H), 7.06–7.24 (m, 11H), 7.41 (d, 2H, J = 7.24 Hz), 7.87 (d, 1H, J = 8.48 Hz), 8.41 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.14, 20.38, 34.91, 38.68, 44.15, 60.98, 70.93, 111.16, 119.96, 122.72, 126.50, 127.06, 127.34, 127.77, 128.35, 128.45, 128.52, 128.69, 136.11, 137.19, 138.35, 139.94, 154.12, 155.09, 158.12, 170.90. MS m/z 496.6 ($M^+ + 1$). Anal.

Calcd. For $C_{30}H_{29}N_3O_4$: C 72.71, H 5.90, N 8.48. Found: C 72.85, H 5.97, N 8.53.

*5.1.6.9. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-p-tolylureido) cyclopropanecarboxylate (**7i**).* Mp: 159–160 °C, yield = 80%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.52 (t, 3H, J = 7.16 Hz, CH_3), 2.32 (s, 3H, CH_3), 2.40–2.44 (m, 1H, Cpr–CH), 2.61–2.64 (m, 1H, Cpr–CH), 3.57 (q, 2H, J = 7.16 Hz, CH_2), 3.75–3.79 (m, 1H, Cpr–CH), 5.39 (s, 2H, $PhCH_2O$), 7.07–7.14 (m, 2H), 6.15 (s, 1H, NH), 7.30–7.39 (m, 6H), 7.45 (d, 1H, J = 8.44 Hz), 7.50 (d, 2H, J = 8.16 Hz), 7.56 (d, 2H, J = 7.56 Hz), 8.05 (d, 1H, J = 8.48 Hz), 8.27 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 11.48, 20.21, 20.93, 35.40, 39.23, 61.25, 70.98, 111.17, 115.25, 119.98, 126.60, 127.23, 127.42, 127.84, 128.39, 128.56, 129.44, 133.60, 135.82, 136.22, 137.14, 139.91, 154.12, 154.93, 155.97, 171.22. MS m/z 496.6 (M^+ + 1). Anal. Calcd. For $C_{30}H_{29}N_3O_4$: C 72.71, H 5.90, N 8.48. Found: C 72.62, H 6.04, N 8.55.

*5.1.6.10. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-methoxyphenyl)ureido)cyclopropanecarboxylate (**7j**).* Mp: 124–126 °C, yield = 78.7%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.45 (t, 3H, J = 7.16 Hz, CH_3), 2.33–2.37 (m, 1H, Cpr–CH), 2.54–2.56 (m, 1H, Cpr–CH), 3.50 (q, 2H, J = 7.16 Hz, CH_2), 3.68–3.73 (m, 1H, Cpr–CH), 3.75 (s, 3H, OCH_3), 5.33 (s, 2H, $PhCH_2O$), 6.72 (br s, 1H, NH), 6.80 (d, 2H, J = 8.96 Hz), 7.00–7.50 (m, 11H), 7.99 (d, 1H, J = 8.44 Hz), 8.66 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 11.00, 18.42, 32.91, 37.40, 53.36, 59.09, 68.92, 109.19, 111.94, 117.83, 119.64, 120.60, 124.40, 124.94, 125.62, 126.26, 126.39, 129.33, 134.01, 135.10, 137.89, 152.07, 152.81, 154.12, 159.74, 171.32. MS m/z 482.6 (M^+ + 1). Anal. Calcd. For $C_{30}H_{29}N_3O_4$: C 72.71, H 5.90, N 8.48. Found: C 72.62, H 6.04, N 8.53.

*5.1.6.11. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-nitrophenyl) ureido)cyclopropanecarboxylate (**7k**).* Mp: 114–116 °C, yield = 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.62 (t, 3H, J = 7.12 Hz, CH_3), 1.90–1.94 (m, 1H, CH), 2.73–2.76 (m, 1H, CH), 3.29–3.33 (q, 2H, J = 7.16 Hz, CH_2), 3.75–3.79 (m, 1H, CH), 5.23 (s, 2H, $PhCH_2O$), 6.33 (br s, 1H, NH), 7.07–7.14 (m, 2H), 7.30–7.39 (m, 6H), 7.45 (d, 1H, J = 8.44 Hz), 7.50 (d, 2H, J = 8.16 Hz), 7.56 (d, 2H, J = 7.56 Hz), 8.05 (d, 1H, J = 8.48 Hz), 8.64 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 12.10, 19.35, 31.83, 37.66, 60.04, 69.88, 109.45, 112.43, 117.76, 119.43, 121.64, 124.88, 124.96, 125.82, 126.72, 126.98, 130.43, 134.87, 136.32, 137.92, 143.44, 152.34, 152.98, 156.72, 172.33. MS m/z 527.6 (M^+ + 1). Anal. Calcd. For $C_{29}H_{26}N_4O_6$: C 66.15, H 4.98, N 10.64. Found: C 66.22, H 4.87, N 10.78.

*5.1.6.12. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-fluorophenyl) ureido)cyclopropanecarboxylate (**7l**).* Mp: 159–160 °C, yield = 82%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.53 (t, 3H, J = 7.12 Hz, CH_3), 2.39–2.42 (m, 1H, Cpr–CH), 2.58–2.61 (m, 1H, Cpr–CH), 3.56 (q, 2H, J = 7.12 Hz, CH_2), 3.74–3.80 (m, 1H, Cpr–CH), 5.23 (s, 2H, $PhCH_2O$), 7.03–7.11 (m, 3H), 6.55 (br s, 1H, NH), 7.30–7.59 (m, 10H), 8.08 (d, 1H, J = 8.48 Hz), 8.27 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 11.98, 18.65, 31.88, 37.44, 59.34, 70.68, 108.48, 113.66, 117.88, 119.33, 122.34, 124.76, 125.43, 125.88, 126.74, 126.88, 131.56, 133.46, 136.77, 137.99, 144.46, 153.41, 156.66, 161.54, 172.56. MS m/z 500.6 (M^+ + 1). Anal. Calcd. For $C_{29}H_{26}FN_3O_4$: C 69.73, H 5.25, N 8.41. Found: C 69.93, H 5.14, N 8.55.

*5.1.6.13. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-(trifluoromethyl)phenyl)ureido)cyclopropanecarboxylate (**7m**).* Mp: 133–135 °C, yield = 78%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.54 (t, 3H, J = 7.12 Hz, CH_3), 1.88–1.92 (m, 1H, Cpr–CH), 2.75–2.78 (m, 1H, Cpr–CH), 3.38 (q, 2H, J = 7.12 Hz, CH_2), 3.75–3.79 (m, 1H, Cpr–CH), 5.20 (s, 2H, $PhCH_2O$), 6.43 (br s, 1H, NH), 7.08–7.12 (m, 2H), 7.11–7.55 (m, 11H), 8.05 (d, 1H, J = 8.56 Hz), 8.62 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.22, 20.35, 20.96, 35.38, 39.43, 61.62, 71.04, 111.74, 115.89, 119.88, 124.34, 126.76, 127.73, 127.79, 127.84, 128.36, 128.66, 129.34, 133.50, 135.87, 136.80, 137.34, 139.98, 154.22, 154.98, 165.45, 171.71. MS m/z 550.5 (M^+ + 1). Anal. Calcd. For $C_{30}H_{26}F_3N_3O_4$: C 65.57, H 4.77, N 7.65. Found: C 65.42, H 4.67, N 7.43.

*5.1.6.14. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-chlorophenyl) ureido)cyclopropanecarboxylate (**7n**).* Mp: 118–120 °C, yield = 80%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.53 (t, 3H, J = 7.12 Hz, CH_3), 2.39–2.42 (m, 1H, Cpr–CH), 2.58–2.61 (m, 1H, Cpr–CH), 3.58 (q, 2H, J = 7.12 Hz, CH_2), 3.76–3.80 (m, 1H, Cpr–CH), 5.39 (s, 2H, $PhCH_2O$), 6.71 (br s, 1H, NH), 7.09–7.11 (m, 2H), 7.26–7.58 (m, 11H), 8.08 (d, 1H, J = 8.44 Hz), 8.55 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.11, 20.64, 20.93, 35.11, 39.69, 61.33, 70.97, 111.11, 116.21, 119.92, 121.31, 122.64, 126.63, 127.18, 127.83, 128.39, 128.94, 136.24, 136.83, 137.08, 139.89, 144.96, 154.10, 154.73, 156.71, 171.30. MS m/z 516.5 (M^+ + 1). Anal. Calcd. For $C_{29}H_{26}ClN_3O_4$: C 67.50, H 5.08, N 8.41. Found: C 67.62, H 5.16, N 8.55.

*5.1.6.15. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(4-bromophenyl) ureido)cyclopropanecarboxylate (**7o**).* Mp: 105–107 °C, yield = 88%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.42 (t, 3H, J = 7.16 Hz, CH_3), 2.20–2.46 (m, 1H, Cpr–CH), 2.31–2.49 (m, 1H, Cpr–CH), 3.46 (q, 2H, J = 7.16 Hz, CH_2), 3.63–3.69 (m, 1H, Cpr–CH), 5.26 (s, 2H, $PhCH_2O$), 6.26 (br s, 1H, NH), 6.39–6.41 (m, 2H), 6.89–7.46 (m, 11H), 7.96 (d, 1H, J = 8.46 Hz), 8.74 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.70, 18.12, 34.21, 38.39, 60.31, 69.88, 109.94, 115.63, 118.85, 120.60, 121.57, 125.62, 126.77, 127.79, 129.90, 130.77, 135.25, 135.93, 136.30, 138.72, 144.48, 152.98, 153.68, 156.66, 170.10. MS m/z 561.4 (M^+ + 1). Anal. Calcd. For $C_{30}H_{29}N_3O_4$: C 62.15, H 4.68, N 7.50. Found: C 62.23, H 4.82, N 7.38.

*5.1.6.16. Ethyl 2-(8-(benzyloxy)quinolin-2-yl)-1-(3-(3,5-dichlorophenyl)ureido)cyclopropanecarboxylate (**7p**).* Mp: 131–133 °C, yield = 82%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.44 (t, 3H, J = 7.12 Hz, CH_3), 2.18–2.34 (m, 1H, Cpr–CH), 2.33–2.51 (m, 1H, Cpr–CH), 3.48 (q, 2H, J = 7.12 Hz, CH_2), 3.72–3.75 (m, 1H, Cpr–CH), 5.23 (s, 2H, $PhCH_2O$), 6.05 (br s, 1H, NH), 6.43–6.51 (m, 2H), 6.84–7.55 (m, 10H), 8.05 (d, 1H, J = 8.56 Hz), 8.43 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 Hz), δ 13.88, 20.56, 21.03, 35.87, 39.41, 61.44, 70.98, 110.91, 115.46, 120.28, 126.74, 127.53, 127.76, 127.82, 128.43, 128.76, 129.42, 133.61, 134.84, 136.76, 137.24, 140.94, 154.33, 154.87, 166.91, 171.62. MS m/z 551.4 (M^+ + 1). Anal. Calcd. For $C_{29}H_{25}Cl_2N_3O_4$: C 63.28, H 4.58, N 7.63. Found: C 63.36, H 4.74, N 7.47.

*5.1.7. General procedure for the synthesis of compounds **8a–p***

To a solution of compound **7** (1 mmol) and EtOH (10 mL) was added sodium (1.2 mmol), and the reaction mixture was stirred at room temperature for 2 h. EtOH was removed under reduced pressure. Ethyl acetate and water were added to the residue. The ethyl acetate layer was dried over anhydrous Na_2SO_4, concentrated, and recrystallized to give compound **8**.

*5.1.7.1. 1-(8-(Benzyloxy)quinolin-2-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione (**8a**).* Mp: 159–160 °C, yield = 92%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.72–1.75 (m, 1H, Cpr–H), 2.05–2.05 (m, 1H, Cpr–H), 2.83–2.85 (m, 1H, Cpr–H), 5.32 (s, 2H, $PhCH_2O$), 7.13 (d, 1H, J = 6.92 Hz), 7.33–7.54 (m, 8H), 8.05 (d, 1H, J = 8.32 Hz), 8.23 (br s, 1H, NH), 10.54 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.12, 36.23, 37.76, 69.54, 110.12, 119.83, 121.45, 125.37, 127.65, 127.71, 127.76, 128.34, 134.69, 137.43, 139.06, 153.51, 157.05, 158.3, 171.12. MS m/z 360.4 (M^+ + 1). Anal. Calcd. For $C_{21}H_{17}N_3O_3$: C 70.18, H 4.77, N 11.69. Found: C 69.91, H 4.82, N 11.43.

*5.1.7.2. 1-(8-(Benzyloxy)quinolin-2-yl)-6-methyl-4,6-diazaspiro[2,4] heptane-5,7-dione (**8b**).* Mp: 142–144 °C, yield = 95%. ^{1}H NMR

(DMSO-d_6, 400 MHz), δ 1.68–1.71 (m, 1H, Cpr–H), 2.06–2.08 (m, 1H, Cpr–H), 2.79–2.82 (m, 1H, Cpr–H), 3.03 (s, 3H, CH_3), 5.35 (s, 2H, $PhCH_2O$), 7.08 (d, 1H, J = 7.12 Hz), 7.36–7.58 (m, 8H), 8.12 (d, 1H, J = 8.24 Hz), 8.46 (br s, 1H, NH), 10.21 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.56, 24.35, 36.87, 37.16, 70.44, 110.23, 118.32, 121.73, 125.97, 127.32, 127.61, 127.78, 129.05, 134.27, 137.81, 139.60, 154.42, 157.15, 157.74, 171.45. MS m/z 374.1 (M^+ + 1). Anal. Calcd. For $C_{22}H_{19}N_3O_3$: C 70.76, H 5.13, N 11.25. Found: C 70.51, H 4.97, N 11.04.

*5.1.7.3. 1-(8-(Benzyloxy)quinolin-2-yl)-6-butyl-4,6-diazaspiro[2,4] heptane-5,7-dione (**8c**).* Mp: 151–153 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 0.89 (t, 3H, J = 7.28 Hz, CH_3), 1.31–1.46 (m, 4H), 1.71–1.73 (m, 1H, Cpr–H), 2.09–2.11 (m, 1H, Cpr–H), 2.85–2.89 (m, 1H, Cpr–H), 3.09–3.22 (m, 2H, CH_2), 5.34 (s, 2H, $PhCH_2O$), 7.15 (d, 1H, J = 7.12 Hz), 7.32–7.55 (m, 8H), 8.05 (d, 1H, J = 8.44 Hz), 8.76 (br s, 1H, NH), 10.77 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 13.22, 19.14, 19.35, 29,87, 36.28, 36.71, 37.82, 69.44, 111.72, 118.53, 122.04, 125.47, 127.26, 127.53, 127.80, 129.33, 134.71, 136.88, 140.50, 155.22, 157.55, 158.76, 170.33. MS m/z 416.1 (M^+ + 1). Anal. Calcd. For $C_{25}H_{25}N_3O_3$: C 72.27, H 6.06, N 10.11. Found: C 72.34, H 6.22, N 10.08.

*5.1.7.4. 1-(8-(Benzyloxy)quinolin-2-yl)-6-isopropyl-4,6-diazaspiro [2,4]heptane-5,7-dione (**8d**).* Mp: 137–139 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.10 (d, 6H, J = 7.28 Hz, J = 17.32 Hz, 2× CH_3), 1.70–1.72 (m, 1H, Cpr–H), 2.07–2.09 (m, 1H, Cpr–H), 2.85–2.88 (m, 1H, Cpr–H), 3.86–3.89 (m, 1H, CH), 5.34 (s, 2H, $PhCH_2O$), 7.15 (d, 1H, J = 7.12 Hz), 7.32–7.55 (m, 8H), 8.03 (d, 1H, J = 8.44 Hz), 8.69 (br s, 1H, NH), 10.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.06, 22.68, 22.83, 35.93, 37.55, 40.06, 69.90, 110.28, 119.54, 121.98, 125.50, 127.53, 127.63, 127.74, 128.33, 134.34, 137.32, 139.05, 153.46, 157.80, 158.77, 170.16. MS m/z 402.1 (M^+ + 1). Anal. Calcd. For $C_{24}H_{23}N_3O_3$: C 71.80, H 5.77, N 10.47. Found: C 71.66, H 5.80, N 10.29.

*5.1.7.5. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(1-hydroxybutan-2-yl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8e**).* Mp: 175–177 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 0.90 (m, 3H, CH_3), 1.75–1.78 (m, 1H, Cpr–CH), 1.88–1.92 (m, 2H, CH_2), 2.12–2.15 (m, 1H, Cpr–CH), 2.88–2.30 (m, 1H, Cpr–CH), 3.75–3.92 (m, 3H, CH_2, CH), 4.06 (br s, 1H, OH), 5.34 (s, 2H, $PhCH_2O$), 7.13 (d, 1H, J = 7.88 Hz), 7.42–7.67 (m, 8H), 8.13 (d, 1H, J = 8.42 Hz). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 11.23, 19.72, 21.24, 36.65, 37.81, 56.34, 63.27, 71.26, 110.27, 119.99, 122.72, 126.34, 127.05, 127.71, 128.32, 128.48, 136.00, 137.25, 139.99, 154.16, 155.23, 159.83, 174.08. MS m/z 478.4 (M^+ + 1). Anal. Calcd. For $C_{27}H_{31}N_3O_5$: C 67.91, H 6.54, N 8.80. Found: C 67.85, H 6.44, N 8.63.

*5.1.7.6. 1-(8-(Benzyloxy)quinolin-2-yl)-6-cyclohexyl-4,6-diazaspiro [2,4]heptane-5,7-dione (**8f**).* Mp: 168–170 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.15–1.72 (m, 10H), 2.08–2.11 (m, 1H, Cpr–H), 2.82–2.84 (m, 1H, Cpr–H), 3.41–3.43 (m, 1H, CH), 3.63–3.65 (m, 1H, Cpr–H), 5.35 (s, 2H, $PhCH_2O$), 7.16 (d, 1H, J = 7.68 Hz), 7.33–7.55 (m, 8H), 8.05 (d, 1H, J = 8.56 Hz). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 13.66, 19.69, 24.16, 31.40, 32.57, 36.25, 38.43, 69.92, 110.31, 119.54, 121.98, 125.59, 127.51, 127.77, 127.85, 128.33, 134.47, 137.29, 139.08, 153.47, 157.46, 158.88, 171.04. MS m/z 442.1 (M^+ + 1). Anal. Calcd. For $C_{27}H_{27}N_3O_3$: C 73.45, H 6.16, N 9.52. Found: C 73.57, H 6.31, N 9.68.

*5.1.7.7. 1-(8-(Benzyloxy)quinolin-2-yl)-6-phenyl-4,6-diazaspiro[2,4] heptane-5,7-dione (**8g**).* Mp: 130–132 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.90–1.92 (m, 1H, Cpr–H), 2.32–2.34 (m, 1H, Cpr–H), 3.19–3.23 (m, 1H, Cpr–H), 5.36 (s, 2H, $PhCH_2O$), 7.03–7.07 (m, 1H), 7.19 (d, 1H, J = 7.24 Hz), 7.30–7.63 (m, 12H), 8.17 (d, 1H, J = 8.56 Hz), 12.33 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.40, 36.14, 37.89, 69.99, 110.88, 119.21, 119.71, 122.40, 123.13, 126.05, 127.48, 127.63, 127.89, 128.35, 128.76, 135.24, 137.25, 138.95, 139.05, 153.43, 156.13, 158.98, 170.55. MS m/z 436.3 (M^+ + 1). Anal. Calcd. For $C_{27}H_{21}N_3O_3$: C 74.47, H 4.86, N 9.65. Found: C 74.58, H 4.93, N 9.46.

*5.1.7.8. 6-Benzyl-1-(8-(benzyloxy)quinolin-2-yl)-4,6-diazaspiro[2.4] heptane-5,7-dione (**8h**).* Mp: 141–143 °C, yield = 92%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.74–1.77 (m, 1H, Cpr–H), 2.13–2.14 (m, 1H, Cpr–H), 2.88–2.92 (m, 1H, Cpr–H), 4.37 (s, 2H, $PhCH_2$), 5.34 (s, 2H, $PhCH_2O$), 7.16 (d, 1H, J = 7.24 Hz), 7.24–7.55 (m, 13H), 8.04 (d, 1H, J = 8.60 Hz), 11.48 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.10, 36.27, 37.48, 42.53, 69.94, 110.25, 119.56, 122.04, 125.59, 126.69, 127.14, 127.21, 127.67, 127.70, 127.76, 128.22, 128.30, 134.44, 137.23, 137.36, 139.04, 139.59, 153.45, 159.57, 171.34. MS m/z 450.6 (M^+ + 1). Anal. Calcd. For $C_{28}H_{23}N_3O_3$: C 74.82, H 5.16, N 9.35. Found: C 74.93, H 5.37, N 9.44.

*5.1.7.9. 1-(8-(Benzyloxy)quinolin-2-yl)-6-p-tolyl-4,6-diazaspiro[2,4] heptane-5,7-dione (**8i**).* Mp: 171–173 °C, yield = 95%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.88–1.90 (m, 1H, Cpr–H), 2.26 (s, 3H, CH_3), 2.30–2.32 (m, 1H, Cpr–H), 3.16–3.20 (m, 1H, Cpr–H), 5.36 (s, 2H, $PhCH_2O$), 7.12 (d, 1H, J = 8.28 Hz), 7.13–7.55 (m, 12H), 8.16 (d, 1H, J = 8.56 Hz), 12.27 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.35, 20.41, 36.05, 37.79, 70.01, 110.88, 119.13, 119.71, 122.42, 125.97, 127.47, 127.61, 127.88, 128.34, 129.13, 131.86, 135.12, 136.56, 137.30, 139.09, 153.49, 156.30, 159.87, 170.28. MS m/z 450.5 (M^+ + 1). Anal. Calcd. For $C_{28}H_{23}N_3O_3$: C 74.82, H 5.16, N 9.35. Found: C 74.79, H 5.23, N 9.29.

*5.1.7.10. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-methoxyphenyl)-4,6-diazaspiro[2.4]heptane-5,7-dione (**8j**).* Mp: 137–139 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.88–1.91 (m, 1H, Cpr–H), 2.30–2.33 (m, 1H, Cpr–H), 3.18–3.22 (m, 1H, Cpr–H), 3.72 (s, 3H, OCH_3), 5.36 (s, 2H, $PhCH_2O$), 6.89 (d, 2H, J = 8.96 Hz), 7.18–7.55 (m, 11H), 8.16 (d, 1H, J = 8.56 Hz), 12.04 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.31, 35.99, 37.77, 55.08, 70.00, 110.86, 113.82, 119.71, 120.70, 122.38, 126.01, 127.48, 127.63, 127.88, 128.35, 132.22, 135.19, 137.27, 139.08, 153.46, 155.05, 156.22, 158.79, 170.62. MS m/z 466.5 (M^+ + 1). Anal. Calcd. For $C_{28}H_{23}N_3O_4$: C 72.24, H 4.98, N 9.03. Found: C 72.39, H 5.02, N 9.17.

*5.1.7.11. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-nitrophenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8k**).* Mp: 125–127 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.90–1.92 (m, 1H, Cpr–H), 2.31–2.33 (m, 1H, Cpr–H), 3.19–3.21 (m, 1H, Cpr–H), 5.34 (s, 2H, $PhCH_2O$), 7.09 (d, 1H, J = 8.82 Hz), 7.18–7.55 (m, 12H), 8.16 (d, 1H, J = 8.56 Hz), 12.22 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.26, 36.95, 37.82, 69.98, 110.84, 113.73, 119.53, 121.73, 124.66, 126.06, 127.38, 127.45, 127.79, 128.48, 132.41, 135.21, 139.95, 146.34, 153.46, 155.25, 156.53, 159.32, 171.43. MS m/z 481.3 (M^+ + 1). Anal. Calcd. For $C_{27}H_{20}N_4O_5$: C 67.49, H 4.20, N 11.66. Found: C 67.61, H 4.13, N 11.59.

*5.1.7.12. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-fluorophenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8l**).* Mp: 165–167 °C, yield = 93%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.91–1.93 (m, 1H, Cpr–H), 2.30–2.32 (m, 1H, Cpr–H), 3.20–3.22 (m, 1H, Cpr–H), 5.35 (s, 2H, $PhCH_2O$), 7.07 (d, 1H, J = 8.84 Hz), 7.21–7.57 (m, 12H), 8.14 (d, 1H, J = 8.44 Hz), 11.68 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 20.03, 36.62, 38.38, 71.05, 111.08, 116.07, 119.72, 121.68, 122.44, 126.89, 127.36, 127.94, 128.47, 128.52, 134.40, 136.32, 137.62, 139.72, 154.23, 154.22, 158.50, 160.64, 171.95. MS m/z 482.6 (M^+ + 1). Anal. Calcd. For $C_{27}H_{20}FN_3O_3$: C 71.51, H 4.45, N 9.27. Found: C 71.43, H 4.54, N 9.39.

*5.1.7.13. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-(trifluoromethyl)phenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8m**).* Mp: 165–167 °C, yield = 93%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.89–1.91 (m, 1H, Cpr–H), 2.28–2.30 (m, 1H, Cpr–H), 3.21–3.23 (m, 1H, Cpr–H), 5.36 (s, 2H, $PhCH_2O$), 7.17 (d, 1H, J = 8.82 Hz), 7.14–7.49 (m, 12H), 8.16 (d, 1H, J = 8.36 Hz), 11.77 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.33, 37.12, 37.89, 70.87, 110.45, 113.74, 119.60, 120.96, 122.23, 126.34, 127.57, 127.14, 127.43, 128.13, 132.25, 135.18, 137.64, 139.34, 153.19, 155.05, 156.82, 158.09, 170.22. MS *m/z* 482.6 ($M^+ + 1$). Anal. Calcd. For $C_{28}H_{20}F_3N_3O_3$: C 66.80, H 4.00, N 8.35. Found: C 66.73, H 4.14, N 8.47.

*5.1.7.14. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-chlorophenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8n**).* Mp: 133–135 °C, yield = 93%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.90–1.93 (m, 1H, Cpr–H), 2.30–2.32 (m, 1H, Cpr–H), 3.24–3.26 (m, 1H, Cpr–H), 5.34 (s, 2H, $PhCH_2O$), 7.21 (d, 1H, J = 8.84 Hz), 7.26–7.57 (m, 12H), 8.22 (d, 1H, J = 8.56 Hz), 11.43 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.14, 35.41, 37.80, 70.35, 110.98, 112.42, 119.65, 120.32, 122.78, 126.66, 127.65, 127.83, 127.89, 128.14, 132.12, 135.67, 137.31, 139.88, 153.65, 154.12, 156.44, 157.70, 170.21. MS *m/z* 470.4 ($M^+ + 1$). Anal. Calcd. For $C_{27}H_{20}ClN_3O_3$: C 69.01, H 4.29, N 8.94. Found: C 69.23, H 4.18, N 9.02.

*5.1.7.15. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(4-bromophenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8o**).* Mp: 128–130 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.89–1.91 (m, 1H, Cpr–H), 2.28–2.30 (m, 1H, Cpr–H), 3.22–3.24 (m, 1H, Cpr–H), 5.33 (s, 2H, $PhCH_2O$), 7.24 (d, 1H, J = 8.88 Hz), 7.28–7.59 (m, 12H), 8.24 (d, 1H, J = 8.72 Hz), 11.21 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 19.39, 35.05, 38.70, 69.87, 110.11, 115.81, 118.92, 120.83, 121.89, 125.76, 126.48, 127.44, 127.90, 130.49, 135.68, 135.01, 136.48, 138.78, 144.11, 152.11, 153.85, 157.62, 170.87. MS *m/z* 515.4 ($M^+ + 1$). Anal. Calcd. For $C_{27}H_{20}BrN_3O_3$: C 63.05, H 3.92, N 8.17. Found: C 63.12, H 4.13, N 8.21.

*5.1.7.16. 1-(8-(Benzyloxy)quinolin-2-yl)-6-(3,5-dimethylphenyl)-4,6-diazaspiro[2,4]heptane-5,7-dione (**8p**).* Mp: 114–116 °C, yield = 90%. ^{1}H NMR (DMSO-d_6, 400 MHz), δ 1.88–1.90 (m, 1H, Cpr–H), 2.26–2.28 (m, 1H, Cpr–H), 3.21–3.23 (m, 1H, Cpr–H), 5.36 (s, 2H, $PhCH_2O$), 7.28 (d, 1H, J = 8.68 Hz), 7.31–7.60 (m, 12H), 8.28 (d, 1H, J = 8.56 Hz), 11.13 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 Hz), δ 20.58, 35.45, 39.33, 70.25, 111.36, 116.81, 119.11, 121.92, 122.44, 126.32, 127.79, 127.97, 128.84, 129.30, 136.57, 136.82, 137.72, 139.27, 144.10, 154.69, 154.35, 157.32, 170.30. MS *m/z* 505.3 ($M^+ + 1$). Anal. Calcd. For $C_{27}H_{19}Cl_2N_3O_3$: C 64.30, H 3.80, N 8.33. Found: C 64.42, H 3.76, N 8.24.

5.2. Anticonvulsant screening

Male Kunming mice (20 ± 2.0 g) were used as experimental animals in this study. Animals of the same age and weight have been selected in order to minimize biological. The animals were approved by the Animal Care Committee of Wuhan University. All the animals were purchased from Wuhan University Laboratory Animal Center (Wuhan China). The tested compounds were injected intraperitoneally to mice as a suspension in 0.5% methylcellulose at dose of 30, 100, and 300 mg/kg to one to four mice. The anticonvulsant activity of the tested compounds were evaluated by two models namely, MES and *sc*PTZ models. Phenytoin and ethosuximide were used as the standard drugs for the comparison. The neurological toxicity was determined in the rotorod test. Procedures employed for evaluation of anticonvulsant activity and neurotoxicity were described elsewhere [28,29].

5.2.1. MES-maximal electroshock seizure pattern test

This activity was tested according to the method of Swinyard [30]. In experiments with mice, a 60-Hz current of 50-mA intensity was applied through corneal electrodes for a 0.25 s duration; with rats, seizure activity was induced by delivery of a 150-mA current (0.2 s) to the cornea. Both procedures caused immediate hindlimb tonic extension. After 0.5 h and 4.0 h of drug administration, electroshocks were via corneal electrodes. Absence of tonic extension suggests that the tested compound was considered as positive criteria.

5.2.2. Pentylenetetrazole (PTZ) induced seizure test

For the chemically induced convulsant test according to the method of Vamecq et al. [31], pentylenetetrazole was dissolved in sufficient 0.9% saline to allow subcutaneous injections to mice or rat. Standard drug in this model was ethosuximide. After 0.5 h and 4.0 h of drug administration the failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) is defined as protection.

5.2.3. Neurotoxicity screening

Minimal motor impairment was measured in mice or rats by using standardized rotorod test [32]. The mouse was placed on a 1 in. diameter knurled plastic rod rotating at 6 rpm. Trained animals were given an ip injection of the test compounds in doses of 30, 100, and 300 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the four trials.

5.2.4. Quantification studies

Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}), that is, the dose of drug required to produce the biological responses in 50% of animals, neurotoxicity was expressed as the median toxic dose (TD_{50}). For determination of the ED_{50} and TD_{50}, groups of 10 mice were given a range of ip doses of the test drug until at least three points were established in the range of 10–90% seizure protection or minimal observed neurotoxicity [33]. From the plot of these data, the respective ED_{50} and TD_{50} values, 95% confidence intervals, slope of the regression line, and standard error of the slope were calculated by means of a computer program written at NINDS, NIH.

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