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Design and Synthesis of Pyrazolyl Thiosemicarbazones as New Anticonvulsants

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A series of pyrazolyl thiosemicarbazone derivatives were synthesized and evaluated for their anticonvulsant activity using the maximal electroshock (MES) method. Interestingly, all compounds prepared showed long duration of protection effect in the MES screens. Among them, compound **5b** was considered as the most promising one with an ED_{50} value of 47.3 mg/kg, and a PI value of 4.8, which was superior to phenobarbital and valproate in the aspect of safety. Furthermore, compound **5b** showed protection against seizures induced by pentylenetetrazole suggesting that compound **5b** may exert anticonvulsant activity through GABA-mediated mechanisms.

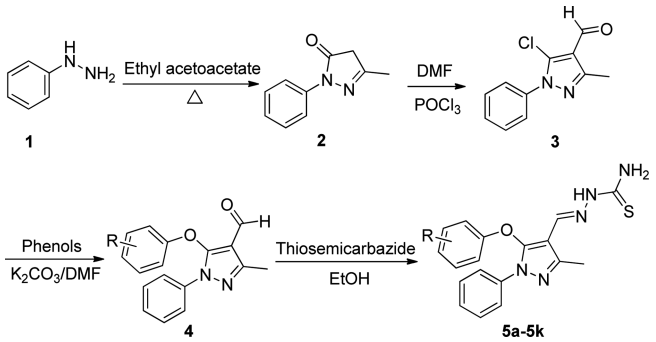
Key Words : Pyrazole, Thiosemicarbazone, Anticonvulsant, Maximal electroshock

Introduction

Epilepsy is a syndrome of cerebral disorders characterized by excessive temporary neuronal discharge resulting in recurrent unprovoked seizures.[1,2] Approximate 1% of the world population at any one time (about 50 million people worldwide) is afflicted with this serious neurological disorder.[3] The conventional antiepileptic drugs (AEDs) like phenytoin, carbamazepine, valproic acid and barbiturates, though widely prescribed, exhibited unfavorable side effects such as drowsiness, ataxia, and hepatotoxicity.[4-6] Recently, several new AEDs, such as lamotrigine, oxcarbazepine, felbamate, rufinamide, have been approved with an improved efficacy and lower toxicity. However, it is roughly estimated that up to 28-30% of patients with epilepsy have inadequate control of seizures with these currently available AEDs.[7] All of these facts warrant the search for new anticonvulsant drugs.

Thiosemicarbazone derivatives are of special importance because of their versatile biological and pharmacological activities. Thiosemicarbazone derivatives have been found abroad application in drug development for the treatment of cancer, bacterial infection, as well as analgesic and anti-allergic agents.[8-10] Recently thiosemicarbazones have emerged as structurally novel anticonvulsants.[11-14]

Pyrazoles are important double nitrogen five-membered heterocyclic compounds. Several pyrazole derivatives have been reported possessing important pharmacological activities which now are useful materials in drug research. In 1998, Unverferth *et al.*[15] described a series of 3-aminopyrroles as anticonvulsants, in which an interaction between pyrrole and voltage-dependent sodium channel were established. As a backup, 3-amino- and 5-aminopyrazoles were also prepared. In these compounds, the strong anticonvulsant effects were displayed *via* blocking sodium channels.[16] Recent years, numbers of molecules containing pyrazole have been synthesized as potential anticonvulsant agents.[17-20] As hydrogen bonding forming functional group, pyrazole has become an important pharmacophore for anticonvulsants.[21]



Scheme 1. The synthesis route of the target compounds (**5a-5k**).

Based on the above reasons, in the present work we planned to attach the thiosemicarbazide to the substituted pyrazole moiety expecting to have a synergistic effect in dealing with epilepsy. A series of pyrazolyl thiosemicarbazone derivatives were synthesized and evaluated for anticonvulsant activity. Their structures were confirmed by IR, NMR, and mass spectra. Their anticonvulsant activities and neurotoxicities were screened using the maximal electroshock (MES)-induced seizure model and the rotarod assay in mice, respectively. Some of the target compounds with better activity were quantified in terms of their anticonvulsant activity, and the compound **5b** was tested in pentylenetetrazole (PTZ) induced seizure test.

Experimental

Chemistry. Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on IRPrestige-21. ^{1}H NMR and ^{13}C NMR spectra were measured on an AV-300 (Bruker, Switzerland), and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Aldrich Chemical Corporation.

Procedures for Synthesis of Compounds 2, 3, and 4. Compounds **2**, **3**, and **4** were previously reported.[22]

Procedures for Preparation of Compounds 5a-5k. To a solution of compound **4** (0.01 mol) in ethanol was added an equimolar quantity of TSC, and the mixture was refluxed for 4-8 h until the completion of the reaction. The solid formed was collected by filtration to give crude product, which was recrystallized from ethanol to afford the products in 69-86% yield.

Characterization for the Target Compounds (5a-5k).

2-((5-Phenoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5a): mp 207-209 ºC, yield 82%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.73 (s, 1H, NH_2), 6.97-7.61 (m, 10H, Ar-H), 7.88 (s, 1H, CH=N), 8.11 (s, 1H, NH_2), 11.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz), δ 19.8, 109.1, 120.4, 127.1, 129.0, 132.7, 134.6, 135.5, 139.9, 142.2, 151.8, 153.2, 161.5, 182.4. IR (KBr) cm^{-1}: 3420, 3251, 3159, 1594, 1572, 1531, 1507. MS *m/z* 352.2 (M + H). The crystal data of **5a** can be seen in the reference.[23]

2-((5-(2-Chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydraziecarbothioamide (5b): mp 189-191 ºC, yield 69%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.74 (s, 1H, NH_2), 6.85-7.60 (m, 9H, Ar-H), 7.85 (s, 1H, CH=N), 8.17 (s, 1H, NH_2), 11.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.7, 109.0, 120.7, 126.2, 127.2, 130.3, 132.8, 134.2, 134.6, 136.1, 139.6, 142.0, 150.9, 153.4, 156.5, 182.5. IR (KBr) cm^{-1}: 3412, 3261, 3155, 1601, 1568, 1534, 1505. MS *m/z* 386.1 (M + H).

2-((5-(3-Chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5c): mp 186-187 ºC, yield 74%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.81 (s, 1H, NH_2), 6.94-7.60 (m, 9H, Ar-H), 7.88 (s, 1H, CH=N), 8.17 (s, 1H, NH_2), 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.9, 109.0, 119.2, 121.0, 127.2, 129.3, 132.8, 134.6, 137.0, 139.6, 139.7, 142.1, 151.2, 153.3, 162.0, 182.4. IR (KBr) cm^{-1}: 3438, 3313, 3151, 1592, 1571, 1550, 1506. MS *m/z* 386.2 (M + H).

2-((5-(4-Chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5d): mp 186-188 ºC, yield 72%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.43 (s, 3H, CH_3), 6.80 (s, 1H, NH_2), 7.04 (d, 2H, *J* = 8.8 Hz), 7.32-7.49 (m, 5H, Ar-H), 7.58 (d, 2H, *J* = 8.8 Hz), 7.87 (s, 1H, CH=N), 8.16 (s, 1H, NH2), 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.9, 100.0, 109.0, 122.3, 127.2, 132.9, 134.6, 135.4, 139.7, 142.1, 151.5, 153.3, 160.2, 182.4. IR (KBr) cm^{-1}: 3421, 3307, 3154, 1599, 1570, 1550, 1505. MS *m/z* 386.1 (M + H).

2-((5-(2,4-Dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5e): mp 217-218 ºC, yield 78%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.81 (s, 1H, NH_2), 6.93-7.77 (m, 8H, Ar-H), 7.83 (s, 1H, CH=N), 8.22 (s, 1H, NH_2), 11.26 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.8, 108.8, 122.2, 127.3, 127.4, 133.0, 133.5, 134.1, 135.5, 139.5, 141.9, 150.7, 153.4, 155.5, 164.9, 182.5. IR (KBr) cm^{-1}: 3421, 3250, 3146, 1602, 1571, 1536, 1507. MS *m/z* 420 (M + H).

2-((5-(2,6-Dichlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5f): mp 163-165 ºC, yield 75%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.37 (s, 3H, CH_3), 7.08 (s, 1H, NH_2), 7.31-7.71 (m, 9H, Ar-H, CH=N), 8.13 (s, 1H, NH_2), 11.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 20.7, 105.3, 127.9, 131.4, 132.7, 133.2, 134.5, 135.5, 138.8, 142.5, 151.3, 152.7, 153.0, 182.4. IR (KBr) cm^{-1}: 3414, 3267, 3142, 1598, 1574, 1539, 1508. MS *m/z* 420.1 (M + H).

2-((5-(4-Bromophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5g): mp 191-193 ºC, yield 82%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.44 (s, 3H, CH_3), 6.82 (s, 1H, NH_2), 6.97-7.59 (m, 9H, Ar-H), 7.87 (s, 1H, CH=N), 8.17 (s, 1H, NH_2), 11.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 15.1, 104.3, 116.1, 118.0, 122.5, 128.0, 129.9, 133.5, 135.0, 137.3, 136.7, 145.8, 155.9, 177.7. IR (KBr) cm^{-1}: 3438, 3288, 3159, 1595, 1572, 1542, 1509. MS *m/z* 430.1 (M + H).

2-((5-(2-Methylphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5h): mp 99-101 ºC, yield 86%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 6.59 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.78 (s, 1H, NH_2), 6.99-7.62 (m, 8H, Ar-H), 7.83 (s, 1H, CH=N), 8.11 (s, 1H, NH_2), 11.21 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.9, 23.8, 108.8, 118.5, 127.0, 128.8, 130.9, 132.6, 132.8, 134.5, 136.8, 140.0, 142.3, 152.4, 153.2, 159.9, 182.4. IR (KBr) cm^{-1}: 3441, 3334, 3156, 1588, 1573, 1555, 1507. MS *m/z* 366.2 (M + H).

2-((5-(4-Methylphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5i): mp 201-203 ºC, yield 81%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.23 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.75 (s, 1H, NH_2), 6.85-7.60 (m, 9H, Ar-H), 7.86 (s, 1H, CH=N), 8.11 (s, 1H, NH_2), 11.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.9, 25.3, 109.0, 120.2, 127.1, 132.6, 134.5, 135.8, 138.1, 140.0, 142.3, 152.1, 153.2, 159.6, 182.4. IR (KBr) cm^{-1}: 3440, 3339, 3153, 1595, 1572, 1557, 1506. MS *m/z* 366.1 (M + H).

2-((5-(2-Methoxyphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5j): mp 192-193 ºC, yield 79%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.41 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.73-7.63 (m, 10H, Ar-H, NH_2), 7.81 (s, 1H, CH=N), 8.16 (s, 1H, NH_2), 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.7, 61.1, 108.2, 118.6, 120.6, 126.2, 127.2, 129.9, 132.6, 134.5, 139.9, 142.4, 150.3, 152.6, 153.2, 153.7, 182.4. IR (KBr) cm^{-1}: 3452, 3340, 3153, 1592, 1567, 1539, 1508. MS *m/z* 382.1 (M + H).

2-((5-(4-Methoxyphenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothioamide (5k): mp 199-201 ºC, yield 77%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.42 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.81 (s, 1H, NH_2), 6.87-7.61 (m, 9H, Ar-H, NH_2), 7.86 (s, 1H, CH=N), 8.13 (s, 1H, NH_2), 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.9, 60.6, 108.8, 120.4, 121.5, 127.1, 132.6, 134.5, 140.0, 142.3, 152.6, 153.1, 155.4, 160.6, 182.4. IR (KBr) cm^{-1}: 3449, 3336, 3154, 1589, 1559, 1534, 1509. MS *m/z* 382.1 (M + H).

Pharmacology. KunMing mice (supplied from the Laboratory of Animal Research, Yanbian University, China) weighting 18–22 g were used for pharmacological study. Animals were allowed free access to food and water except during the experiment and housed at controlled room temperature with 12 h light/dark schedule. All compounds were dissolved in DMSO with the injection volume of 0.05 mL per 20 g, which had no effect on the test system.

The Maximal Electroshock Seizure (MES) Test. Anticonvulsant activity of the synthesized compounds was determined through the evaluation of the ability of the compounds to protect mice against MES-induced seizures. The MES test was carried out following procedures proposed by the NIH anticonvulsant drug development (ADD) program.[24,25] Seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. The current was applied *via* clip electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of tonic maximal extension of the hind leg. In preliminarily screening, each compound was administered at the dose levels of 30, 100 and 300 mg/kg for evaluating preliminarily the anticonvulsant activity and neurotoxicity at 0.5 and 4 h interval after intraperitoneal administration (*i.p.*). For determination of the median effective dose (ED_{50}) and the median toxic dose (TD_{50}), the next phase screening was carried out. Groups of 10 mice were given a range of intraperitoneal doses of the tested compound until at least three points were established in the range of 10–90% seizure protection or neurotoxicity. From the plot of this data, the respective ED_{50}, TD_{50} values, and 95% confidence intervals were calculated by probit analysis.

PTZ-induced Seizures. At 2.5 h after the administration of compound **5b**, carbamazepine, and vehicle DMSO, 85 mg/kg PTZ dissolved in saline was administered subcutaneously (*s.c.*). The animals (10 mice in one group) placed in individual cages and observed for 30 min. The numbers of clonic and tonic seizures as well as the number of deaths were noted.[20,21]

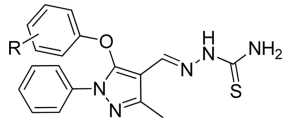
Neurotoxicity Screening (NT). The neurotoxicity of the compounds was measured in mice by the rotarod test.[24,25] Mice were trained to stay on a rotarod of diameter 3.2 cm which rotates at 10 rpm. Trained animals were given *i.p.* injection of the test compounds. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials.

Results and Discussion

Chemistry. The target compounds (**5a-5k**) were synthesized according to the route depicted in Scheme 1. Briefly, phenylhydrazine was reacted with ethyl acetoacetate (EAA) to afford 3-methyl-1-phenyl-2-pyrazolin-5-one (**2**) with a yield of 79%. Compound **2** was subjected to a Vilsmeier Haack reaction to provide 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**3**) with a yield of 83%, which was subsequently reacted with different substituted phenols to obtain the intermediates **4** with a yield of 88%. Finally, the target compounds (**5a-5k**) were synthesized by refluxing **4** with thiosemicarbazide (TSC) in ethanol with yields of 79-86%. Liu *et al.*[26] reported another methodology to obtain the pyrazole thiosemicarbazones. In this method, pyrazole thiosemicarbazones were synthesized by reaction of pyrazole hydrazones with isothiocyanates in dry ethanol at room temperature.

The structures of the target compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

Table 1. Preliminary anticonvulsant activity and neurotoxocity of compounds **5a-5k** administered *i.p.* to mice



Compds.	R	MES[a] (mg/kg)						Toxicity (mg/kg)					
		0.5 h			4 h			0.5 h			4 h		
		30	100	300	30	100	300	30	100	300	30	100	300
5a	H	0/3	***2/3***	***3/3***	***1/3***	***2/3***	***3/3***	0/3	0/3	***2/3***	0/3	***1/3***	***3/3***
5b	2-Cl	0/3	***2/3***	***3/3***	***1/3***	***3/3***	***3/3***	0/3	***1/3***	***2/3***	0/3	0/3	***2/3***
5c	3-Cl	0/3	***1/3***	***2/3***	0/3	***2/3***	***3/3***	0/3	***1/3***	***2/3***	0/3	0/3	***1/3***
5d	4-Cl	-[b]	0/3	***1/3***	-	***1/3***	***2/3***	-	0/3	***1/3***	-	0/3	***1/3***
5e	2,4-2Cl	-	0/3	***1/3***	-	***1/3***	***1/3***	-	0/3	***1/3***	-	0/3	***1/3***
5f	2,6-2Cl	-	0/3	***1/3***	-	***1/3***	***1/3***	-	0/3	0/3	-	0/3	0/3
5g	4-Br	-	0/3	***1/3***	-	***1/3***	***2/3***	-	0/3	0/3	-	***1/3***	***1/3***
5h	2-CH_3	0/3	***1/3***	***2/3***	0/3	***1/3***	***2/3***	-	0/3	***1/3***	-	***1/3***	***2/3***
5i	3-CH_3	-	0/3	***1/3***	-	0/3	***2/3***	-	0/3	***1/3***	-	0/3	***1/3***
5j	2-OCH_3	***1/3***	***2/3***	***3/3***	***1/3***	***2/3***	***3/3***	-	0/3	***1/3***	0/3	***1/3***	***2/3***
5k	4-OCH_3	-	0/3	***1/3***	-	0/3	***1/3***	-	0/3	0/3	-	0/3	***1/3***

All positive reaction numbers are in bold italic. [a]Maximal electroshock test (number of animals protected/number of animals tested), the number of mice is three. [b]Not tested.

Anticonvulsant Activity. A very important step in anti-epileptic drug discovery is the choice of an appropriate animal model for the initial screening. At present, there are three models *in vivo* - the MES, the PTZ, and the kindling model - which are routinely used by most AEDs discovery programs. Among these, the MES and PTZ seizure models represent the two animal seizure models most widely used in the search for new AEDs.[27,28] In this study, the MES model was used for screening the anticonvulsant activity of target compounds. In the preliminary screening process (MES and rotarod tests), each compound was administration in mice. The results were presented in Table 1.

All the tested compounds showed anti-MES activity at 300 mg/kg indicative of their ability to prevent seizure spread. At the dose of 100 mg/kg, compounds **5a-5c**, **5h**, and **5j** showed protection against the MES model at 0.5 h period and kept the protection to 4 h, which indicated these compounds are potent having a rapid onset of action and long duration of action. For compounds **5d-5g**, the protection against the MES model was observed at 4 h at 100 mg/kg. Compounds that showed protection against the MES model at 30 mg/kg include **5a**, **5b**, and **5j**. Among them, compound **5j** showed activity at 0.5 h and 4.0 h periods, while compounds **5a** and **5b** showed activity only at 4 h. In the acute neurotoxicity test, most compounds showed neurotoxicity at the dose of 300 mg/kg. Compounds **5d**, **5f**, **5i**, and **5k** did not show neurotoxicity at the dose of 100 mg/kg, while the others showed neurotoxicity at 0.5 h or 4.0 h period at the same dose. None is found to be neurotoxic at the dose of 30 mg/kg.

From the data in Table 1, it can be seen that each compound has almost equal activity at the end of 0.5 h and 4 h. This fact indicated that the time to peak effect (TPE) of compounds **5a-5k** are likely to present in the time range of 0.5 to 4 h. To obtain the TPE of them, we conducted a time-course test for the selected **5j**, in which compound **5j** reached the TPE at 2.5 h after *i.p.* administration (Figure 1). Therefore, the 2.5 h time interval was chosen as the assessment time for the test compounds in the next quantification tests.

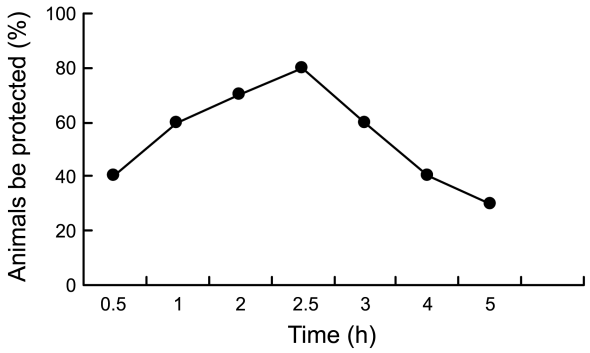


Figure 1. Time-course of compound **5j** (50 mg/kg) in the maximal electroshock seizure test (*i.p.*).

On the basis of the results recorded in the preliminary screening, compounds **5a-5c**, and **5j** were subjected to the next phase of trials concerning quantification of their anti-convulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice. Results of the quantitative tests for the selected compounds, together with the corresponding data for the currently marketed antiepileptic drugs, including phenobarbital and valproate, are shown in Table 2.

As shown in Table 2, all the test compounds showed weaker anticonvulsant activity compared to phenobarbital but better than valproate. 2-((5-(2-Chlorophenoxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothio-amide (**5b**) possessed nice anti-MES activity with ED_{50} of 47.3 mg/kg, and a protective index of 4.8, which was superior to phenobarbital and valproate in the aspect of safety.

For further exploring the anticonvulsant activity of these compounds, PTZ-induced seizure model was made to **5b**. As shown in Table 3, 80% protection against PTZ induced tonic seizures and death was observed when pretreated by **5b** (50 mg/kg), which suggested compound **5b** can be against the seizure spread induced by PTZ. PTZ has been reported to produce seizures by inhibiting γ-aminobutyric acid (GABA)

Table 2. Quantitative anticonvulsant evaluation in mice (*i.p.*)

Compds.	R	ED_{50} (mg/kg) (MES)	TD_{50} (mg/kg) (NT)	**PI** [a]
5a	H	58.9 (51.5-67.3)[b]	176.0 (152.6-203.0)	3.0
5b	2-Cl	47.3 (41.0-54.6)	227.2 (196.9-262.1)	4.8
5c	3-Cl	76.0 (65.9-87.7)	253.5 (219.7-292.5)	3.3
5j	2-OCH_3	65.7 (57.5-75.1)	264.1 (228.9-304.7)	4.0
Phenobarbital	-	21.8 (21.8-25.5)	69.1 (62.8-72.9)	3.2
Valproate	-	272 (247-338)	426 (369-450)	1.6

[a]PI = Protective index (TD_{50}/ ED_{50}). [b]The 95% confidence limits.

Table 3. Effects of compound **5b** on Pentylenetetrazol-induced seizures in mice (*i.p.*)

Chemical substances	Compound	Doses (mg/kg)	Test time (h)	Clonic seizures (%)	Tonic seizures (%)	Lethality (%)
Pentylenetetrazol	DMSO	-	0.5	100	100	100
	Carbamazepine	50	0.5	100	0	10
	5b	50	2.5	70	20	20

neurotransmission.[29,30] GABA, one of the main inhibitory neurotransmitter in the cerebral cortex, has been linked to epilepsy closely. When the GABAergic neurotransmission is disturbed, seizures may ensue. And GABA agonists can inhibit/attenuate seizures and potentially serve as anticonvulsants.[31] Based on these, it is speculated that the mechanism of action of the compound **5b** may be involved in the GABAergic neurotransmission.

Conclusion

A series of 2-((5-phenoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinecarbothiomide derivatives (**5a-5k**) were synthesized and studied for their anticonvulsant activity. The results of this study demonstrated that pyrazolyl semicarbazones have potent anticonvulsant activity. Among the compounds synthesized, compound **5b** was found to have promising anticonvulsant activity, which gave an ED_{50} of 47.3 mg/kg and a TD_{50} of 227.2 mg/kg, resulting in a PI value of 4.8. In addition, compound **5b** demonstrated antagonistic activity against seizures induced by PTZ, which suggested that compound **5b** may exert anticonvulsant activity through GABA-mediated mechanisms. This study provides a new nucleus/structure for further design of new anticonvulsant agents.

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