Arch. Pharm. Chem. Life Sci. 2015, *348*, 868–874

ARCH PHARM
Archiv der Pharmazie

Full Paper

Design and Synthesis of Novel Phenylpiperazine Derivatives as Potential Anticonvulsant Agents

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Eighteen new 5-benzylidene-3-(4-arylpiperazin-1-ylmethyl)-2-thioxo-imidazolidin-4-ones were designed as hybrid structures from previously reported anticonvulsant compounds, synthesized and tested for anticonvulsant activity. Initial anticonvulsant screening was performed using the strychnine (2 mg/kg IP) potent generalized-induced seizure and pentylenetetrazole (PTZ) (60 mg/kg IP) acute clonic-induced convulsion screens in mice. All the molecules were found to be effective in at least one seizure model, compounds **10**, **13**, **15**, **17**, and **18** were active against both types of seizures induced. Compound **13** turned out to be the most active candidate within the strychnine model, having an average survival time of 6 min close to that of the positive control phenytoin, while compound **8** showed 100% protection from the induced PTZ seizures, resembling the protection of the positive control phenobarbital. Initial SAR studies for anticonvulsant activity are discussed.

Keywords: 2-Thiohydantoin / Anticonvulsant / Epilepsy / Phenylpiperazine

Received: August 4, 2015; Revised: September 22, 2015; Accepted: September 28, 2015

DOI 10.1002/ardp.201500272

Introduction

Epilepsy is a disease of complex nature and of different etiology. It is a devastating neurological disorder that afflicts approximately 50 million people worldwide [1]. For epilepsy treatment, nearly 95% of clinically available drugs were approved before 1985 and they could provide satisfactory seizure control for 60–70% of patients [2]. In recent times, several new drugs have emerged to treat epilepsy. Although these drugs have shown to be effective in controlling the seizures, their efficacy does not appear to be superior to that of the established antiepileptic drugs as phenytoin [3]. However phenytoin **II** (Fig. 1) continues to create significant side effects and toxicity due to its narrow therapeutic index, high degree of serum protein binding, nonlinear elimination pharmacokinetics, and considerable individual variations in metabolism [4].

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The 2-thiohydantoins had marked an anticonvulsant activity which prompted the preparation of several series of substituted-2-thiohydantoins for evaluation as anticonvulsants. They are thought to be of general interest as anticonvulsants because structural requirements for optimal anticonvulsant activity in the 2-thiohydantoin compounds were found to differ greatly from those of the hydantoins, where the 2-thiohydantoin compounds have greater protective effect against convulsions [5].

N-Phenylpiperazine compounds constitute a very large chemical class and some of these compounds have the ability to cross the blood–brain barrier due to the small size and the lipophilic nature of their molecules. Thus, some *N*-phenylpiperazine derivatives promote activity upon the central nervous system and are used in the treatment of various mental disorders, including anxiety disorders [6], Alzheimer's disease [7], psychosis [8], and depression [9]. Besides, a lot of compounds with *N*-phenylpiperazine moiety were tested for their anticonvulsant properties, where most of them were reported to display protection against different types of induced seizures [10].

Based on the literature review, the phenylpiperazine derivative *N*-[(4-arylpiperazin-1-yl)-methyl]-3-arylpyrrolidine-2,5-dione **I** and the 2-thiohydantoin derivative 3-(alkyl/aryl)-5,5-diphenyl-2-thioxoimidazolidine-4-one **III** (Fig. 1) were

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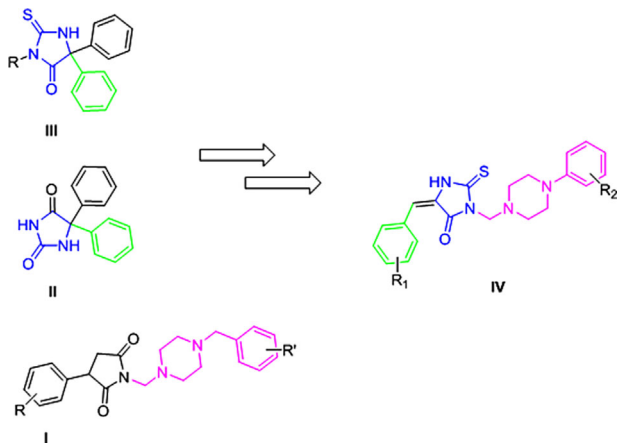

Figure 1. Anticonvulsant candidates for the new hybrid synthesized scaffold.

found to show significant anticonvulsant activity [5a, 10a, 11]. In this study, we report the synthesis and the pharmacological evaluation of novel anticonvulsant analogs through structure modification rather than a mechanism-driven design because of the complex nature of epilepsy, gathering the important features in these candidates to satisfy the criteria required for the anticonvulsant activity [10b] having two different nitrogen heteroatomic systems (a 2-thiohydantoin and a piperazine ring), two phenyl rings (one at the 5-arylidene thiohydantoin intermediate and the other at the *N*-phenylpiperazine) and the carbonyl group found at the 2-thiohydantoin giving a 5-benzylidene-3-(4-aryl-piperazin-1-ylmethyl)-2-thioxo-imidazolidin-4-one scaffold **IV** (Fig. 1). The newly synthesized compounds were tested for anticonvulsant activity against chemically induced convulsion using strychnine and PTZ as positive controls.

Results and discussion

Chemistry

The general synthesis of 5-benzylidene-3-(4-aryl-piperazin-1-ylmethyl)-2-thioxoimidazolidin-4-one derivatives is illustrated in Scheme 1. The final products were obtained in two steps: Knoevenagel condensation reaction between a benzaldehyde derivative and 2-thiohydantoin with piperidine as the catalyst giving the intermediate 5-arylidene thiohydantoin derivatives. Mannich bases are then synthesized from those intermediates, when the latter were allowed to react with formaldehyde and aryl piperazines in ethanol at room temperature overnight, 5-benzylidene-3-(4-aryl-piperazin-1-ylmethyl)-2-thiohydantoin derivatives **1–18** were obtained.

The structural elucidation of all synthesized compounds was done via different spectroscopic analytical techniques, such as FT-IR spectroscopy, electron impact mass spectrometry, ^{1}H NMR spectroscopy, and elemental analysis.

Infrared spectra showed weak broad band at 3156–3375 cm^{-1}, corresponding to (–NH) stretching and sharp bands at 1708–1739 cm^{-1}, corresponding to (–C=O) stretching.

Mass spectra confirmed the molecular weight of the synthesized compounds. The molecular ion peaks confirmed the molecular weight of the synthesized compounds. The isotopic pattern was used to confirm the presence of chloro- and bromo-substituent.

Compounds having chlorine or bromine showed two ion peaks (M^+ and M^++2) with peak heights ratio of 3:1 and 1:1 in case of chlorine and bromine containing compounds, respectively.

In the ^{1}H NMR spectra, two significant singlet peaks were common in all the spectra of the synthesized compounds. The first one corresponds to the proton of the benzylidene moiety in the range from 6.63 to 7.08 ppm, which confirmed the success of the Knoevenagel condensation. The second corresponds to the two protons of the methylene carbon linking the phenylpiperazine and the thiohydantoin units in the range from 4.95 to 5.45 ppm, which confirmed success of Mannich addition. The presence of two multiplets of four protons each in the range from 2.7 to 4.0 ppm confirmed the presence of the piperazine ring.

Anticonvulsant activity

The brain uptake of drugs is generally related to the drug lipophilicity, which can be expressed as the log *P* [12]; the log *P*-values of all the synthesized compounds were calculated (Table 1) and were found to be greater than 2.

A potent generalized seizure model can be produced by IP injection of strychnine, interacting with GABA-benzodiazepine receptors [13], and serving as a noncompetitive inhibitor on the glycine receptors [14]; phenytoin was used as a positive control inhibiting the voltage-dependent Na^+ channels [12].

Tendency of increased survival time compared to the strychnine-treated group was observed; besides, compounds **4**, **10**, **11**, **13**, **15**, **16**, **17**, and **18** showed to be statistically significant on comparing them to that of the positive control phenytoin considering the standard deviation of the survival time (Table 1); the presence of *p*-chloro substituent on the benzylidene moiety (compounds **9–16**) has increased the activity of the majority of the compounds on being compared to their congeners without *p*-chloro substituent (compounds **1–8**), and this is obvious when comparing compounds **10**, **11**, **13**, **15**, and **16** to compounds **2**, **3**, **5**, **7**, and **8**, respectively. Studying the presence of bulkier more lipophilic halogen like bromine in the same position of *p*-chloro substituent on the benzylidene moiety (compound **17**) has indeed shown 2.5-fold elongation in the average survival time following strychnine injection when compared to its previously synthesized analogs, compounds **1** and **9**. Studying the effect of the presence of two oxygenated substituents on the developed scaffold, compound **18** having *p*-OMe and 2-OH substituent on the benzylidene and phenylpierazine units, respectively,

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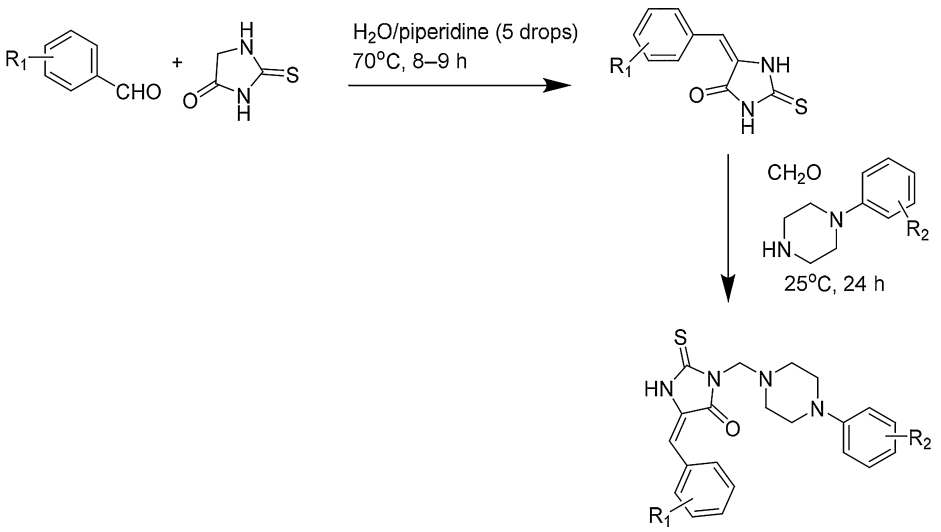

1—18

Compound	R_1	R_2	Compound	R_1	R_2
1	H	H	**10**	Cl	2-Cl
2	H	2-Cl	**11**	Cl	2-F
3	H	2-F	**12**	Cl	4-F
4	H	4-F	**13**	Cl	2-OH
5	H	2-OH	**14**	Cl	4-OH
6	H	4-OH	**15**	Cl	$2\text{-}OCH_3$
7	H	$2\text{-}OCH_3$	**16**	Cl	$2\text{-}OC_2H_5$
8	H	$2\text{-}OC_2H_5$	**17**	Br	H
9	Cl	H	**18**	OCH_3	2-OH

Scheme 1. General scheme for the new synthesized scaffold.

did not show better activity than compound **13** and kept an average survival time following strychnine injection of 4 min.

On the other hand, PTZ is a central nervous system stimulant. Acute clonic convulsions resulting from the submaximal dose of PTZ (60 mg/kg IP) is analogous to petit mal type convulsions (absence seizures) in man [15]. PTZ is a $GABA_A$ receptor antagonist that reduces the chloride conductance; PTZ-induced seizures could be blocked by phenobarbital that was used as a positive control [16]. Most of the compounds have shown a percentage protection ranging from 33% up to 100% (Table 2), where the protected mice showed no convulsions within an observation time of 30 min.

Presence of *p*-chloro substituent on the benzylidene moiety (compounds **9–16**) again has increased and enhanced the activity when compared to their congeners with no *p*-chloro substituent. This is obvious when comparing compounds **9**, **10**, **11** to compounds **1**, **2**, and **3**. Compound **17** bearing a *p*-Br substituent on the benzylidene moiety and a bare phenylpiperazine unit has shown 83% protection against the acute clonic convulsions induced by the injected PTZ dose versus 33 and 50% protection shown by its analogs, compounds **1** and **9**, respectively.

Compound **18** bearing two oxygenated substituents on its scaffold showed similar percentage protection of 83% to its analog compound **13**.

Conclusion

Eighteen novel compounds were synthesized as novel anticonvulsant analogs of a hybrid structure from previously reported anticonvulsant compounds. The synthesized compounds have Log *P*-values greater than 2, indicating the relative lipophilicity of these candidates which may affect their brain uptake. The compounds proved to be potential anticonvulsant agents through the two *in vivo* screening tests, strychnine and PTZ-induced convulsions.

For the strychnine-induced potent generalized seizures model, all the compounds have shown tendency of increased

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Table 1. Anticonvulsant activity of the tested compounds at a dose of 100 mg/kg prior to using strychnine 2 mg/kg, and their log *P*-values.

Compound	Log *P*	Survival time (min ± SD)
Strychnine	0.63	2.53 ± 0.9
Phenytoin	2.14	6.83 ± 0.98
1	3.58	1.63 ± 1.11
2	4.13	3.02 ± 1.86
3	3.73	2.58 ±0.73
4	3.73	3.84 ± 3.29
5	2.84	2.97 ± 1.56
6	2.84	2.82 ± 0.74
7	3.45	3.24 ± 1.34
8	3.79	2.13 ± 0.95
9	4.13	1.57 ± 0.55
10	4.69	4.66 ± 2.94
11	4.29	4.29 ± 2.89
12	4.29	2.63 ± 1.36
13	3.74	6.06 ± 3.02
14	3.74	2.48 ± 0.74
15	4.01	3.88 ± 1.83
16	4.35	4.32 ± 1.56
17	4.4	4.22 ± 3.28
18	3.06	4.13 ± 3.84

survival time compared to the strychnine-treated group with a statistical significance for most of the compounds on comparing them to the phenytoin-treated group, where compound **13** showed to be the most active candidate with an average survival time of 6 min. While for the PTZ-induced acute clonic convulsions model, most of the synthesized compounds showed percentage protection from convulsions that ranged from 33 to 100%, where compound **8** showed 100% protection from the induced seizures. Based on the structural features of the highly active candidates in both models, we can conclude that the presence of a bulky halogen in the size of bromine or chlorine on the *para* position of the benzylidene moiety located on position 5 of the thiohydantoin core and *ortho*-oxygenated substituent on the phenylpiperazines unit linked to position 3 via methylene carbon would ensure optimum activity of the candidates bearing this novel chemical scaffold.

Table 2. Anticonvulsant activity of the tested compounds at a dose of 100 mg/kg prior using PTZ.

Compound	Protection (%)
Phenobarbital	100
1	33
2	0
3	0
4	33
5	83
6	66
7	66
8	100
9	50
10	83
11	50
12	33
13	83
14	83
15	83
16	50
17	83
18	83

Experimental

Chemistry

All starting materials were obtained from Sigma–Aldrich and all organic solvents used were obtained from El-Gomhuoria Company and were of pure analytical grade used without further purification. Melting points (°C) were determined by open capillary tube method using Buchi B-540 mp apparatus and were uncorrected. Elemental microanalyses were performed at the Micro-Analytical Center, Faculty of Science, Cairo University, values were within ±0.4% of the theoretical ones unless otherwise indicated. The IR spectra were recorded on Alpha FT-IR spectrophotometer. The ^{1}H NMR spectra, in $CDCl_3$ or DMSO-d_6 as a solvent, were recorded on Varian Mercury spectrophotometer at 300 MHz. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were performed by gas chromatography method on Shimadzu Qp-2010 Plus, by electron ionization mode at potential of 70 eV. The progress of the reaction was monitored by TLC using fluorescent precoated silica gel plates and detection of the components was made by short ultraviolet light at λ = 254 nm and methylene chloride/methanol (95:5) as the eluting system.

*General procedure for the synthesis of 5-benzylidene-3-(4-aryl-piperazin-1-ylmethyl)-2-thioxo-imidazolidin-4-one derivatives **1–18***

An equimolar reaction between thiohydantoin, an aromatic aldehyde and piperidine (five drops) in water (30 mL) were stirred and refluxed at 70°C for 8–9 h. The precipitated product was filtered, dried, and subjected to column chromatography on silica gel for further purification, using a mixture of methylene chloride/methanol (95:5) as the eluent. Every intermediate together with formaldehyde (1 mL, 35% solution) and an *N*-arylpiperazine in absolute ethanol (30 mL) were left over night stirring at room temperature. The resulting residual solid was crystallized from aqueous ethanol to give the expected structure.

*5-Benzylidene-3-(4-phenylpiperazin-1-ylmethyl)-2-thioxoimidazolidin-4-one (**1**)*

Yellow solid. Yield: 76%; mp 191–193°C; TLC: $R_f = 0.68$; IR: 3246 (NH), 2826, 2942 (CH_2), 1731 (C=O). ^{1}H NMR (300 Hz,

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$CDCl_3$) δ: 2.94–2.96 (m, 4H, piperazine), 3.17–3.18 (m, 4H, piperazine), 4.97 (s, 2H, CH_2), 6.75 (s, 1H, CH), 6.76–7.48 (m, 10H, aromatic), 8.72 (s, brs, 1H, NH). EI-MS: *m/z* (%) 377.90, M^+, (0.56). Anal. calcd. for $C_{21}H_{22}N_4OS$ (378.49): C: 66.64, H: 5.86, N: 14.80; Found: C: 66.86, H: 5.15, N: 14.53.

*5-Benzylidene-3-[4-(2-chlorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**2**)*
Brown solid. Yield: 79%; mp 218–220°C; TLC: $R_f = 0.31$; IR: 3334 (NH), 2813, 2930 (CH_2), 1720 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 3.39–3.41 (m, 4H, piperazine), 3.44–3.46 (m, 4H, piperazine), 5.44 (s, 2H, CH_2), 6.71 (s, 1H, CH), 6.81–7.48 (m, 9H, aromatic), 9.88 (s, brs, 1H, NH). EI-MS: *m/z* (%) 412.00, M^+, (28.57) and 414.00, M^++2, (22.71). Anal. calcd. for $C_{21}H_{21}ClN_4OS$ (412.94): C: 61.08, H: 5.13, N: 13.57; Found: C: 61.25, H: 5.15, N: 13.53.

*5-Benzylidene-3-[4-(2-fluorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**3**)*
Orange solid. Yield: 83%; mp 188–190°C; TLC: $R_f = 0.33$; IR: 3375 (NH), 2823, 2951 (CH_2), 1710 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.98–2.99 (m, 4H, piperazine), 3.08–3.09 (m, 4H, piperazine), 4.98 (s, 2H, CH_2), 6.76 (s, 1H, CH), 6.92–7.52 (m, 9H, aromatic). EI-MS: *m/z* (%) 395.80, M^+, (21.80). Anal. calcd. for $C_{21}H_{21}FN_4OS$ (396.48): C: 63.62, H: 5.34, N: 14.13; Found: C: 63.89, H: 5.53, N: 14.47.

*5-Benzylidene-3-[4-(4-fluorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**4**)*
Yellow solid. Yield: 95%; mp 205–207°C; TLC: $R_f = 0.62$; IR: 3226 (NH), 2818, 2951 (CH_2), 1708 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.93–2.96 (m, 4H, piperazine), 3.08–3.11 (m, 4H, piperazine), 4.97 (s, 2H, CH_2), 6.75 (s, 1H, CH), 6.83–7.51 (m, 9H, aromatic), 8.73 (s, brs, 1H, NH). EI-MS: *m/z* (%) 395.90, M^+, (0.42). Anal. calcd. for $C_{21}H_{21}FN_4OS$ (396.48): C: 63.62, H: 5.34, N: 14.13; Found: C: 63.24, H: 5.59, N: 14.44.

*5-Benzylidene-3-[4-(2-hydroxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**5**)*
Red solid. Yield: 75%; mp 112–114°C; TLC: $R_f = 0.48$; IR: 3343 (NH), 2825, 2945 (CH_2), 1739 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.75–2.96 (m, 4H, piperazine), 3.72–3.76 (m, 4H, piperazine), 5.45 (s, 2H, CH_2), 6.74 (s, 1H, CH), 6.88–7.47 (m, 9H, aromatic). EIMS: *m/z* (%) 394.00, M+, (64.04). Anal. calcd. for $C_{21}H_{22}N_4O_2S$ (394.49): C: 63.94, H: 5.62, N: 14.20; Found: C: 63.90, H: 5.79, N: 14.52.

*5-Benzylidene-3-[4-(4-hydroxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**6**)*
Red solid. Yield: 68%; mp 180–182°C; TLC: $R_f = 0.40$; IR: 3342 (NH), 2819, 2944 (CH_2), 1726 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.72–2.95 (m, 4H, piperazine), 3.72–3.77 (m, 4H, piperazine), 5.44 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.78–7.46 (m, 9H, aromatic). EIMS: *m/z* (%) 394.90, M^+, (66.67). Anal. calcd. for $C_{21}H_{22}N_4O_2S$ (394.49): C: 63.94, H: 5.62, N: 14.20; Found: C: 63.64, H: 5.32, N: 14.41.

*5-Benzylidene-3-[4-(2-methoxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**7**)*
Brown solid. Yield: 90%; mp 135–137°C; TLC: $R_f = 0.33$; IR: 3332 (NH), 2827, 2921 (CH_2), 1724 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 3.42–3.43 (m, 4H, piperazine), 3.85–3.87 (m, 4H, piperazine), 3.88 (s, 3H, OCH_3), 5.44 (s, 2H, CH_2), 6.70 (s, 1H, CH), 6.80–7.48 (m, 9H, aromatic), 9.83 (s, brs, 1H, NH). EI-MS: *m/z* (%) 407.90, M^+, (15.55). Anal. calcd. for $C_{22}H_{24}N_4O_2S$ (408.52): C: 64.68, H: 5.92, N: 13.71; Found: C: 64.21, H: 5.52, N: 13.96.

*5-Benzylidene-3-[4-(2-ethoxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**8**)*
Brown solid. Yield: 71%; mp 179–181°C; TLC: $R_f = 0.36$; ^{1}H NMR (300 Hz, $CDCl_3$) δ: 1.44–1.46 (t, 3H, OCH_2CH_3), 3.42–3.44 (m, 4H, piperazine), 3.59–3.61 (m, 4H, piperazine), 4.07–4.09 (q, 2H, OCH_2CH_3), 5.43 (s, 2H, CH_2), 6.77 (s, 1H, CH), 6.81–7.49 (m, 9H, aromatic), 8.77 (s, brs, 1H, NH). EI-MS: *m/z* (%) 421.00, M^+, (44.29). Anal. calcd. for $C_{23}H_{26}N_4O_2S$ (422.54): C: 65.38, H: 6.20, N: 13.26; Found: C: 65.72, H: 6.63, N: 13.23.

*5-(4-Chlorobenzylidene)-3-(4-phenylpiperazin-1-ylmethyl)-2-thioxo-imidazolidin-4-one (**9**)*
Bright yellow solid. Yield: 69%; mp 184–186°C; TLC: $R_f = 0.50$; IR: 3223 (NH), 2824, 2946 (CH_2), 1710 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 3.17–3.20 (m, 4H, piperazine), 3.92–3.96 (m, 4H, piperazine), 4.97 (s, 2H, CH_2), 6.71 (s, 1H, CH), 6.84–7.47 (m, 9H, aromatic). EI-MS: *m/z* (%) 412.10, M^+, (1.70). Anal. calcd. for $C_{21}H_{21}ClN_4OS$ (412.94): C: 61.08, H: 5.13, N: 13.57; Found: C: 61.35, H: 5.42, N: 13.39.

*5-(4-Chlorobenzylidene-3-[4-(2-chlorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**10**)*
Brown solid. Yield: 64%; mp 146–148°C; TLC: $R_f = 0.34$; IR: 3267 (NH), 2811, 2930 (CH_2), 1727 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 3.15–3.17 (m, 4H, piperazine), 3.21–3.23 (m, 4H, piperazine), 6.47 (s, 2H, CH_2), 7.08 (s, 1H, CH), 7.12–7.77 (m, 8H, aromatic). EI-MS: *m/z* (%) 447.00, M^+, (67.62) and 449.00, M^++2, (49.52). Anal. calcd. for $C_{21}H_{20}Cl_2N_4OS$ (447.38): C: 56.38, H: 4.51, N: 12.52; Found: C: 56.71, H: 4.61, N: 12.05.

*5-(4-Chlorobenzylidene)-3-[4-(2-fluorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**11**)*
Yellowish brown solid. Yield: 66%; mp 193–195°C; TLC: $R_f = 0.45$; IR: 3373 (NH), 2818, 2948 (CH_2), 1707 (C=O). ^{1}H NMR (300 Hz, DMSO) δ: 2.79–2.81 (m, 4H, piperazine), 2.97–2.99 (m, 4H, piperazine), 4.79 (s, 2H, CH_2), 6.63 (s, 1H, CH), 6.96–7.82 (m, 8H, aromatic). EI-MS: *m/z* (%) 430.00, M^+, (30.57) and 432.00, M^++2, (19.62). Anal. calcd. for $C_{21}H_{20}ClFN_4OS$ (430.93): C: 58.53, H: 4.68, N: 13.00; Found: C: 58.83, H: 4.85, N: 12.78.

*5-(4-Chlorobenzylidene)-3-[4-(4-fluorophenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**12**)*
Yellow solid. Yield: 76%; mp 195–197°C; TLC: $R_f = 0.43$; IR: 3349 (NH), 2827, 2955 (CH_2), 1713 (C=O). ^{1}H NMR (300 Hz,

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$CDCl_3$) δ: 2.92–2.95 (m, 4H, piperazine), 3.07–3.11 (m, 4H, piperazine), 4.96 (s, 2H, CH_2), 6.675 (s, 1H, CH), 6.83–7.46 (m, 8H, aromatic). EI-MS: *m/z* (%) 429.90, M^+, (73.58) and 431.9, M^++2, (66.04). Anal. calcd. for $C_{21}H_{20}ClFN_4OS$ (430.93): C: 58.53, H: 4.68, N: 13.00; Found: C: 58.25, H: 4.58, N: 12.63.

*5-(4-Chlorobenzylidene)-3-[4-(2-hydroxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**13**)*
Dark yellow solid. Yield: 51%; mp 179–181°C; TLC: $R_f = 0.45$; IR: 3375 (NH), 2816, 2934 (CH_2), 1736 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.79–3.14 (m, 4H, piperazine), 3.72–3.76 (m, 4H, piperazine), 5.44 (s, 2H, CH_2), 6.65 (s, 1H, CH), 6.72–7.54 (m, 8H, aromatic). EI-MS: *m/z* (%) 429.00, M^+, (37.84) and 431.00, M^++2, (31.35). Anal. calcd. for $C_{21}H_{21}ClN_4O_2S$ (428.94): C: 58.80, H: 4.93, N: 13.06; Found: C: 58.83, H: 5.05, N: 13.39.

*5-(4-Chlorobenzylidene)-3-[4-(4-hydroxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**14**)*
Red solid. Yield: 82%; mp 140–142°C; TLC: $R_f = 0.50$; IR: 3178 (NH), 2820, 2947 (CH_2), 1726 (C=O). ^{1}H NMR (300 Hz, $CDCl_3$) δ: 2.71–3.04 (m, 4H, piperazine), 3.72–3.75 (m, 4H, piperazine), 5.44 (s, 2H, CH_2), 6.64 (s, 1H, CH), 6.67–7.46 (m, 8H, aromatic). EIMS: *m/z* (%) 429.00, M^+, (20.00) and 431.00, M^++2, (18.97). Anal. calcd. for $C_{21}H_{21}ClN_4O_2S$ (428.94): C: 58.80, H: 4.93, N: 13.06; Found: C: 58.46, H: 4.63, N: 12.79.

*5-(4-Chlorobenzylidene)-3-[4-(2-methoxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**15**)*
Dark brown semisolid. Yield: 64%; TLC: $R_f = 0.47$; ^{1}H NMR (300 Hz, $CDCl_3$) δ: 3.41–3.43 (m, 4H, piperazine), 3.61–3.63 (m, 4H, piperazine), 3.88 (s, 3H, OCH_3), 5.43 (s, 2H, CH_2), 6.71 (s, 1H, CH), 6.88–7.44 (m, 8H, aromatic), 9.80 (s, brs, 1H, NH). EI-MS: *m/z* (%) 442.00, M^+, (60.00) and 444.00, M^++2, (56.84). Anal. calcd. for $C_{22}H_{23}ClN_4O_2S$ (442.96): C: 59.65, H: 5.23, N: 12.65; Found: C: 59.73, H: 4.92, N: 12.49.

*5-(4-Chlorobenzylidene)-3-[4-(2-ethoxyphenyl)-piperazin-1-ylmethyl]-2-thioxoimidazolidin-4-one (**16**)*
Dark brown semisolid. Yield: 61%; TLC: $R_f = 0.42$; ^{1}H NMR (300 Hz, $CDCl_3$) δ: 1.43–147 (t, 3H, OCH_2CH_3), 3.34–3.36 (m, 4H, piperazine), 3.35–3.52 (m, 4H, piperazine), 4.04–4.08 (q, 2H, OCH_2CH_3), 5.43 (s, 2H, CH_2), 6.86 (s, 1H, CH), 6.89–7.44 (m, 8H, aromatic), 9.80 (s, brs, 1H, NH). EI-MS: *m/z* (%) 456.00, M^+, (70.48) and 458.00, M^++2, (11.43). Anal. calcd. for $C_{23}H_{25}ClN_4O_2S$ (456.99): C: 60.45, H: 5.51, N: 12.26; Found: C: 60.32, H: 5.44, N: 12.10.

*5-(4-Bromobenzylidene)-3-(4-phenylpiperazin-1-ylmethyl)-2-thioxoimidazolidin-4-one (**17**)*
Bright yellow solid. Yield: 56%; mp 218–220°C; TLC: $R_f = 0.46$; IR: 3226 (NH), 2823, 2948 (CH_2), 1707 (C=O). ^{1}H NMR (300 Hz, DMSO) δ: 2.76–2.78 (m, 4H, piperazine), 3.07–3.09 (m, 4H, piperazine), 4.78 (s, 2H, CH_2), 6.60 (s, 1H, CH), 6.90–7.66 (m, 9H, aromatic). EI-MS: *m/z* (%) 456.00, M^+, (46.85) and 458.00, M^++2, (56.76). Anal. calcd. for $C_{21}H_{21}BrN_4OS$ (457.39): C: 55.14, H: 4.63, N: 12.25; Found: C: 55.55, H: 4.23, N: 11.85.

*3-[4-(2-Hydroxyphenyl)-piperazin-1-ylmethyl]-5-(4-methoxybenzylidene)-2-thioxoimidazolidin-4-one (**18**)*
Red solid. Yield: 67%; mp 129–131°C; TLC: $R_f = 0.26$; ^{1}H NMR (300 Hz, $CDCl_3$) δ: 22.95–2.97 (m, 4H, piperazine), 3.39–3.41 (m, 4H, piperazine), 3.88 (s, 3H, OCH_3), 5.43 (s, 2H, CH_2), 6.68 (s, 1H, CH), 6.77–7.40 (m, 8H, aromatic). EI-MS: *m/z* (%) 424.00, M^+, (0.5). Anal. calcd. for $C_{22}H_{24}N_4O_3S$ (424.52): C: 62.24, H: 5.70, N: 13.20; Found: C: 62.67, H: 5.5, N: 12.95.

Determination of partition coefficient (log P)

The Log *P*-values of the synthesized compounds were calculated by ChemDraw Ultra 7.0.1 software.

Anticonvulsant screening

The 18 synthesized compounds **1**–**18** were evaluated for anticonvulsant activity against PTZ and strychnine-induced seizures in mice.

Strychnine seizure pattern test
Male albino mice weighing 18–25 g were housed in groups of six. The animals were acclimated to their environment for at least 2 days before the experiments and were allowed free access to food and water before being tested. The mice were divided into negative control group, strychnine group, positive control group, and 18 test groups; each group consisted of six animals. The negative control group received 2% Tween 80 in water at a dose of 10 mL/kg IP, which is used as the vehicle for suspending all the tested drugs and compounds. The strychnine group received strychnine at a dose of 2 mg/kg IP. The positive control group received phenytoin at the dose of 100 mg/kg IP, 45 min before IP injection of strychnine (2 mg/kg IP). The test groups received the test compounds at the dose of 100 mg/kg IP, 45 min before IP injection of strychnine (2 mg/kg). The mice were observed and the average survival time was recorded [12, 17].

PTZ seizure pattern test

Male albino mice, weighing 18–25 g were divided into positive control group and 18 test groups ($n = 6$ per group). The positive control group received phenobarbital at the dose of 30 mg/kg IP 1 h before the administration of PTZ at the dose of 60 mg/kg IP. The test groups received the testing compounds at the dose of 100 mg/kg IP before the PTZ administration. Animals devoid of clonic convulsions were considered to be protected and results were represented as percentage protection [12, 18].

The authors have declared no conflicts of interest.

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