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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design and synthesis of novel *N*-substituted-3-chloro-2-azetidinone derivatives as potential anticonvulsant agents

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Abstract A new series of *N*-[3-chloro-2-(substitutedphenyl)-4-oxo-azetidin-1-yl]isonicotinamide (**2a–l**) were synthesized through condensation reaction of isoniazide with substituted aldehyde. The newly synthesized compounds were characterized by spectral data (IR, ^{1}H NMR, mass spectra) and elemental analysis. Compound **2e** exhibited excellent anticonvulsant activity and no neurotoxicity in comparison to reference drug phenytoin.

Keywords Azetidinone · MES · PTZ · Neurotoxicity · CNS depressant

Introduction

Epilepsy, an ubiquitous disease characterized by recurrent seizures that affects more than 60 million people worldwide and 2.5 million people in USA, according to epidemiological studies (Wasterlain *et al.*, 1989; Loscher, 1998). Drugs presently available in the market for the treatment of epilepsy do not provide a complete cure and have an effect only in 60–70% of patients. Moreover, these drugs cause various side effects such as drowsiness, gastrointestinal disturbance, hepatotoxicity, and megaloblastic anemia (Perucca, 1996; Lin and Kadaba, 1997), including some life-threatening conditions (Al-Soud *et al.*, 2003).

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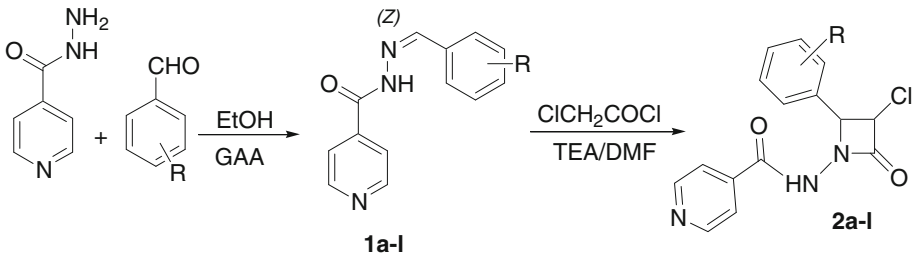
2-Azetidinones, commonly known as *β*-lactams, are heterocyclic compounds well known to organic and medicinal chemists. The activities of widely used antibiotics such as penicillins, cephalosporins, and carbapenems are attributed to the presence of 2-azetidinone ring (Singh, 2004). Literature survey reveals that beside their antibacterial activity (Patel and Mehta, 2006) 2-azetidinones also possess various biological activities that include anticonvulsant (El-Helby and Wahab, 2003), carbonic anhydrase inhibition (Russo *et al.*, 1994), local anesthetic (Costakes and Tsatsa, 1978), hypoglycemic (Chernykh and Sidorenko, 1981), and anti-inflammatory (Sreenivasa *et al.*, 2005). The *β*-lactams also serve as synthons for many biologically important classes of organic compounds (Deshmukh *et al.*, 2004). Thus, various activities attributed to 2-azetidinone ring hold the potential in the development of novel antiepileptic agents (Singh, 2004). Therefore, the potential therapeutic importance of azetidinone rings prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities.

Result and discussion

Synthesis

The most common method for the synthesis of 2-azetidinones is the Staudinger keteneimine cycloaddition, which involves the reaction of imines with acid chloride in the presence of a tertiary base (Staudinger, 1907). In the present work, we have synthesized *N*-[3-chloro-2-(substitutedphenyl)-4-oxo-azetidin-1-yl]isonicotinamide (**2a–l**) in a two-step procedure, as shown in Scheme 1. Various isonicotinic acids (substituted-benzylidene)-hydrazide (**1a–l**) were



Scheme 1 Protocol for synthesis of N-[3-chloro-2-(substitutedphenyl)-4-oxo-azetidin-1-yl]isonicotinamide derivatives. R: a = 4-OH, b = 2-OH, c = 2-OCH_3, d = 4-$N(CH_3)_2$, e = 4-CH_3, f = 3,4-di-OCH_3, g = 3-OCH_3-4OH, i = 2-NO_2, j = 4-Cl, k = 2-Cl, l = H

synthesized by treating isonicotinohydrazide with different substituted benzaldehydes in absolute ethanol. Compounds (**1a–l**) were refluxed with triethylamine and chloroacetaldehyde to form *N*-[3-chloro-2-(substitutedphenyl-4-oxo-azetidin-1-yl]isonicotinamides (**2a–l**) in moderate to good yields (60–80%). Thin layer chromatography (TLC) was used throughout to monitor and optimize the reactions for purity and completion. Synthesized compounds were characterized by IR, ^{1}H NMR, mass spectroscopy, and elemental analysis.

Pharmacology

All newly synthesized compounds were evaluated for their anticonvulsant activity. Neurotoxicity and antidepressant activity are shown in Tables 1 and 2. Most of the compounds showed significant anticonvulsant activity, except for *ortho* derivatives **2b**, **2c**, and **2k** (no anticonvulsant activity at dosages up to 100 mg/kg, i.p.). One can suppose that *ortho* substituent may possibly block the azetidinone ring receptor interaction.

Analyzing the activities of all synthesized derivatives **2a–l**, the following structure–activity relationship (SAR) was observed. It was found that the azetidinone derivatives having CH_3 group showed maximum anticonvulsant activity in comparison to OH, OCH_3, NO_2, $N(CH_3)_2$, Cl, and H group/atom on the whole level. The position of the substituents on the phenyl ring greatly influenced the anticonvulsant activity, the activity order is $p > p$–$m > o$. The *p*-CH_3 derivative **2e** exhibited the highest at minimum dose 30 mg/kg in maximum electroshock seizure (MES) at both 0.5 and 4.0 h and 100 and 30 mg/kg, i.p. in subcutaneous pentylenetetrazole (scPTZ) at 0.5 and 4.0 h, respectively. The *ortho* and *meta* derivative **2f** and **2g** exhibited weaker activity than *para* substituted derivatives **2a**, **2d**, **2e**, **2h**, and **2j**. In this series, most of the tested compounds showed no neurotoxicity except for compounds **2a** and **2h**, which showed neurotoxicity at the highest dose (300 mg/kg) after 4.0 h, possibly because the presence of highly polar group at *para* position.

Compound **2d**, **2e**, **2f**, **2j**, and **2l** showed significant anticonvulsant activity and were also tested for their CNS depressant effect (Table 2). The tested compounds showed 49.8, 21.6, 33.8, 54.5, and 11.5% increase in immobility time with respect to controls whereas the standard drug carbamazepine showed 30.6% increase in the immobility

Table 1 Anticonvulsant and neurotoxicity screening of *N*-substituted-3-chloro-2-azetidinones

Compound	R	MES[a]		PTZ[a]		Neurotoxicity[a]	
		0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
2a	4-OH	–	100	–	300	–	300
2b	2-OH	–	300	–	–	–	–
2c	2-OCH_3	–	300	–	–	–	–
2d	4-$N(CH_3)_2$	100	100	–	100	–	–
2e	4-CH_3	30	30	100	30	–	–
2f	3,4-Di-OCH_3	100	100	100	100	–	–
2g	3-OCH_3, 4-OH	300	100	–	300	–	–
2h	4-NO_2	–	100	300	100	–	300
2i	2-NO_2	–	300	–	300	–	–
2j	4-Cl	300	100	100	100	–	–
2k	2-Cl	–	300	–	–	–	–
2l	H	100	100	100	100	–	–
Phenytoin[b]		30	30	–	–	100	100
Carbamazepine[b]		30	100	100	300	–	30

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

[b] Activity reported (show 100% protection at respective dose)

Table 2 CNS depressant study on selected active compounds by forced swim pool test method

Compound	R	Duration of immobility (s) (mean ± SEM)	Increased of immobility (%)
2d	4-$N(CH_3)_2$	102.83 ± 1.49	49.83
2e	4-CH_3	75.16 ± 1.16	21.66
2f	3,4-Di-OCH_3	87.33 ± 0.66	33.83
2j	4-Cl	110.50 ± 0.76	54.54
2l	H	65.50 ± 0.73	11.50
Carbamazepine		84.16 ± 0.47	30.66
Control		53.5 ± 0.42	–

time, indicating a lower CNS depressant effect for compounds **2e** and **2l**.

Conclusion

A series of *N*-[3-chloro-2-(substitutedphenyl)-4-oxo-azetidin-1-yl]isonicotinamide derivatives were synthesized. The anticonvulsant effect and the neurotoxicity of the compounds were calculated with MES test, Sc-PTZ, and rotarod tests with intraperitoneally injected mice. Among the synthesized it was found that *N*-[3-chloro-2-(4-methylphenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2e**) possessed significant anticonvulsant activity in comparison to standard drug phenytoin and carbamazepine (showed activity at 30 mg/kg body weight without neurotoxicity). On the basis of these results it can be concluded that the anticonvulsant activity was affected by two factors. Firstly the introduction of electron withdrawing/releasing groups, where anticonvulsant activity decreases with the introduction of electron withdrawing groups like OH, NO_2, Cl and significant increases of anticonvulsant activity were observed with the substitution of electron donating groups like CH_3, OCH_3, $N(CH_3)_2$, and H. Moreover, the molecular symmetry is the 2nd factor influencing the biological activity because unsubstituted and *para*-substituted compounds showed good activity as compared to *ortho*- and *meta*-substituted compounds. Compound **2e** showed excellent anticonvulsant activity due to substitution of electron releasing group (*p*-CH_3) which increases the lipophilicity and on the other hand, *para* substitution facilitates molecule receptor interactions.

Experimental

General chemistry

All chemicals used in the synthesis were supplied by E. Merck and S.D. Fine Chemicals. Melting points are determined by open capillary tube method and are uncorrected. Purity of the compound was checked on TLC using iodine vapors as visualizing agents. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). ^{1}H NMR spectra were obtained on a Bruker DRX-300 (300 MHz FT NMR) spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as the internal reference (chemical shifts in δ ppm). Elemental analysis (C, H, and N) were undertaken with Perkin-Elmer model 240C analyzer. Mass spectra were recorded at Jeol SX-102 spectrometer.

General procedure for synthesis of isonicotinic acid (substituted-benzylidene)-hydrazide (**1a–l**)

To a solution of isoniazide (0.01 mol) in absolute ethanol (30 ml) few drops of glacial acetic acid and substituted benzaldehyde (0.01 mol) were added. The reaction mixture was refluxed for 3 h on water bath. The reaction mixture was poured onto crushed ice, a solid mass separated was filtered, washed with water and recrystallized from ethanol.

*Isonicotinic acid (4-hydroxy-benzylidene)-hydrazide (**1a**)*

Yield 67%; m.p.: 242–245°C; IR (KBr, cm^{-1}): 3546 (OH), 3447 (NH), 2917 (NCH), 1671 (C=O); ^{1}H NMR ($CDCl_3$), δ (ppm): 11.9 (bs, 1H, CONH), 9.31 (s, 1H, OH), 8.52 (s, 1H, N–CH), 8.1–8.4 (m, 4H, pyridine), 7.1–7.69 (m, 4H, Ar–H); MS: *m/z* 241 (M^+); Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42; Found: C, 64.61; H, 4.43; N, 17.48.

*Isonicotinic acid (2-hydroxy-benzylidene)-hydrazide (**1b**)*

Yield 73%; m.p.: 174–176°C; IR (KBr, cm^{-1}): 3521 (OH), 3398 (NH), 2924 (NCH), 1676 (C=O); ^{1}H NMR ($CDCl_3$), δ (ppm): 10.03 (bs, 1H, CONH), 9.43 (s, 1H, OH), 8.34 (s, 1H, N–CH), 7.64–7.91 (m, 4H, pyridine), 7.1–7.59 (m, 4H, Ar–H); MS: *m/z* 241 (M^+); Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42; Found: C, 64.57; H, 4.42; N, 17.41.

*Isonicotinic acid (2-methoxy-benzylidene)-hydrazide (**1c**)*

Yield 70%; m.p.: 131–133°C; IR (KBr, cm^{-1}): 3425 (NH), 3028 (NCH), 1668 (C=O); ^{1}H NMR ($CDCl_3$), δ (ppm):

12.07 (bs, 1H, CONH), 8.7 (s, 1H, N–CH), 7.8–8.4 (m, 4H, pyridine), 7.4–7.76 (m, 4H, Ar–H), 2.98 (s, 3H, OCH_3); MS: *m/z* 255 (M^+); Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46; Found: C, 65.74; H, 5.02; N, 16.34.

*Isonicotinic acid (4-dimethylamino-benzylidene)-hydrazide (**1d**)*

Yield 75%; m.p.: 192–194°C; IR (KBr, cm^{-1}): 3475 (NH), 3012 (NCH), 1659 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 12.18 (bs, 1H, CONH), 8.3 (s, 1H, N–CH), 8.2–8.5 (m, 4H, pyridine), 6.9–7.75 (m, 4H, Ar–H), 2.89 (s, 6H, $2CH_3$); MS: *m/z* 268 (M^+); Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88; Found: C, 67.04; H, 6.11; N, 20.69.

*Isonicotinic acid (4-methyl-benzylidene)-hydrazide (**1e**)*

Yield 70%; m.p.: 212–214°C; IR (KBr, cm^{-1}): 3425 (NH), 3028 (NCH), 1668 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 11.07 (bs, 1H, CONH), 8.6 (s, 1H, N–CH), 7.9–8.7 (m, 4H, pyridine), 6.9–7.76 (m, 4H, Ar–H), 2.50 (s, 3H, CH_3); MS: *m/z* 239 (M^+); Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56; Found: C, 70.18; H, 5.32; N, 17.35.

*Isonicotinic acid (3,4-dimethoxy-benzylidene)-hydrazide (**1f**)*

Yield 68%; m.p.: 167–169°C; IR (KBr, cm^{-1}): 3425 (NH), 3028 (NCH), 1679 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 11.37 (bs, 1H, CONH), 8.51 (s, 1H, N–CH), 7.8–8.3 (m, 4H, pyridine), 6.8–7.2 (m, 3H, Ar–H), 3.87 (s, 6H, $2OCH_3$); MS: *m/z* 285 (M^+); Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73; Found: C, 62.98; H, 5.13; N, 14.58.

*Isonicotinic acid (4-hydroxy-3-methoxy-benzylidene)-hydrazide (**1g**)*

Yield 65%; m.p.: 187–189°C; IR (KBr, cm^{-1}): 3387 (NH), 3087 (NCH), 1675 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 12.25 (bs, 1H, CONH), 9.6 (s, 1H, OH), 8.42 (s, 1H, N–CH), 7.6–8.2 (m, 4H, pyridine), 6.9–7.73 (m, 3H, Ar–H), 3.76 (s, 3H, OCH_3); MS: *m/z* 271 (M^+); Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49; Found: C, 61.83; H, 4.71; N, 15.29.

*Isonicotinic acid (4-nitro-benzylidene)-hydrazide (**1h**)*

Yield 75%; m.p.: 155–157°C; IR (KBr, cm^{-1}): 3467 (NH), 3014 (NCH), 1678 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 11.76 (bs, 1H, CONH), 8.32 (s, 1H, N–CH), 7.92–8.56 (m, 4H, CH-pyridine), 6.75–7.54 (m, 4H, Ar–H); MS: *m/z* 270 (M^+); Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73; Found: C, 57.65; H, 3.57; N, 20.58.

*Isonicotinic acid (2-nitro-benzylidene)-hydrazide (**1i**)*

Yield 76%; m.p.: 123–125°C; IR (KBr, cm^{-1}): 3464 (NH), 3011 (NCH), 1673 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 10.76 (bs, 1H, CONH), 8.56 (s, 1H, N–CH), 8.21–8.49 (m, 4H, CH-pyridine), 6.76–7.54 (m, 4H, Ar–H); MS: *m/z* 270 (M^+); Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73; Found: C, 57.69; H, 3.61; N, 20.59.

*Isonicotinic acid (4-chloro-benzylidene)-hydrazide (**1j**)*

Yield 73%; m.p.: 225–227°C; IR (KBr, cm^{-1}): 3399 (NH), 2969 (NCH), 1653 (C=O), 679 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 12.27 (bs, 1H, CONH), 8.52 (s, 1H, N–CH), 7.3–8.1 (m, 4H, pyridine), 6.91–7.73 (m, 4H, Ar–H); MS: *m/z* 259 (M^+), 261 (M^++2); Anal. Calcd for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18; Found: C, 60.01; H, 3.67; N, 16.04.

*Isonicotinic acid (2-chloro-benzylidene)-hydrazide (**1k**)*

Yield 67%; m.p.: 177–179°C; IR (KBr, cm^{-1}): 3403 (NH), 2976 (NCH), 1643 (C=O), 674 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 12.07 (bs, 1H, CONH), 8.41 (s, 1H, N–CH), 7.3–8.0 (m, 4H, pyridine), 6.81–7.72 (m, 4H, Ar–H); MS: *m/z* 259 (M^+), 261 ($M^+ + 2$); Anal. Calcd for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18; Found: C, 59.97; H, 3.71; N, 16.21.

*Isonicotinic acid benzylidene-hydrazide (**1l**)*

Yield 72%; m.p.: 102–104°C; IR (KBr, cm^{-1}): 3425 (NH), 3028 (NCH), 1668 (C=O); ^1H NMR ($CDCl_3$), δ (ppm): 12.07 (bs, 1H, CONH), 7.95 (s, 1H, N–CH), 7.63–7.89 (m, 4H, pyridine), 6.92–7.75 (m, 5H, Ar–H); MS: *m/z* 225 (M^+); Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66; Found: C, 69.17; H, 4.71; N, 18.54.

General procedure for synthesis of N-[3-chloro-2-(substitutedphenyl)-4-oxo-azetidin-1-yl]isonicotinamide derivatives (**2a–l**)

A solution of coumpound **1a–l**, triethylamine (0.02 mol) and chloroacetylchloride (0.02 mol) in DMF (40 ml) was refluxed for 3 h on water bath. The reaction mixture was poured onto crushed ice, a solid mass separated out which was filtered, washed with water and recrystallized from ethanol.

*N-[3-Chloro-2-(4-hydroxy-phenyl)-4-oxoazetidin-1yl]isonicotinamide (**2a**)*

Yield 70%; m.p.: 292–294°C; IR (KBr, cm^{-1}): 3425 (NH), 3019 (CH), 1671 (C=O), 657 (C–Cl); ^1H NMR ($CDCl_3$), δ

(ppm): 11.24 (bs, 1H, CONH), 9.32 (s, 1H, OH), 8.41–8.79 (m, 4H, pyridine), 7.67–7.98 (m, 4H, Ar–H), 7.13 (d, 1H, N–CH), 5.49 (d, 1H, CH–Cl); MS: *m/z* 317 (M^+), 319 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 11.16; Found: C, 56.58; H, 3.69; N, 10.98.

*N-[3-Chloro-2-(2-hydroxy-phenyl)-4-oxoazetidin-1yl]isonicotinamide (**2b**)*

Yield 73%; m.p.: 174–176°C; IR (KBr, cm^{-1}): 3412 (NH), 3029 (CH), 1656 (C=O), 677 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.04 (bs, 1H, CONH), 9.21 (s, 1H, OH), 8.38–8.79 (m, 4H, pyridine), 7.77–7.93 (m, 4H, Ar–H), 7.08 (d, 1H, N–CH), 5.48 (d, 1H, CH–Cl); MS: *m/z* 317 (M^+), 319 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 11.16; Found: C, 56.59; H, 3.67; N, 11.21.

*N-[3-Chloro-2-(2-methoxy-phenyl)-4-oxoazetidin-1yl]isonicotinamide (**2c**)*

Yield 70%; m.p.: 160–162°C; IR (KBr, cm^{-1}): 3425 (NH), 3023 (CH), 1670 (C=O), 687 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.91 (bs, 1H, CONH), 7.75–8.79 (m, 4H, pyridine), 7.3 (d, 1H, N–CH), 6.54–6.95 (m,4H, Ar–H), 5.47 (d, 1H, CH–Cl), 3.67 (s, 3H, OCH_3); MS: *m/z* 331 (M^+) 333 ($M^+ + 2$); Anal. Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67; Found: C, 57.76; H, 4.13; N, 12.81.

*N-[3-Chloro-2-(4-dimethylamino-phenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2d**)*

Yield: 70%; m.p.: 230–232°C; IR (KBr, cm^{-1}): 3460 (NH), 3052 (CH), 1655 (C=O), 671 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.63 (bs, 1H, CONH), 8.31 (d, 1H, N–CH), 7.77–8.29 (m, 4H, pyridine), 6.54–6.95 (m, 4H, Ar–H), 5.43 (d, 1H, CH–Cl), 2.74 (s, 6H, $2CH_3$); MS: *m/z* 344 (M^+), 346 ($M^+ + 2$); Anal. Calcd for $C_{17}H_{17}ClN_4O_2$: C, 59.22; H, 4.97; N, 16.25; Found: C, 59.03; H, 4.76; N, 16.11.

*N-[3-Chloro-2-(4-methyl-phenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2e**)*

Yield: 60%; m.p.: 140–142°C; IR (KBr, cm^{-1}): 3387 (NH), 3012 (CH), 1684 (C=O), 676 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.86 (bs, 1H, CONH), 8.42 (d, 1H, N–CH), 7.89–8.39 (m, 4H, pyridine), 7.54–7.95 (m, 4H, Ar–H), 5.49 (d, 1H, CH–Cl), 2.54 (s, 3H, CH_3); MS: *m/z* 315 (M^+), 317 ($M^+ + 2$); Anal. Calcd for $C_{16}H_{14}ClN_3O_2$: C, 60.86; H, 4.47; N, 13.31; Found: C, 60.67; H, 4.29; N, 13.17.

*N-[3-Chloro-2-(3,4-dimethoxyl-phenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2f**)*

Yield: 80%; m.p.: 180–182°C; IR (KBr, cm^{-1}): 3416 (NH), 3021 (CH), 1674 (C=O), 665 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 12.07 (bs, 1H, CONH), 8.35 (d, 1H, N–CH), 7.79–8.11 (m, 4H, pyridine), 7.14–7.55 (m, 3H, Ar–H), 5.23 (d, 1H, CH–Cl), 3.79 (s, 6H, $2OCH_3$); MS: *m/z* 361 (M^+), 363 ($M^+ + 2$); Anal. Calcd for $C_{17}H_{16}ClN_3O_4$: C, 56.44; H, 4.46; N, 11.61; Found: C, 56.23; H, 4.28; N, 11.47.

*N-[3-Chloro-2-(4-hydroxy-3-methoxy-phenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2g**)*

Yield: 70%; m.p.: 211–213°C; IR (KBr, cm^{-1}): 3405 (NH), 3029 (CH), 1651 (C=O), 685 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 12.13 (bs, 1H, CONH), 10.23(s, 1H, OH), 8.05 (d, 1H, N–CH), 7.76–8.18 (m, 4H, pyridine), 7.24–7.57 (m, 3H, Ar–H), 5.73 (d, 1H, CH–Cl), 3.73 (s, 3H, OCH_3); MS: *m/z* 347 (M^+), 349 ($M^+ + 2$); Anal. Calcd for $C_{16}H_{14}ClN_3O_4$: C, 55.26; H, 4.06; N, 12.08; Found: C, 55.03; H, 3.89; N, 12.18.

*N-[3-Chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2h**)*

Yield: 80%; m.p.: 192–194°C; IR (KBr, cm^{-1}): 3415 (NH), 3011 (CH), 1661 (C=O), 672 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.97 (bs, 1H, CONH), 8.11 (d, 1H, N–CH), 7.76–7.98 (m, 4H, pyridine), 7.14–7.58 (m, 4H, Ar–H), 5.62 (d, 1H, CH–Cl); MS: *m/z* 346 (M^+) 348 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{11}ClN_4O_4$: C, 51.96; H, 3.20; N, 16.16; Found: C, 51.75; H, 3.04; N, 16.01.

*N-[3-Chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2i**)*

Yield: 74%; m.p.: 170–172°C; IR (KBr, cm^{-1}): 3434 (NH), 2978 (CH), 1660 (C=O), 668 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 10.95 (bs, 1H, CONH), 8.12 (d, 1H, N–CH), 7.75–7.87 (m, 4H, pyridine), 7.17–7.53 (m, 4H, Ar–H), 5.49 (d, 1H, CH–Cl); MS: *m/z* 346 (M^+) 348 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{11}ClN_4O_4$: C, 51.96; H, 3.20; N, 16.16; Found: C, 51.79; H, 3.14; N, 16.23.

*N-[3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2j**)*

Yield: 72%; m.p.: 270–272°C; IR (KBr, cm^{-1}): 3398 (NH), 3017 (CH), 1679 (C=O), 681 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 11.67 (bs, 1H, CONH), 8.17 (d, 1H, N–CH), 7.78–8.01 (m, 4H, pyridine), 7.34–7.79 (m, 4H, Ar–H), 5.47 (d, 1H, CH–Cl); MS: *m/z* 335 (M^+) 337

($M^+ + 2$); Anal. Calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50; Found: C, 53.47; H, 3.19; N, 12.39.

*N-[3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl]isonicotinamide (**2k**)*

Yield: 85%; m.p.: 205–207°C; IR (KBr, cm^{-1}): 3356 (NH), 3027 (CH), 1656 (C=O), 676 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 10.54 (bs, 1H, CONH), 8.03 (d, 1H, N–CH), 7.67–7.98 (m, 4H, pyridine), 7.32–7.76 (m, 4H, Ar–H), 5.43 (d, 1H, CH–Cl); MS: *m/z* 335 (M^+) 337 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50; Found: C, 53.48; H, 3.14; N, 12.36.

*N-(3-Chloro-2-oxo-4-phenyl-azetidin-1-yl)-isonicotinamide (**2l**)*

Yield: 70%; m.p.: 131–133°C; IR (KBr, cm^{-1}): 3402 (NH), 3023 (CH), 1686 (C=O), 661 (C–Cl); ^1H NMR ($CDCl_3$), δ (ppm): 12.08 (bs, 1H, CONH), 8.21 (d, 1H, N–CH), 7.68–8.11 (m, 4H, pyridine), 7.44–7.98 (m, 5H, Ar–H), 5.74 (d, 1H, CH–Cl); MS: *m/z* 301 (M^+) 303 ($M^+ + 2$); Anal. Calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93; Found: C, 59.63; H, 4.14; N, 13.49.

Pharmacology

All the compounds were screened for anticonvulsant activity adopting the anticonvulsant screening program (ASP) including maximal electroshock test (MES), the subcutaneous pentylene tetrazole (scPTZ), and evaluation of neurotoxicity (TOX) (Krall *et al.*, 1978; Porter *et al.*, 1984; Kupferberg, 1989). The mice weighing 18–25.5 g of either sex were used, and the number of animals used was six in each group. PEG-400 was used for dissolving the test compounds in MES, ScPTZ, and Minimal Motor Impairment Test. The compounds were administered intraperitoneally (0.1 ml/10 g) to mice, at doses of 30, 100, and 300 mg/kg body weight.

Maximal electroshock seizer

In the MES test, the mice were subjected to 50 mA of 60 Hz alternating current from a convulsiometer for 0.2 s through a pair of electrodes attached to each ear. The duration of the tonic hind limb extensor phase, and the number of animals protected from convulsions were noted. Phenytoin was used as standard drug.

Subcutaneous pentylene tetrazole

Pentylene tetrazole was used as convulsant, phenytoin and carbamazepine are used as standard drugs. Convulsion was induced 1 h after administration of the standard drug or the test compounds by i.p. injection of PTZ (30, 100, and 300 mg/kg) dissolved in saline to a volume of 0.1 ml/10 g body weight. The time needed for the development of unequivocal sustained clonic seizer activity involving the limbs (isolated myoclonic jerks or other preconvulsive chewing behavior were not counted) was carefully noted. Animals which did not meet this criteria were considered protected.

Minimal motor impairment (neurotoxicity)

The undesirable effects (toxicity) were studied by monitored the animals for overt sign of impaired neurological or muscular function. In mice, rotorod procedure was used, which rotate at a speed of 6 rpm. The dose at which animals fell off this rotating rod three times during a 1 min period was considered.

CNS depression study

The forced swim method (Porsolt's swim pool test) is followed to study CNS depression (Porsolt *et al.*, 1978). Mice are placed in a chamber (diameter 45 cm, height: 20 cm) containing water up to a height of 15 cm at 25 ± 2°C. Two swim sessions are conducted, an initial 15 min pre-test, followed by a 5 min test session 24 h later. The animals are administered an i.p. injection (30 mg/kg) of the test compounds 30 min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5 min test period are measured.

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