Microwave-Assisted Facile Synthesis and anticonvulsant evaluation of Novel N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1, 3-dioxoisoindolin-2-yl)acetamides

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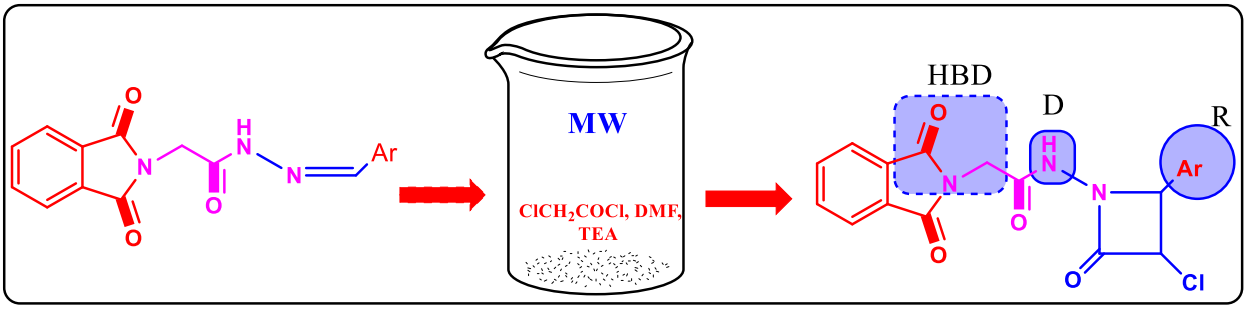
Graphical abstract



Abstract

Herewith, we report the design and synthesis of a series of N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide **7(a-l)** derivatives, obtained by condensation of Schiff's base and chloroacetyl chloride in dimethyl formamide as solvent and few drops of triethyl amine as a catalyst under microwave irradiation for about 3-4 min (700 W) at 80^0C based on four component pharmacophoric model to get structural prerequisite indispensable for anticonvulsant activity. The synthesized derivatives were investigated for CNS depressant, maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (sc-PTZ) induced seizure and neurotoxicity screening. Most of the compounds were found to be potent in MES model. The anticonvulsant screening data shows that 65% of the compounds were found to be active against MES model when compared to 35% sc-PTZ model.

Keywords: Dioxoisoindolin-2-yl; Azetidinone; Microwave irradiation; Anticonvulsant evaluation; CNS depression.

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Introduction:

Epilepsy is a chronic disorder affecting 50 million people worldwide [1–3]. It is characterized by recurrent seizures due to abnormal excessive and synchronous neuronal activity in the brain. Epilepsy, being one of the most common and serious neurological disorder is characterized by recurrent seizures which results from a temporary electrical disturbance of the brain due to an imbalance between excitatory and inhibitory neurotransmitters. About one third of the patients do not respond well to current multiple drug therapy [4, 5].

A global campaign against epilepsy conducted by World Health Organization (WHO) in partnership with International Bureau for Epilepsy (IBE) and International League against Epilepsy (ILAE) suggested that around 1% of world population at any time is afflicted with this neurological disorder [6, 7]. Phenytoin, carbamazepine, lamotrigine, sulfamate and topiramate are recent antiepileptic drugs which have been clinically effective against different types of seizures. Moreover, these drugs cause various side effects such as drowsiness, gastrointestinal disturbance, hepato-toxicity, and megaloblastic anemia.

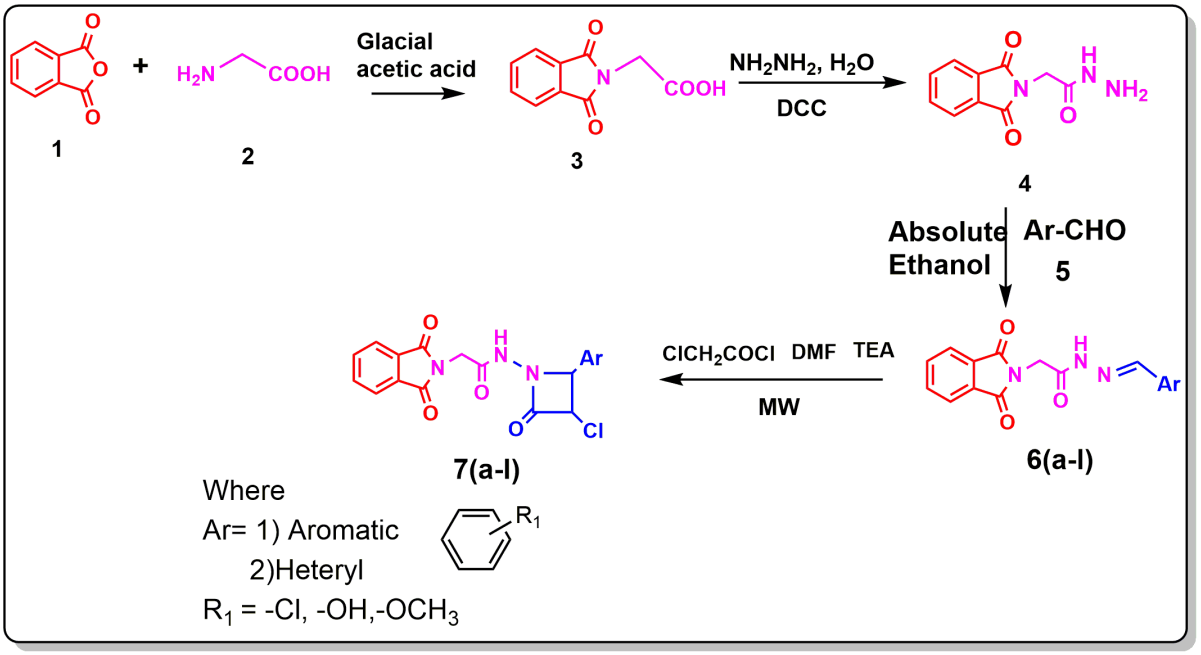
Many researchers have investigated phthalimide and azetidinone moieties due to their potential anticonvulsant and CNS depressant activities [8-20]. On the basis of the above findings from literature survey and considering the need for the development of potent CNS active agents, in continuation to our earlier efforts in finding better, novel anticonvulsant agents [21-24] it was thought worthwhile to synthesize heterocyclic system containing phthalimide and azetidinone ring to give coupled derivatives having more potent anticonvulsant activity.

In the present work, our objective was to design and synthesize new compounds having dioxoindolin moiety coupled with azetidinone nucleus via amide linkage, as a pharmacophore, with the hope to get compounds with enhanced anticonvulsant activity. Thus, novel, **N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl) acetamide 7(a-l)** derivatives were synthesized as antiepileptic drugs that shows similar mode of action on neuronal sodium channels as phenytoin [25]. All the synthesized titled compounds comprised of the essential pharmacophoric elements that are necessary for good anticonvulsant activity as suggested by Unverferth et al. [26], which are indicated by rectangles in Fig. 1. The essential structural features which could be responsible for an interaction with the active site were a hydrophobic unit (R), an electron donor (D) group, and a hydrogen donor/acceptor (HBD) unit [27]. The title compounds were synthesized by microwave method as it gives less pollution, shorter reaction time, increased rate of reaction, more yield, cleaner and greener eco-friendly synthetic protocol.

Results and discussions

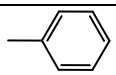
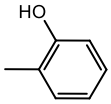
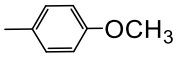
Chemistry

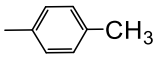
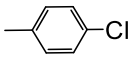
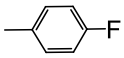
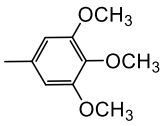
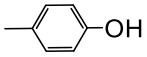
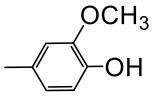
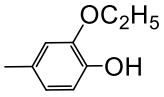
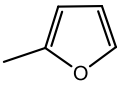
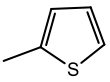
The synthetic protocol employed for the synthesis of **N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide 7(a-l)** derivatives is presented in Scheme 1. N-substituted benzylidene/methylene-2-(1,3-dioxo isoindolin-2-yl) acetohydrazides **6(a-l)** was obtained as per procedure [28] which upon reaction with chloro acetyl chloride in DMF and using few drops of triethyl amine as a catalyst under microwave irradiation for about 3-4 min (700 W), gives final derivatives**7(a-l).** The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. The assignments of the structures were based on elemental and spectral data. The physical data of the synthesized compounds is presented in Table 1. The proposed structures of final compounds were confirmed by the data obtained from IR, NMR, Mass and elemental analysis.



Scheme 1: Synthesis of target derivatives **7(a-l).**

Table 1: Physical constants data for N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide 7(a-l)

Code	Ar	Molecular formula	Mol. wt.	% Yield	Time (min)	M.P. ^{0}C	R_f value
7a		$C_{19}H_{14}ClN_3O_4$	383.79	79	4	130-135	0.62
7b		$C_{19}H_{14}ClN_3O_5$	399.78	84	3	137-140	0.61
7c		$C_{20}H_{16}ClN_3O_5$	413.81	78	3.5	170-173	0.66

7d		$C_{20}H_{16}ClN_3O_4$	397.81	86	4.5	146-148	0.56
7e		$C_{19}H_{13}Cl_2N_3O_4$	418.23	78	4	151-153	0.65
7f		$C_{19}H_{13}ClFN_3O_4$	401.78	68	3	140-142	0.78
7g		$C_{22}H_{20}ClN_3O_7$	473.86	58	2	141-143	0.56
7h		$C_{19}H_{14}ClN_3O_5$	399.78	78	3	178-180	0.65
7i		$C_{20}H_{16}ClN_3O_6$	429.81	75	2.5	162-165	0.55
7j		$C_{21}H_{18}ClN_3O_6$	443.84	79	4	154-155	0.58
7k		$C_{17}H_{12}ClN_3O_5$	373.75	82	4.5	130-134	0.46
7l		$C_{17}H_{12}ClN_3O_4S$	389.81	83	3.5	171-173	0.54

Anticonvulsant activity

A series of novel **N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide 7(a-l)** were obtained under microwave irradiation in good yield and require shorter reaction times.

All the synthesized compounds were evaluated for their anticonvulsant activity by MES and sc-PTZ model and have shown best protection against MES test (Table 2). In MES test, the anticonvulsant activity of the newly synthesized compounds was carried out at 0.5 and 4 h at the dose of 100 mg/kg. The compounds **7a**, **7d**, and **7e** have shown best protection at both time intervals. In MES test, the compounds **7b**, **7c**, **7g**, and **7h** showed protection at 0.5 h, while compounds **7f**, **7i** and **7j** showed protection at 4 h. In sc-PTZ test (Table 2), among synthesized compounds, **7a**, **7c**, **7d** and **7h** showed protection at both intervals while compound **7a, 7e, 7f, 7i** and **7j** showed protection at 0.5 h at the dose 100 mg/kg.

Table 2: Anticonvulsant and neurotoxicity screening of the synthesized compounds 7(a-l).

Comp.	MES Screen		Sc PTZ Screen		Neurotoxicity Screen
	0.5 h	4h	0.5 h	4h	4h
7a	100	100	100	100	Non-toxic
7b	100	-	100	-	Toxic
7c	100	-	100	100	Non-toxic
7d	100	100	100	100	Non-toxic
7e	100	100	100	-	Non-toxic
7f	-	100	100	-	Toxic
7g	100	-	-	-	Non-toxic
7h	100	-	100	100	Non-Toxic
7i	-	100	100	-	Non-toxic
7j	-	100	100	-	Non-toxic
7k	-	-	-	-	Toxic
7l	-	-	-	-	Non-toxic
Phenytoin	100	100	X	X	X

Dose 100 mg/kg of the compound was administered and the protection and neurotoxicity were measured after 0.5 and 4 h. The figures indicate the minimal dose required to cause protection or neurotoxicity in 50% or more of the animals. The dash (-) indicates the absence of anticonvulsant activity or neurotoxicity. (X) denotes not tested.

Neurotoxicity screening

In neurotoxicity screening, the compounds **7a**, **7c**, **7d**, **7e**, **7g**, **7i** and **7j** were found to be nontoxic at a dose of 100 mg/kg while compounds **7b**, **7f**, **7h** and **7k** were found to be toxic at the same dose after 4 h (Table 2).

Behavioural activity

From the behavioural activity of synthesized compounds using actophotometer, the compounds **7a**, **7c** and **7e** showed no behavioural despair effect when compared to diazepam at 0.5 h. The compounds **7a**, **7b**, **7e**, and **7h** showed no behavioural despair effect when compared to diazepam at 4 h (Table 3). All the other compounds were found to decrease behavioural activity of the animals at 100 mg/kg compared to diazepam.

Table 3: Behavioural study of the synthesized compounds 7(a-l) using actophotometer

Comp.	Activity Score	Post Treatment [a]	
	Control (24 h before	0.5h	4h
7a	163.41±5.192	34.20±3.720**	27.60±2.015ns
7b	115.79±4.294	85.20±5.305**	63.40±3.250ns
7c	120.82±3.942	69.20±0.663**	51.40±9.522**
7d	150.61±10.628	52.00±11.375ns	82.60±2.182**
7e	135.59±6.547	99.60±3.265**	18.00±1.414ns
7f	141.44±8.060	61.60±7.501**	63.40±5.240**
7g	134.22±5.380	39.20±3.184ns	98.80±4.259**
7h	110.63±5.60	73.00±3.715**	21.80±2.835ns
7i	140.60±8.453	60.80±4.748**	42.20±12.265**
7j	120.18±3.736	83.00±8.185**	72.00±11.459ns
7k	118.41±2.731	102.60±9.770**	90.20±9.937ns
7l	138.63±3.076	101.60±2.713**	50.80±8.114ns
Diazepam[b]	170.60±2.839	71.80±13.309**	

a) Each value represents the mean SEM significantly different from the control at $p<0.05$; ns denotes not significant at $p<0.05$ (Student's t-test); locomotor activity score was measured for 10 min. b) The compound was tested at dose level of 4 mg/kg (i.p.).

Experimental

Chemistry

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled unless otherwise noted. Synthetic microwave oven Milestone micro synth system was used for synthesis of final title compounds. The progress of the reaction was monitored by TLC, silica gel-G (Merck) coated aluminium plates, visualized by iodine vapor. Infrared (IR) and nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra of the synthesized compounds were recorded on JASCO FTIR (PS 4000) using KBr pellets and Bruker Avance II (400MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm), using TMS as an internal standard. Elemental analyses (C, H, and N) were undertaken with a Shimadzu FLASHEA112 analyzer and all analyses were

consistent with theoretical values (within ±0.5%) unless indicated. The mass spectra were recorded on a Waters MicroMass ZQ 2000 spectrometer.

General procedure for the preparation of N-substituted benzylidene/methylene-2-(1, 3-dioxo isoindolin-2-yl) acetohydrazides 6(a-l)

N'-Substituted benzylidene/methylene-2-(1, 3-dioxoisoindolin-2-yl) acetohydrazide **6(a-l)** were synthesized as per given procedure [28].

General procedure for the preparation of N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide 7(a-l)

In an Erlenmeyer flask compound Schiff base **6(a-l)** (0.01 mol) and DMF (15mL) were taken. To it chloro acetyl chloride (0.01 mol) and triethyl amine (0.01 mol) as a catalyst was added slowly. The reaction mixture was irradiated inside a synthetic microwave oven for about 3-4 min (700 W) at 80^0C. After completion of reaction (monitored by TLC), mixture was poured into ice cold water. The solid product formed was filtered, dried and recrystallized from ethanol. The structures of the final compounds of the series **7(a-l)** were confirmed by the spectral data and elemental analysis as given below [29].

N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7a)

IR (KBr, υ_{max} in cm^{-1}): 3333 (N-H of amide), 3011 (C-H of aromatic), 1770 (C=O of azetidinone), 1715, 1710 (C=O of Phthalimide), 1675 (C=O of amide), 1605 (C-C of aromatic), 1314 (C-N), 1280 (N-N); ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 4.6 (s, 2H, -CH_2 of alkyl), 5.08 (s, 1H, -CH of lactam ring), 7.27-7.91 (m, 4H, Ar-H), 9.2 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 143, 132, 128, 126, 123, 64, 50; MS m/z: 382 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_4$: C, 59.46; H, 3.68; Cl, 8.50; N, 10.95; Found: C, 59.40; H, 3.55; Cl, 8.47; N, 10.91.

N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7b)

IR (KBr, υ_{max} in cm^{-1}): 3330 (N-H of amide), 3014 (C-H of aromatic), 1769 (C=O of azetidinone), 1713, 1716 (C=O of Phthalimide), 1670 (C=O of amide), 1610 (C-C of aromatic), 1310 (C-N), 1285 (N-N); ^{1}H NMR (DMSO d_6, 400 MHz) δ ppm: 4.58 (s, 2H, -CH_2 of alkyl), 5.06 (s, 1H, -CH of lactam ring), 6.89-7.91 (m, 4H, Ar-H), 9.15 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 154, 132, 128, 126, 123, 121, 64, 61, 50; MS m/z: 398.78 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_5$: C, 57.08; H, 3.53; Cl, 8.56; N, 10.51; Found: C, 57.01; H, 3.50; Cl, 8.54; N, 10.45.

N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7c)

IR (KBr, υ_{max} in cm^{-1}): 3335 (N-H of amide), 3012 (C-H of aromatic), 1770 (C=O of azetidinone), 1713, 1712 (C=O of Phthalimide), 1660 (C=O of amide), 1604 (C-C of aromatic), 1311 (C-N),

1277 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.28 (s, 3H, -OCH_3 of phenyl ring), 5.3 (s, 1H, -CH of lactam ring), 5.7 (s, 2H, -CH_2 of alkyl), 6.9 -7.75 (m, 4H, Ar-H), 9.1 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 158, 135, 132, 126, 123, 114, 67, 64, 55, 50; MS m/z: 414 (M+1); Anal. Calcd. for $C_{20}H_{16}ClN_3O_5$: C, 58.05; H, 3.90; Cl, 8.57; N, 10.15; O, 19.33; Found: C, 58.10; H, 3.85; Cl, 8.55; N, 10.17.

N-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7d)

IR (KBr, υ_{max} in cm^{-1}): 3327 (N-H of amide), 3009 (C-H of aromatic), 1766 (C=O of azetidinone), 1710, 1714 (C=O of Phthalimide), 1675 (C=O of amide), 1601 (C-C of aromatic), 1309 (C-N), 1287 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 2.18 (s, 3H, -CH_3 of phenyl ring), 4.6 (s, 2H, -CH_2 of alkyl), 5.44 (s, 1H, -CH of lactam ring), 7.09-7.98 (m, 4H, Ar-H), 9.16 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 140, 136, 132, 128, 125, 123, 67, 64, 50, 21; MS m/z: 397 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_4$: C, 60.38; H, 4.05; Cl, 8.91; N, 10.56; Found: C, 60.34; H, 3.99; Cl, 8.93; N, 10.51.

N-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7e)

IR (KBr, υ_{max} in cm^{-1}): 3345 (N-H of amide), 3152 (C-H of aromatic), 1762 (C=O of azetidinone), 1703, 1719 (C=O of Phthalimide), 1640 (C=O of amide), 1609 (C-C of aromatic), 1314 (C-N), 1285 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.5 (s, 2H, -CH_2 of alkyl), 5.40 (s, 1H, -CH of lactam ring), 7.84 -7.91 (m, 4H, Ar-H), 9.16 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 141, 132, 128, 127, 123, 67, 64, 50; MS m/z: 418 (M+1); Anal. Calcd. for $C_{19}H_{13}C_{l2}N_3O_4$: C, 54.56; H, 3.13; Cl, 16.95; N, 10.05;Found: C, 54.51; H, 3.08; Cl, 16.90; N, 10.01.

N-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7f)

IR (KBr, υ_{max} in cm^{-1}): 3340 (N-H of amide), 3160 (C-H of aromatic), 1756 (C=O of azetidinone), 1706, 1714 (C=O of Phthalimide), 1635 (C=O of amide), 1610 (C-C of aromatic), 1320 (C-N), 1281 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.5 (s, 2H, -CH_2 of alkyl), 5.40 (s, 1H, -CH of lactam ring), 7.84 -7.91 (m, 4H, Ar-H), 9.16 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 139, 132, 128, 123, 67, 64, 50; MS m/z: 402 (M+1); Anal. Calcd. for $C_{19}H_{13}C_{l2}N_3O_4$: C, 54.56; H, 3.13; Cl, 16.95; N, 10.05; Found: C, 54.51; H, 3.08; Cl, 16.90; N, 10.01.

N-(3-chloro-2-oxo-4-(3,4,5-trimethoxyphenyl)azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7g)

IR (KBr, υ_{max} in cm^{-1}): 3338 (N-H of amide), 3156 (C-H of aromatic), 1754 (C=O of azetidinone), 1710, 1717 (C=O of Phthalimide), 1640 (C=O of amide), 1625 (C-C of aromatic), 1317 (C-N), 1278 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 3.72 (s, 3H, -OCH_3 of phenyl ring),4.60 (s, 2H, -CH_2 of alkyl), 5.10 (s, 1H, -CH of lactam ring), 6.65 -7.90 (m, 4H, Ar-H), 9.05(s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 152, 137, 132, 123, 68, 64, 56, 50; MS m/z: 473

(M+1); Anal. Calcd. for $C_{22}H_{20}ClN_3O_7$: C, 55.76; H, 4.25; Cl, 7.48; N, 8.87; Found: C, 55.72; H, 4.21; Cl, 7.43; N, 8.85.

N-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7h)

IR (KBr, υ_{max} in cm^{-1}): 3497 (-OH stretching), 3335 (N-H of amide), 3152 (C-H of aromatic), 1754 (C=O of azetidinone), 1715, 1720 (C=O of Phthalimide), 1640 (C=O of amide), 1625 (C-C of aromatic), 1310 (C-N), 1280 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.56 (s, 2H, -CH_2 of alkyl), 5.15 (s, 1H, -CH of lactam ring), 6.71 -7.92 (m, 4H, Ar-H), 9.1 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 156, 136, 132, 127, 123, 115, 67, 64, 50; MS m/z: 400 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_5$: C, 57.08; H, 3.53; Cl, 8.87; N, 10.51; Found: C, 57.02; H, 3.48; Cl, 8.85; N, 10.49;

N-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7i)

IR (KBr, υ_{max} in cm^{-1}): 3457 (-OH stretching), 3345 (N-H of amide), 3015 (C-H of aromatic), 1750 (C=O of azetidinone), 1720, 1722 (C=O of Phthalimide), 1640 (C=O of amide), 1610 (C-C of aromatic), 1315 (C-N), 1280 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.18 (s, 3H, -OCH_3 of phenyl ring), 5.16 (s, 1H, -CH of lactam ring), 5.3(s, 1H,-OH of aromatic ring), 5.8 (s, 2H, -CH_2 of alkyl), 6.9-8.2 (m, 4H, Ar-H), 9.08 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 147, 146, 137, 132, 123, 119, 110, 67, 64, 50; MS m/z: 430 (M+1); Anal. Calcd. for $C_{19}H_{14}ClN_3O_4$: C, 55.89; H, 3.75; Cl, 8.25; N, 9.78; Found: C, 55.83; H, 3.71; Cl, 8.20; N, 9.72;

N-(3-chloro-2-(3-ethoxy-4-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl) acetamide (7j)

IR (KBr, υ_{max} in cm^{-1}): 3450(-OH stretching), 3340 (N-H of amide), 3020 (C-H of aromatic), 1755 (C=O of azetidinone), 1715, 1720 (C=O of Phthalimide), 1638 (C=O of amide), 1617 (C-C of aromatic), 1320 (C-N), 1275 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 1.3 (s, 1H,-CH_3 of phenyl) 4.13(dd,2H,-CH_2 of phenyl ring), 5.08 (s, 1H, -CH of lactam ring), 4.55 (s,2H, -CH_2 of alkyl), 7.84-7.91 (m, 4H, Ar-H), 9.13 (s, 1H, -NH) 9.80 (s, 1H, -OH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163,148, 146, 132, 123, 115, 110, 67, 64, 50, 14; MS m/z: 444(M+1); Anal. Calcd. for $C_{21}H_{18}ClN_3O_6$: C, C, 56.83; H, 4.09; Cl, 7.99; N, 9.47; Found: C, 56.77; H, 4.03; Cl, 7.94;N, 9.41.

N-(3-chloro-2-(furan-2-yl)-4-oxoazetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (7k)

IR (KBr, υ_{max} in cm^{-1}): 3329 (N-H of amide), 3009 (C-H of aromatic), 1765 (C=O of azetidinone), 1710, 1716 (C=O of Phthalimide), 1680 (C=O of amide), 1615 (C-C of aromatic), 1316 (C-N), 1275 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.6 (s, 2H, -CH_2 of alkyl), 5.29 (s, 1H, -CH of lactam ring), 7.84 -7.91 (m, 4H, Ar-H), 9.13 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170,

168, 163, 151, 141, 132, 123, 110, 109, 65, 62, 50; MS m/z: 374(M+1); Anal. Calcd. for $C_{17}H_{12}ClN_3O_5$: C, 54.63; H, 3.24; Cl, 9.48; N, 11.24; Found: C, 54.59; H, 3.20; Cl, 9.42; N, 11.21;.

N-(3-chloro-2-oxo-4-(thiophen-2-yl) azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl) acetamide (7l)

IR (KBr, υ_{max} in cm^{-1}): 3331 (N-H of amide), 3010 (C-H of aromatic), 1775 (C=O of azetidinone), 1718, 1713 C=O of Phthalimide), 1670 (C=O of amide), 1610 (C-C of aromatic), 1311 (C-N), 1282 (N-N); ^{1}H NMR (DMSOd_6, 400 MHz) δ ppm: 4.5 (s, 2H, -CH_2 of alkyl), 5.10 (s, 1H, -CH of lactam ring), 7.84 -7.93 (m, 4H, Ar-H), 9.01 (s, 1H, -NH); ^{13}C NMR (100MHz DMSO ppm): 170, 168, 163, 132, 129, 128, 127, 123, 64, 50; MS m/z: 390 (M+1); Anal. Calcd. for $C_{17}H_{12}ClN_3O_4S$: C, 52.38; H, 3.10; Cl, 9.09; N, 10.78; Found: C, 52.33; H, 3.05; Cl, 9.04; N, 10.73.

Conclusion

By using green synthetic protocol we have been able to synthesize **N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1, 3-dioxoisoindolin-2-yl) acetamide 7(a-l)** derivatives in better yield, in shorter duration and to cause least pollution for investigation of anticonvulsant and CNS depressant activities. This was achieved by avoiding use of excessive solvents and by using synthetic microwave for faster reactions. The derivatives exhibited promising activity in MES and sc-PTZ test. The rotarod test was used for neurotoxicity evaluation and shows significant results. The compounds **7c (**R= methoxy), **7e (R=** chloro**)** and 7**h (R=** hydroxy**)** was found to be most potent CNS depressant compounds .The compounds 7**d (R=** methyl**) 7e (R=** chloro**), 7h(**R= hydroxy) have shown excellent anticonvulsant activity when compared with results of standard (** P< 0.01,*P<0.05). From correlation of activity with the structure of synthesized derivatives it has been observed that groups like electron donating group **(7e)** and (**7d**) attached to the phenyl ring increased CNS activity. In conclusion compound **7c, 7d, 7e, 7f**, and **7h** can be further optimized and developed as a lead molecule. Thus, **N-(3-chloro-2-oxo-4-substituted phenyl azetidin-1-yl)-2-(1,3-dioxoisoindolin-2-yl)acetamide 7(a-l)** have been obtained in good yield in an eco-friendly synthetic protocol and have exhibited potential anticonvulsant activity and can be developed as a lead molecule.

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