Original Article

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Design, synthesis, anticonvulsant screening and 5HT$_{1A/2A}$ receptor affinity of *N*(3)-substituted 2,4-imidazolidinediones and oxazolidinediones

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ABSTRACT: In the present study, a series of *N*(3)-substituted 2,4-imidazolidinediones and oxazolidinediones derivatives (1-16) were synthesized and tested for anticonvulsant activity using the maximal electroshock seizure test. Affinity towards receptor (5-HT$_{1A/2A}$) was also studied. Their neurotoxicity was determined using the rotarod test. Structures of compounds were confirmed by spectroscopic methods. Compounds 1, 2, 5, 7, 9, and 10 exhibited significant anticonvulsant activity as compared to the standard drug phenytoin. Affinity toward receptor (5-HT$_{1A/2A}$) was studied *in vivo* for compounds 1, 2, 5, 7, 9, and 10. Rectal body temperature, lower lip retractions and head twitch responses in Wistar rats/albino mice were determined for this purpose. The tested compounds showed affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors (agonists/antagonists and presynaptic/postsynaptic). Replacement of piperazine by aniline derivatives provides good outcomes in terms of affinity for 5-HT$_{1A/2A}$.

Keywords: Epilepsy, anticonvulsant, acetamide, phenytoin, oxazolidine-2,4-dione, aniline, piperazine

1. Introduction

Serotonin (5-HT) plays an important role in many physiological and pathophysiological processes in the brain (*1*). The link between 5-HT and the inhibition of epilepsy was suggested by Bonnycastle (*2*). They demonstrated that a series of anticonvulsants raise the brain 5-HT level. Serotonergic neurotransmission modulates a wide variety of experimentally induced seizures and is involved in the enhanced seizure susceptibility observed in rodents genetically prone to epilepsy (*3*). Welsh *et al*. observed in their study that the rat model of myoclonic epilepsy is associated with a profound loss of 5-HT throughout the brain (*4*). Drugs *viz*. valproic acid, lamotrigine, carbamazepine, phenytoin, and zonisamide are found to stimulate basal 5-HT levels, as part of their anticonvulsant action. Generally, agents that elevate the extracellular 5-HT levels, such as 5-hydroxytryptophan and serotonin reuptake blockers, inhibit both focal and generalized seizures (*5*).

The 5-HT$_{1A}$ receptors are to date one of the best characterized subtypes and it is generally accepted that they are involved in psychiatric disorders such as depression and anxiety. Several compounds from different chemical classes possess high affinity for 5-HT$_{1A/2A}$ receptors. Among them, 5-HT$_{1A}$ receptor partial agonists and 5-HT$_{2A}$ receptor antagonists are of particular interest, since clinical studies indicate that these drugs are effective in treating mood disorders. Consequently, it has been suggested that compounds which interact simultaneously with 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors may have a more advantageous therapeutic profile.

Autoradiographic analysis of 5-HT receptors in fully kindled rat brain showed a selective increase in 5-HT$_{1A}$ binding in the dentate gyrus. These findings suggest that 5-HT$_{1A}$ receptors may have an inhibitory role in the generation of hippocampal seizures. According to the studies by Gariboldi *et al.*, intrahippocampal or systemic administration of 8-hydroxy-*N,N*-dipropyl-2-aminotetralin (8-OH-DPAT), a specific 5-HT$_{1A}$ receptor agonist, to rats resulted in protective effects against seizure activity induced in the hippocampus by kainic acid (*6*). Several classes of compounds are known to bind to 5-HT$_{1A}$ receptor sites. Among them, 4-arylpiperazines that are linked to a terminal cyclic amide *via* a long chain are effective as antianxiety and antidepressant drugs (*7*). It has also been found that stimulation of 5-HT$_2$ receptors is linked to the anticonvulsant action of some methylphenylpiperazine derivatives (5-HT$_{2A}$/5-HT$_{2C}$) in an animal maximal electroshock seizure (MES) test (*8,9*). Presently the effectiveness of antiepileptic drugs (AEDs) in reducing the severity and number of seizures is less than 70%. Moreover the treatment is coupled with adverse side effects ranging from cosmetic (gingival hyperplasia) to life threatening

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(hepatotoxicity, megaloblastic anemia) (*10-12*).

One of the structures among the compounds studied for anticonvulsant activity is the acetamide and propionamide nucleus. Ameltolide (*13*), ralitoline (*14*), and some phthalimide derivatives (*15*) are the best examples with potent anticonvulsant activity in the MES test (Figure 1). Ameltolide was developed by Eli Lilly (Indianapolis, IN, USA), which originated from the approach of Clark *et al*. This research group isolated the 4-aminobenzamide pharmacophore, which subsequently led to the design of a number of new and potent anticonvulsant agents (*16-20*). Apart from the acetamide and propionamide nucleus, hydantoin and oxazolidine-2,4-dione are also one of the most commonly used antiepileptic pharmacophores. Many heterocyclic compounds attached to piperazine *via* an alkyl linkage have already been proved as potent anticonvulsants by many scientists (*21-23*). The molecules contain 5- or 6-member heterocyclic rings, one or two carbonyl groups as well as a required aromatic system which was confirmed by the structure-activity relationship studies of clinically available AEDs and other anticonvulsant active compounds. Many studies on the structure-affinity relationship of the 1-arylpiperazineclass of 5-HT_{1A} receptor ligands have been reported (*24,25*). Misztal *et al*. (*26*) assumed that the terminal amide fragment in buspirone-like ligands stabilized the 5-HT_{1A} receptor-ligand complex by either *p*-electron or local dipole-dipole interaction.

Based on the above findings, in the present study our interest was focused to target the 5-$HT_{1A/2A}$ receptor. Herein derivatives of 5-phenyloxazolidine-2,4-dione and 5,5-diphenyl hydantoin (these moieties are already well established prototypes for antiepileptic drugs) attached to piperazine and aniline derivatives *via* an acetamide linkage (*18,20*) have been synthesized. Various electron donating and electron-attracting groups in the *para* position of aniline and piperazine were synthesized. Compound **4** (*p*-tolyl-acetamide derivative of 2,4-imidazolidinedione) reported earlier for anticonvulsant activity (*27*) has been included in the present study for the purpose of comparison with other synthesized compounds. Based on potency-structure relationships, we designed analogues related to ameltolide and hydantoin/oxazolidinedione. The synthesized compounds were evaluated for anticonvulsant, neurotoxicity and $5HT_{1A/2A}$ *in vivo* receptor affinity.

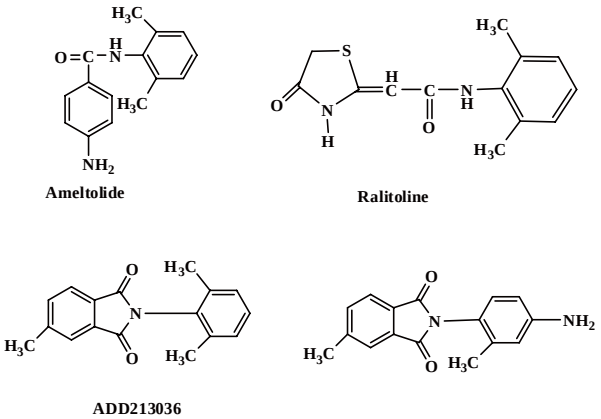


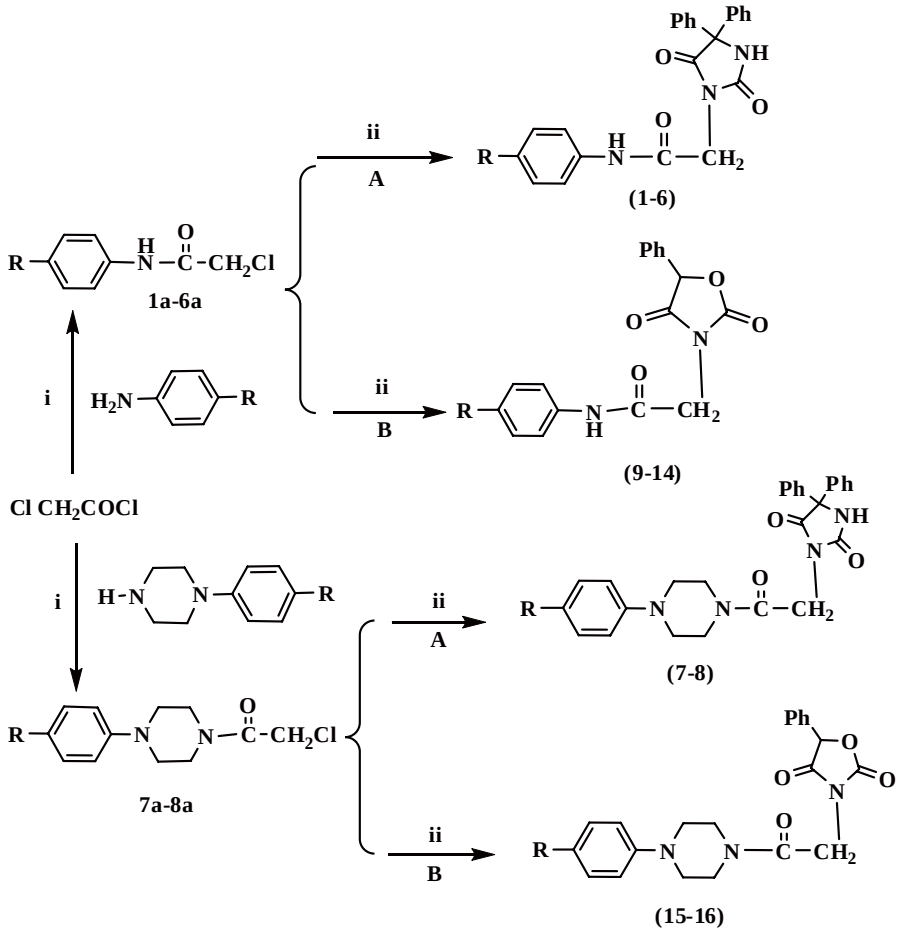
Figure 1. Potent anticonvulsant compounds bearing anilide (acetamide linkage) function.

2. Materials and Methods

All the substituted aniline and piperazine derivatives, 8-OH-DPAT, WAY 100653 (*N*-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-*N*-pyridin-2-yl-cyclohexanecarboxamide trihydrochloride), (±)-DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane), ketanserine were purchased from Sigma-Aldrich Chemicals Pvt. Ltd. (St. Louis, MO, USA) and solvents were purchased from Merck (Darmstadt, Germany) and were used without further purification. The purity of the compounds was confirmed by thin-layer chromatography (TLC) performed on Merck silica gel 60 F254 aluminium sheets (Merck), using various developing systems. Spots were detected by their absorption under UV light (λ = 254 nm) and by visualization with I_2. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX (300 MHz) spectrometer. Chemical shifts are reported in parts per million units relative to Tetramethylsilane (TMS) used as an internal standard. Coupling constants (*J*) are reported in Hertz (Hz). The infrared spectras were generated using a Shimadzu 8300 FTIR Spectrophotometer using KBr pellets and the nujol mull method. Spectral outputs were recorded either in absorbance or in transmittance mode as a function of wave number. The spectrum was collected from 4,000 to 400 cm^{-1}. Mass spectra were analyzed on a Finnigan MAT LCQ (APCI). Elemental analysis was carried out on EXTER analytical inc. CE-440 Elemental analysis, autosampler. Melting points (M.P.) were determined in open capillaries on a STUART SMP10, UK and are uncorrected. Signal multiplicities are represented by the following abbreviations: s (singlet), b (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet).

2.1. *Chemistry*

In the present investigation a new series of *N*(3)-substituted 2,4-imidazolidinediones and oxazolidinediones derivatives (Scheme 1, Figure 2) were synthesized using procedures explained in the literature (*28-30*). All the compounds were synthesized by classic two-step methods as illustrated in Scheme 1 (Table 1). In the first step, reacting 2-chloroacetylchloride with appropriately substituted anilines and piperazine yielded acetamide derivatives (**1a-8a**). In the second step, those intermediates were condensed with 5,5-diphenyl hydantoin and 5-phenyl oxazolidine-2,4-dione to furnish the title compounds **1-6**, **7**, **8** and **9-14**, **15**,



A= 5, 5-diphenyl hydantoin; B=5-phenyl oxazolidine-2,4 dione

Scheme 1. Synthesis of the compounds: (*i*) Glacial acetic acid, ice bath (30 min)-RT (1 h); (*ii*) DMF; reflux.

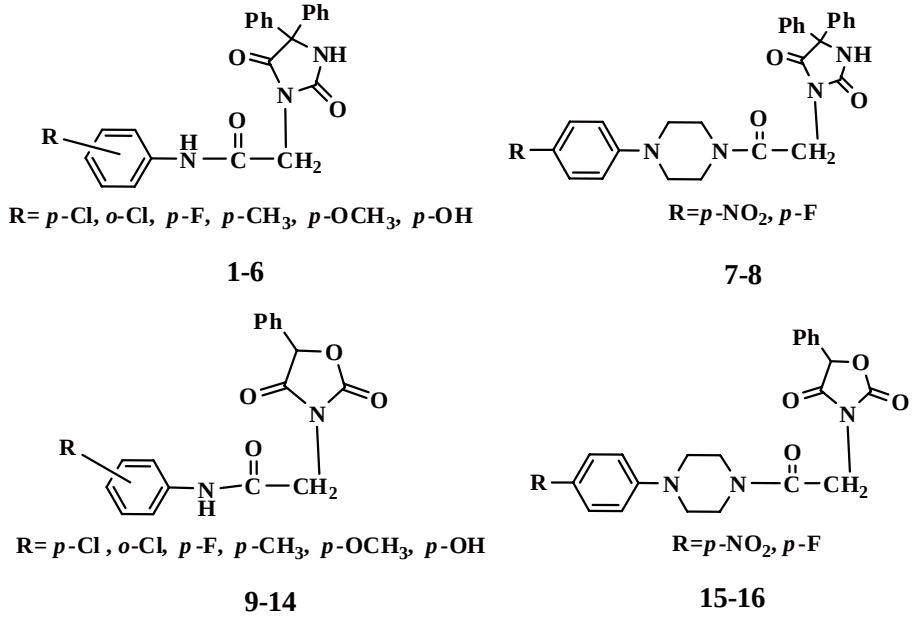
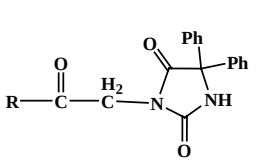
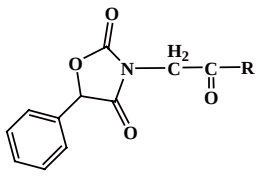


Figure 2. Chemical structures of the synthesized compounds.

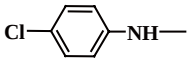
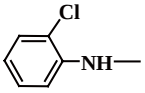
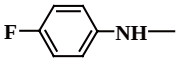
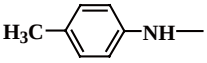
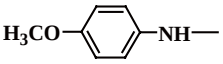
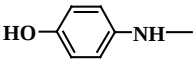
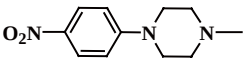
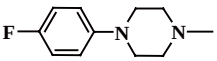
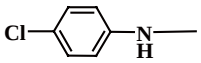
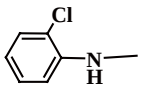
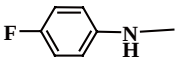
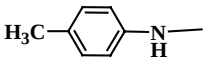
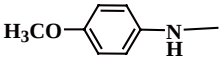
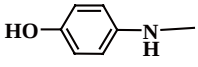
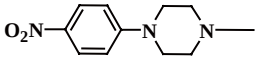
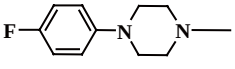
Table 1. Structures and physicochemical data of compounds



1-8



9-16

No.	R	Formula	Yield in %	Mol wt (calc)
1		$C_{23}H_{18}ClN_3O_3$	55	419.86
2		$C_{23}H_{18}ClN_3O_3$	57	419.86
3		$C_{23}H_{18}FN_3O_3$	60	403.41
4		$C_{24}H_{21}N_3O_3$	45	399.44
5		$C_{24}H_{21}N_3O_4$	54	415.44
6		$C_{23}H_{19}N_3O_4$	60	401.41
7		$C_{27}H_{25}N_5O_5$	58	499.52
8		$C_{27}H_{25}FN_4O_3$	62	472.51
9		$C_{17}H_{13}ClN_2O_4$	55	344.75
10		$C_{17}H_{13}ClN_2O_4$	56	344.75
11		$C_{17}H_{13}FN_2O_4$	45	328.29
12		$C_{18}H_{16}N_2O_4$	45	324.33
13		$C_{18}H_{16}N_2O_5$	45	340.33
14		$C_{17}H_{14}N_2O_5$	40	326.30
15		$C_{21}H_{20}N_4O_6$	50	424.14
16		$C_{21}H_{20}FN_3O_4$	53	397.40

16, respectively. 5-Phenyl oxazolidine-2,4-dione and 5,5-diphenyl hydantoin were synthesized in the lab using reported procedures (*31-34*). The title compounds were evaluated for anti-MES activity, neurotoxicity and *in vivo* receptor affinity for 5-$HT_{1A/2A}$.

2.1.1. *Synthesis of acetamide derivatives (**1a-8a**)*

Intermediates were prepared according to methods reported in the literature (*28-30*). For this purpose, appropriately substituted aniline/piperazine (0.066 mol)

was dissolved in 25 mL glacial acetic acid. 2-Chloroacetyl chloride (0.074 mol) was added dropwise to this solution while cooling in an ice-bath. The reaction mixture was stirred in an ice-bath for 0.5 h followed by 1 h at room temperature. The mixtures were poured into saturated sodium acetate solution. Obtained precipitates were filtered off and washed with cold water and purified by recrystallization from ethanol/water.

2.1.2. *General procedure for the synthesis of compounds* ***(1-16)***

Acetamide derivatives (0.002 mol) (**1a-8a**) and 5,5-diphenyl hydantoin (A)/5-phenyl oxazolidine-2,4-dione (B) (0.01 mol) in 20 mL *N,N*-dimethylformamide (DMF) were refluxed. The reaction was terminated, using monitoring of products with TLC. The reaction mixture was poured into cold water. The precipitates were filtered off and washed with water. After drying, the precipitate was purified by crystallization from ethanol. The physicochemical data of compounds are reported in Table 1.

2.2. *Pharmacology*

2.2.1. *MES*

Banaras Hindu University, Institute of Medical Sciences, Institutional Animal Ethical Committee (IAEC), approved all experiments for animal testing. MES is recognized as the 'gold standard' in the early stages of testing (*35*). Male albino mice (25-35 g) and Wistar rats (200-250 g) of either sex were used. Laboratory temperature was maintained at 20 ± 1°C under conditions of a 12 h light and dark schedule. Before experimentation, animals were allowed 1 week of adaptation. Food was withdrawn 12-15 h before commencing the experiment, while water was withdrawn immediately before the experiment. Each group consisted of 6 animals per dose. Each animal was used once.

The compounds were administered orally (suspension in a 1% Tween 80/water mixture) and intraperitoneally (suspension in 0.5% methylcellulose). The rotarod test was carried out to determine minimal neurotoxicity before the experiments.

The anticonvulsive activity of the compounds was evaluated by defining the abolition of the hind-leg tonic maximal extension component of the seizure (*36*). Maximal seizure is induced by application of an electrical current across the brain through corneal electrodes. The stimulus parameters are 50 mA, AC in a pulse of 60 Hz for 200 Ms (0.2 sec). After applying shock, mice/rats were observed for the type of convulsion produced and the hind limb extensor response was taken as the end point. Animals were tested at 0.5 and 4 h after administration of compounds. The animals that showed a positive hind limb extensor response were used for testing drug substances.

2.2.2. *Neurotoxicity test*

A neurological toxicity test (TOX) induced by a compound was detected in mice using the standardized rotarod test. Untreated control mice, when placed on a 6 rpm rotation rod, can maintain their equilibrium for a prolonged period of time. Neurological impairment is demonstrated by the inability of mice to maintain equilibrium for 1 min in each of three successive trials.

2.2.3. *In vivo receptor binding studies*

All drug solutions were prepared in a 1% aqueous solution of Tween 80 and were freshly prepared before use [Investigated compounds: 8-OH-DPAT, WAY 100653, (±)-DOI, and ketanserine]. 8-OH-DPAT and WAY 100653 were injected subcutaneously (*s.c.*), and (±)-DOI was given intraperitoneally (*i.p.*). The data obtained were analyzed by one-way analysis of variance followed by Dunnet's test. All scoring were carried out by an observer who was unaware of the specific drug treatment. Male albino mice (25-35 g) and Wistar rats (200-250 g) of either sex, were used. Groups consisted of 6-8 animals per dose.

2.2.3.1. *Lower lip retraction (LLR)*

The LLR was assessed according to the method described by Berendsen *et al.* (*38*). The rats were individually placed in cages and were scored three times (at 15, 30, and 45 min) after the administration of the tested compounds or 8-OH-DPAT (0 = lower incisors not visible, 0.5 = partly visible, 1 = clearly visible). The total maximum score amounted to 3/rat. In a separate experiment, the effect of the investigated compounds or WAY 100635 on LLR induced by 8-OH-DPAT (1 mg/kg) was tested. The investigated compounds or WAY 100635 were administered 45 and 15 min, respectively, prior to 8-OH-DPAT, and the animals were scored 15, 30, and 45 min after 8-OH-DPAT administration.

2.2.3.2. *Rectal body temperature of rats*

8-OH-DPAT (5 mg/kg) decreases rectal body temperature in rats. Effects of tested compounds given alone on rectal body temperature of rats (measured with an Ellab thermometer) were recorded 30, 60, 90, and 120 min after administration and compared with the effect of WAY 100635 (0.1 mg/kg). Results were expressed as change in body temperature (Δt) compared to basal body temperature, as measured at the beginning of the experiment. Compounds were administered 45 min prior to 8-OH-DPAT.

2.2.3.3. *Head twitch method*

In order to habituate the rats to the experimental

environment, each animal was randomly transferred to a cage, 30 min before injection of the compound (±)-DOI or vehicle. Head twitches were induced in mice by (±)-DOI (2.5 mg/kg). Immediately after treatment, head twitches (rapid right and left movements of the head with little or no involvement of the trunk) were counted for 20 min (*37*). The investigated compounds were administered 60 min before (±)-DOI. Their 5-HT_{2A} antagonistic activity was compared to ketanserin (ID_{50} = 0.14 mg/kg), a well-known 5-HT_{2A} receptor antagonist.

3. Results and Discussion

3.1. *Chemistry*

In this study, sixteen new *N*(3)-substituted 2,4-imidazolidinediones and oxazolidinediones derivatives were synthesized to evaluate anticonvulsant activity using the MES test. Chemical structures of title compounds were confirmed by elemental analysis, ^{1}H, ^{13}C NMR, IR and mass spectra data. Intermediates (compounds **1a-16a**) were verified by FT-IR spectra (spectra not shown).

IR spectra of compounds shows N-H and C=O stretching bands in the region of 3,486-3,112 cm^{-1} and 1,620-1,680 cm^{-1} respectively, indicating the presence of an -CONH-. Nitro groups show two intense peaks, one is in the range of 1,300-1,400 cm^{-1} for the symmetric stretching mode while the other one is 1,500-1,600 cm^{-1} for the asymmetric stretching mode. The -OH group has a distinct peak at 3,550-3,600 cm^{-1}. The strong bands in the 3,000-2,850 cm^{-1} regions are due to C-H stretch. In the acetamide series, ^{1}H NMR spectra confirmed the presence of expected proton signals with relevant splitting patterns and integrations. The chemical shifts and splitting patterns of protons in each compound differed depending on the nature of the substituent and substitution patterns. The compounds were further verified by mass spectral analyses where the molecular ion peaks were in complete agreement with the calculated molecular weight for individual compounds. The compounds having chloro substituent (compounds **1**, **2**, **9**, **10**) have relatively small molecular ions whereas the $[M\text{-}Cl]^{+}$ ions derived by loss of chlorine were more intense. C, H, N and O determinations were found to be within range.

3.2. *Anticonvulsant activity*

3.2.1. *MES & Rota- Rod test*

The anticonvulsant activity for all synthesized compounds was established by the MES tests after intraperitoneal injection (*i.p.*) to mice at doses of 30, 100, and 300 mg/kg. The neurotoxicity (NT) was determined by the minimal motor impairment-rotarod screening. Preliminary screening results indicated that some of the title compounds have diversified anti-MES activity.

Compound **1**, **2**, **5**, **7**, **9**, and **10** showed protection against MES and in addition they were devoid of neurotoxicity. While compounds **3**, **4**, **11**, **12**, **13**, and **16** are active but also impart neurotoxicity and compounds **6**, **8**, **14**, and **15** were inactive. All results are presented in Table 2.

On the basis of obtained data in *i.p.* MES screening in mice and according to the anticonvulsant screening project (ASP) procedure selected, compounds (**1**, **2**, **5**, **7**, **9**, and **10**) were evaluated orally in rats at doses of 30 mg/kg for two different time intervals (0.5 and 4 h) for both anticonvulsant and neurotoxic properties (Table 3) (*39*).

Compounds **1** and **9** were found to be the most active among all synthesized ones with dose levels of 30 and 100 mg/kg for 4 h, while others (**2**, **5**, **7**, and **10**) were active at high dose levels (100/300 mg/kg). Compound **3**, **4**, **11**, **12**, **13**, and **16** are also active but suffer from neurotoxicity and therefore these compounds will not be considered for further study. Compounds **6**, **8**, **14**,

Table 2. Evaluation of all synthesized compounds in MES tests after intraperitonial injection (30, 100, 300 mg/kg) to mice (Phase 1)

No.	MES (h)[a]		NT (h)[b]	
	0.5	4	0.5	4
1	30	100	-	-
2	-	100	-	-
3	100	300	100	-
4	100	-	100	-
5	100	300	-	-
6	-	-	-	-
7	100	300	-	-
8	-	-	-	-
9	30	100	-	-
10	100	300	-	-
11	100	300	-	100
12	30	100	-	100
13	100	300	100	-
14	-	-	-	-
15	-	-	-	-
16	-	300	100	300
Phenytoin	30	30	100	100

[a] Maximal electroshock seizure test (h, hours); [b] Neurotoxicity (Determined by rotarod).

Table 3. Evaluation of compounds 1, 2, 5, 7, 9, 10 in MES tests after oral administration (30 mg/kg) to rats (Phase 6a)

No.	MES (h)[a]		NT (h)[b]	
	0.5	4	0.5	4
1	1/6	4/6	0/6	0/6
2	0/6	3/6	0/6	0/6
5	2/6	4/6	0/6	0/6
7	3/6	4/6	0/6	0/6
9	2/6	4/6	0/6	0/6
10	2/6	3/6	0/6	0/6
Phenytoin	6/6	5/6	-	-

[a] MES test (number of animals protected/number of animals tested); [b] Neurotoxicity (number of animals exhibiting toxicity/number of animals tested).

and **15** were found to be inactive in this test and were also excluded from further consideration. Some of the compounds (**3**, **4**, **11**, **12**, **13**, and **16**) were found to be neurotoxic according to the rotarod test. Preliminary screening results are presented in Tables 2 and 3.

3.2.2. *In vivo receptor binding studies*

Compounds, which are active in MES and devoid of neurotoxicity were further considered for *in vivo* receptor binding studies (Tables 4-7). Various animal models were used for estimation of receptor affinity for 5-HT_{1A} (*i*) rectal body temperature (measured with an Ellab thermometer), (*ii*) lower lip retraction in rats were recorded, while (*iii*) head twitches were recorded in mice for the determination of probable affinity towards 5-HT_{2A} receptors (*37,40*). The standards used in the study are 8-OH-DPAT (5-HT_{1A} agonist), WAY 100653 (5-HT_{1A} antagonist), (±)-DOI (5-HT_{2A} agonist), and ketanserine (5-HT_{2A} antagonist).

In the presynaptic model, compounds which produced hypothermia like 8-OH-DPAT (5-HT_{1A} agonist) were considered as presynaptic agonists and *vice versa*. Among the tested one, **2**, **7**, and **9** produced hypothermia while **1**, **5**, and **10** were not active in the test. In another experiment induction of lower lip retraction was studied using 8-OH-DPAT compared to WAY 100635 (5-HT_{1A} antogonist). Compounds **1**, **2**, and **9** served as post synaptic agonist while **5**, **7**, and **10** were found to be antagonist. To estimate affinity toward 5-HT_{2A} receptors the head twitch method was used. Like ketanserin, a reference 5-HT_{2A} receptor antagonist

Table 4. The effect of the investigated compounds and WAY 100635 on the body temperature in rats

Treatment	Dose (mg/kg)	Δt SEM			
		30 min	60 min	90 min	120 min
Vehicle	-	-0.1 ± 0.1	0.0 ± 0.1	-0.2 ± 0.1	0.0 ± 0.1
1	10	-0.7 ± 0.2	-0.7 ± 0.1	-0.8 ± 0.2	-0.7 ± 0.2
	20	-1.8 ± 0.3	-1.8 ± 0.3	-1.6 ± 0.2	-1.7 ± 0.2
2	10	-0.6 ± 0.1	-0.8 ± 0.1	-0.9 ± 0.3	-1.9 ± 0.2
	20	-2.0 ± 0.1	-2.5 ± 0.2	-2.9 ± 0.1	-1.5 ± 0.1
5	10	-0.5 ± 0.1	-0.6 ± 0.2	-0.6 ± 0.1	-0.6 ± 0.1
	20	-1.2 ± 0.3	-1.1 ± 0.2	-1.2 ± 0.2	-1.1 ± 0.1
7	10	-0.4 ± 0.2	-0.8 ± 0.1	-0.9 ± 0.2	-0.6 ± 0.3
	20	-1.5 ± 0.3	-1.7 ± 0.1	-1.9 ± 0.1	-1.5 ± 0.1
9	10	-0.4 ± 0.1	-0.6 ± 0.2	-0.7 ± 0.1	-0.5 ± 0.1
	20	-1.0 ± 0.1	-1.1 ± 0.1	-1.4 ± 0.1	-1.1 ± 0.1
10	10	-0.2 ± 0.1	-0.2 ± 0.1	-0.3 ± 0.2	-0.2 ± 0.1
	20	-1.2 ± 0.2	-1.3 ± 0.3	-1.2 ± 0.1	-1.2 ± 0.1
WAY100635	0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1

The investigated compounds (*i.p.*) and WAY 100635 (*s.c.*) were administered 30 min before the test. The absolute mean initial body temperatures were within a range of 36.3 ± 0.5°C. $p < 0.001$ *vs.* vehicle.

Table 5. Induction of lower lip retraction (LLR) by the investigated compounds and WAY 100635 (A) and their effect on 8-OH-DPAT (B)

Treatment	Dose (mg/kg)	Mean SEM LLR score	
		A	B
Vehicle	-	0.1 ± 0.1	2.8 ± 0.2
1	10	1.0 ± 0.1	2.3 ± 0.2
	20	1.8 ± 0.3	2.4 ± 0.2
2	10	1.5 ± 0.2	2.8 ± 0.2
	20	2.2 ± 0.1	NT
5	10	0.1 ± 0.2	0.4 ± 0.1
	20	0.9 ± 0.1	0.8 ± 0.1
7	10	0.1 ± 0.1	0.4 ± 0.1
	20	0.5 ± 0.3	0.6 ± 0.2
9	10	1.4 ± 0.1	2.2 ± 0.1
	20	2.5 ± 0.2	NT
10	10	0.1 ± 0.1	0.4 ± 0.2
	20	0.3 ± 0.2	0.6 ± 0.3
WAY 100635	0.1	0.1 ± 0.1	0.3 ± 0.2

The investigated compounds (*i.p.*) and WAY 100635 (*s.c.*) were administrated 15 min before the test **(A)**, or 45 min before 8-OH-DPAT (1 mg/kg, *s.c.*) **(B)**. $p < 0.01$ *vs.* vehicle **(A)** or *vs*. vehicle + 8-OH-DPAT (**B**). NT: not tested.

Table 6. The effect of compounds 5, 7, 10 and ketanserin on the (±)-DOI-induced head twitch response in mice

Treatment	ID_{50} (mg/kg, *i.p.*)[a]
5	7 (5.4-9.2)
7	10 (6.2-15.3)
10	8 (5.9-11.7)
Ketanserine	0.12 (0.07-0.20)

[a] ID_{50}, the dose inhibiting head twitches in mice by 50%; confidence limit (90%) given in parenthesis. Investigated compounds were administrated *i.p.* 60 min before (±)-DOI (2.5 mg/kg, *i.p.*).

Table 7. Functional *in vivo* 5-$HT_{1A/2A}$ receptor activity of the investigated compounds

Compound	5HT_{1A} activity		5HT_{2A} activity
	Presynaptic	Postsynaptic	
1	Non active	Agonist	NA
2	Agonist	Agonist	NA
5	Non active	Antagonist	Antagonist
7	Agonist	Antagonist	Antagonist
9	Agonist	Agonist	NA
10	Non active	Antagonist	Antagonist

compounds **5**, **7**, and **10** (which exhibited the highest 5-HT_{2A} receptor affinity) inhibited head twitches induced by (±)-DOI, a 5-HT_{2A} receptor agonist, in mice. Hence, compound **5**, **7**, and **10** may be classified as 5-HT_{2A} receptor antagonist.

It has already been reported that alone 5-HT_{2A} is not responsible for inhibition of the head twitch response evoked by (±)-DOI. Selective antagonists of dopamine D1 and D2 receptors or α1-adrenoreceptors can also be responsible for the same response (*41*,*42*). Thus, it cannot be excluded that mechanisms other than 5-HT_{2A} receptor blockade are involved in reduction of (±)-DOI-induced head twitches by these compounds.

4. Conclusion

In this investigation *N*(3)-substituted 2,4-imidazolidinediones and oxazolidinediones derivatives were obtained by utilizing various *para*-substituted aniline and piperazine derivatives. The results showed that selected compounds (**1**, **2**, **5**, **7**, **9**, and **10**) can be assumed to be potential ligands for 5-$HT_{1A/2A}$ and the piperazine ring can be replaced by the aniline nucleus. This not only decreases the bulkiness but also increases the activity of the entity. Considering the functional profile of the investigated compounds few of them can act as potential anticonvulsant compounds.

Synthesized compounds in phase 1 (anticonvulsant screening) show that electronegative substitution was more active than electropositive substitution, whereas in the subsequent phase 6a trial, compounds with *para* substitution are more active than *ortho* substitution among the electronegative substituents.

In the functional receptor activity for 5-HT_{1A} the chloro derivatives **1**, **2**, and **9** act as agonist whereas compound **7**, which is a piperazine derivative, acts as a presynaptic agonist and post synaptic antagonist. For 5-HT_{2A} compounds **5**, **7**, and **10** act as antagonist.

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Appendix

Characterization data of compounds synthesized in the current study.

***N*-(4-chlorophenyl)-2-(2,5-dioxo-4,4-diphenyl-imidazolidin-1-yl)-acetamide (1)**: Melting point: 294-296°C; Yield: 55%; IR (KBr, ν_{max} cm^{-1}): 3,254 (NH Str), 2,945 (C-H), 1,721 (C=O), 1,672 (NH Bend), 790 (C-Cl Str); Mass: 420 (M + 1), 421 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.062 (s, NH, sec amide), 7.685-7.371 (m, 4H, 1Ph), 7.249-7.019 (m, 10H, 2Ph), 6.146 (s, 1H, N-H, phenytoin), 3.960 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 161.2, 143, 138.9, 129.4, 128, 126, 121, 72.6, 47.1; Elemental analysis: calcd for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; Cl, 8.44; N, 10.01; O, 11.43%. Found: C, 65.72; H, 4.28; Cl, 8.39; N, 9.97; O, 11.39%.

***N*-(2-chlorophenyl)-2-(2,5-dioxo-4,4-diphenyl-**

imidazolidin-1-yl)-acetamide (2): Melting point: 298-300°C; Yield: 57%; IR (KBr, ν_{max} cm^{-1}): 3,265 (NH Str), 2,980 (C-H), 1,726 (C=O), 1,622 (NH Bend), 810 (C-Cl Str); Mass: 420 (M + 1), 421 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.192 (s, NH, sec amide), 7.198-7.009 (m, 10H, 2Ph), 7.149-6.94 (m, 4H, 1Ph), 6.210 (s, 1H, N-H, phenytoin), 4.095 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 161.2, 143, 141.2, 138.9, 129, 129.1, 128.4, 126.8, 126, 125.7, 125.5, 72.6, 47.1; Elemental analysis: calcd for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; Cl, 8.44; N, 10.01; O, 11.43%. Found: C, 65.73; H, 4.29; Cl, 8.38; N, 9.99; O, 11.41%.

2-(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-*N*-(4-fluoro-phenyl)-acetamide (3): Melting point: 272-173°C; Yield: 60%; IR (KBr, ν_{max} cm^{-1}): 3,305 (NH), 2,900 (CH), 1,722 (C=O), 1,656 (NH Bend), 1,120 (C-F Str); Mass: 404 (M + 1), 405 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.090 (s, NH, sec amide), 7.585-7.271 (m, 4H, 1Ph), 7.149-7.019 (m, 10H, 2Ph), 6.208 (s, 1H, N-H, phenytoin), 3.890 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 161.2, 157.7, 143.0, 136.4, 129, 128.4, 126, 122.0, 115.7, 72.6, 47.1; Elemental analysis: calcd for $C_{23}H_{18}FN_3O_3$: C, 68.48; H, 4.50; F, 4.71; N, 10.42; O, 11.90%. Found: C, 68.41; H, 4.48; F, 4.69; N, 10.38; O, 11.87%.

2-(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-*N*-*p*-tolyl-acetamide (4): Melting point: 292-294°C; Yield: 45%; IR (KBr, ν_{max} cm^{-1}): 3,323 (NH), 2,900 (-CH_3 Str), 1,722 (C=O), 1,656 (NH Bend), 1,380 (C-H Bend); Mass: 400 (M + 1), 401 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.174 (s, NH, sec amide), 7.549-7.319 (m, 10H, 2Ph), 7.295-7.156 (m, 4H, 1Ph), 6.001 (s, 1H, N-H, phenytoin), 4.160 (s, 2H, -CH_2-), 2.355 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 161.2, 143.0, 137.8, 133.3, 129.4, 129.0, 128.4, 126, 120.3, 72.6, 47.1, 20.9; Elemental analysis: calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52; O, 12.02%. Found: C, 72.14; H, 5.29; N, 10.49; O, 12.00%.

2-(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-*N*-(4-methoxy-phenyl)-acetamide (5): Melting point: 294-296°C; IR (KBr, ν_{max} cm^{-1}): 3,355 (NH), 2,967 (-CH_3 Str), 1,730 (C=O), 1,612 (NH Bend), 1,012 (C-H Bend); Mass: 416 (M + 1), 417 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.098 (s, NH, sec amide), 7.440-7.309 (m, 10H, 2Ph), 7.295-6.750 (m, 4H, 1Ph), 6.098 (s, 1H, N-H, phenytoin), 4.160 (s, 2H, -CH_2-), 3.734 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 161.2, 157.6, 143.0, 133.3, 129.0, 128.4, 126, 121.4, 114.3, 72.6, 56.0, 47.1; Elemental analysis: calcd for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11; O, 15.40 %. Found: C, 69.35; H, 5.13; N, 10.12; O, 15.39%.

2-(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-*N*-(4-hydroxy-phenyl)-acetamide (6): Melting point: 296-298°C; Yield: 60%; IR (KBr, ν_{max} cm^{-1}): 3,590 (OH Str), 3,335 (NH), 2,912 (-CH_3 Str), 1,711 (C=O), 1,638 (N-H Bend); Mass: 402 (M + 1), 403 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.190 (s, NH, sec amide), 7.340-7.209 (m, 10H, 2Ph), 7.195-6.750 (m, 4H, 1Ph), 6.098 (s, 1H, N-H, phenytoin), 5.172 (brs, 1H, -OH), 4.060 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 168.2, 161.2, 152.9, 143.0, 133.3, 129.0, 128.4, 126, 121.8, 115.9, 72.6, 47.1; Elemental analysis: calcd for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47; O, 15.94%. Found: C, 68.83; H, 4.72; N, 10.42; O, 15.90%.

3-{2-[4-(4-Nitrophenyl)-piperazin-1-yl]-2-oxo-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (7): Melting point: 280-282°C; Yield: 58%; IR (KBr, ν_{max} cm^{-1}): 3,335 (NH), 2,912 (-CH_3 Str), 1,711(C=O), 1,635 (N-H Bend), 1,545 (-NO_2), 1,350 (-NO_2), 1,290 (CN Str), 1,180; Mass: 500 (M + 1), 501 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.370-7.116 (m, 10H, 2Ph), 6.990-6.873 (m, 4H, Ar-H), 5.906 (s, 1H, N-H, phenytoin), 4.060 (s, 2H, -CH_2-), 3.616-3.436 (m, 8H, Piperazine); ^{13}C NMR ($CDCl_3$): 169.1, 161.2, 150.6, 143.0, 137.9, 128.4, 124.5, 114.0, 72.6, 57.4, 48.7, 45.3; Elemental analysis: calcd for $C_{27}H_{25}N_5O_5$: C, 64.92; H, 5.04; N, 14.02; O, 16.01%. Found: C, 64.93; H, 5.05; N, 14.00; O, 16.02%.

3-{2-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (8): Melting point: 281-283°C; Yield: 62%; IR (KBr, ν_{max} cm^{-1}): 3,335 (NH), 2,912 (-CH_3 Str), 1,711 (C=O), 1,638 (N-H Bend), 1,350 (CN Str), 1,120 (C-F Str); Mass: 473 (M + 1), 474 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.870-7.116 (m, 10H, 2Ph), 6.790-6.573 (m, 4H, Ar-H), 5.986 (s, 1H, N-H, phenytoin), 4.380 (s, 2H, -CH_2-), 3.516-3.336 (m, 8H, Piperazine); ^{13}C NMR ($CDCl_3$): 169.1, 161.2, 151.6, 140.1, 129.0, 128.4, 116.4, 114.0, 72.6, 57.4, 48.7, 45.3; Elemental analysis: calcd for $C_{27}H_{25}FN_4O_3$: C, 68.63; H, 5.33; F, 4.02; N, 11.86; O, 10.16%. Found: C, 68.64; H, 5.31; F, 4.03; N, 11.84; O, 10.12%.

***N*-(4-chlorophenyl)-2-(2,4-dioxo-5-phenyl-oxazolidin-3-yl)-acetamide (9)**: Melting point: 117-119°C; Yield: 55%; IR (KBr, ν_{max} cm^{-1}): 3,254 (NH), 2,932 (-CH_3 Str), 1,719 (C=O), 1,656 (N-H Bend), 790 (C-Cl Str); Mass: 345 (M + 1), 346 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.190 (s, 1H, NH, sec amide), 7.587-7.260 (m, 4H, Ar-H), 7.235-6.116 (m, 5H, 1Ph), 6.201 (1H, methine) 4.460 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.1, 168.2, 155.8, 138.9, 135.9, 129.8, 129.4, 129.1, 121.8, 89.5, 46.2; Elemental analysis: calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; Cl, 10.28; N, 8.13; O, 18.56%. Found: C, 59.20; H, 3.81; Cl, 10.25; N, 8.15; O, 18.54%.

***N*-(2-chlorophenyl)-2-(2,4-dioxo-5-phenyl-oxazolidin-3-yl)-acetamide (10)**: Melting point:

114-116°C; Yield: 56%; IR (KBr, ν_{max} cm^{-1}): 3,245 (NH), 2,911(-CH_3 Str), 1,767 (C=O), 1,621 (N-H Bend), 778 (C-Cl Str); Mass: 345 (M + 1), 346 (M + 2); ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 8.090 (s, 1H, NH, sec amide), 7.480 (s, 1H, O-H, Ar), 7.250-7.120 (s, 1H, m-H, Ar), 7.197-7.019 (m, 5H, 1Ph), 6.945 (dd, 1H, p-H, Ar), 6.105 (1H, methine), 4.460 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.1, 168.2, 155.8, 141.2, 135.9, 129.8, 129.1, 127.4, 126.8, 125.7, 125.5, 121.8, 89.5, 46.2; Elemental analysis: calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; Cl, 10.28; N, 8.13; O, 18.56%. Found: C, 59.25; H, 3.80; Cl, 10.29; N, 8.16; O, 18.52%.

2-(2,4-Dioxo-5-phenyl-oxazolidin-3-yl)-*N*-(4-fluoro-phenyl)-acetamide (11): Melting point: 150-152°C; Yield: 45%; IR (KBr, ν_{max} cm^{-1}): 3,314 (NH), 2,935 (-CH_3 Str), 1,726 (C=O), 1,645 (N-H Bend), 1,112 (C-F Str); Mass: 329 (M + 1), 330 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.117 (s, 1H, NH, sec amide), 7.620-7.450 (s, 4H, Ar), 7.197-7.019 (m, 5H, 1Ph), 6.167 (1H, methine), 4.460 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.1, 168.2, 155.8, 136.4, 135.9, 129.8, 129.0, 122.0, 115.7, 89.5, 46.2; Elemental analysis: calcd for $C_{17}H_{13}FN_2O_4$: C, 62.19; H, 3.99; F, 5.79; N, 8.53; O, 19.49%. Found: C, 62.16; H, 3.94; F, 5.72; N, 8.54; O, 19.42%.

2-(2,4-Dioxo-5-phenyl-oxazolidin-3-yl)-*N*-*p*-tolyl-acetamide (12): Melting point: 150-152°C; Yield; 45%; IR (KBr, ν_{max} cm^{-1}): 3,343 (NH), 2,934 (-CH_3 Str), 1,723 (C=O), 1,645 (N-H Bend), 1,368 (C-H Bend); Mass: 325 (M + 1), 326 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.117 (s, 1H, NH, sec amide), 7.570-7.390 (m, 4H, Ar), 7.197-7.019 (m, 5H, 1Ph), 6.134 (1H, methine), 4.298 (s, 2H, -CH_2-), 2.307 (s, 2H, -CH_3); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 155.8, 137.8, 135.9, 133.3, 129.8, 129.4, 129.0, 127.4, 120.3, 89.5, 46.2, 20.9; Elemental analysis: calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64; O, 19.73%. Found: C, 66.60; H, 4.95; N, 8.61; O, 19.72%.

2-(2,4-Dioxo-5-phenyl-oxazolidin-3-yl)-*N*-(4-methoxy-phenyl)-acetamide (13): Melting point: 152-154°C; Yield: 45%; IR (KBr, ν_{max} cm^{-1}): 3,323 (NH), 2,956 (-CH_3 Str), 1,722 (C=O), 1,609 (N-H Bend), 1,016 (C-H Bend); Mass: 341 (M + 1), 342 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.117 (s, 1H, NH, sec amide), 7.620-7.420 (m, 4H, Ar), 7.197-7.019 (m, 5H, 1Ph), 6.156 (1H, methine), 4.298 (s, 2H, -CH_2-), 3.607 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 157.6, 155.8, 135.9, 133.3, 129.0, 129.8, 127.4, 121.4, 114.3, 89.5, 56.0, 46.2; Elemental analysis: calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23; O, 23.51%. Found: C, 63.50; H, 4.71; N, 8.24; O, 23.50%.

2-(2,4-Dioxo-5-phenyl-oxazolidin-3-yl)-*N*-(4-hydroxy-phenyl)-acetamide (14): Melting point: 152-154°C; Yield: 40%; IR (KBr, ν_{max} cm^{-1}): 3,578 (OH), 3,323 (NH), 2,922 (-CH_3 Str), 1,709 (C=O), 1,628 (N-H Bend); Mass: 327 (M + 1), 328 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.117 (s, 1H, NH, sec amide), 7.620-7.460 (m, 4H, Ar), 7.197-7.019 (m, 5H, 1Ph), 6.189 (1H, methine), 5.048 (brs, 1H, OH), 4.298 (s, 2H, -CH_2-); ^{13}C NMR ($CDCl_3$): 169.2, 168.2, 155.8, 152.9, 135.9, 133.3, 129.8, 129, 127.4, 121.8, 115.9, 89.5, 46.2; Elemental analysis: calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59; O, 24.52%. Found: C, 62.56; H, 4.33; N, 8.55; O, 24.51%.

3-{2-[4-(4-Nitrophenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-phenyl-oxazolidine-2,4-dione (15): Melting point: 98-100°C; Yield: 50%; IR (KBr, ν_{max} cm^{-1}): 3,354 (NH), 2,909 (-CH_3 Str), 1,723 (C=O), 1,644 (N-H Bend), 1,534 (-NO_2), 1,352 (-NO_2), 1,278 (CN Str), 1,178; Mass: 425 (M + 1), 426 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2970-7.016 (m, 5H, 1Ph), 6.890-6.773 (m, 4H, Ar), 6.209 (1H, methine), 4.102 (s, 2H, -CH_2-), 3.706-3.536 (m, 8H, Piperazine); ^{13}C NMR ($CDCl_3$):169.1, 155.8, 150.6, 137.9, 135.9, 129.8, 129.0, 127.4, 124.5, 114.0, 89.5, 57.4, 48.7, 44.4; Elemental analysis: calcd for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.75; N, 13.20; O, 22.62%. Found: C, 59.40; H, 4.72; N, 13.21; O, 22.60%.

3-{2-[4-(4-Fluorophenyl)-piperazin-1-yl]-2-oxo-ethyl}-5-phenyl-oxazolidine-2,4-dione (16): Melting point: 97-99°C; Yield: 53%; IR (KBr, ν_{max} cm^{-1}): 3,334 (NH), 2,923 (-CH_3 Str), 1,721 (C=O), 1,622 (N-H Bend), 1,333 (CN Str), 1,130 (C-F Str); Mass: 398 (M + 1), 399 (M + 2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2970-7.016 (m, 5H, 1Ph), 6.790-6.573 (m, 4H, Ar), 6.145 (1H, methine), 4.022 (s, 2H, -CH_2-), 3.706-3.536 (m, 8H, Piperazine); ^{13}C NMR ($CDCl_3$): 169.1, 155.8, 140.1, 135.9, 129.8, 129.0, 114.7, 89.5, 57.4, 48.7, 44.4; Elemental analysis: calcd for $C_{21}H_{20}FN_3O_4$: C, 63.47; H, 5.07; F, 4.78; N, 10.57; O, 16.10%. Found: C, 63.45; H, 5.01; F, 4.72; N, 10.54; O, 16.11%.