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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and anticonvulsant screening of some substituted piperazine and aniline derivatives of 5-phenyl-oxazolidin-2,4-diones and 5,5-diphenylimidazolidin-2,4 diones

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Abstract Substituted piperazine and aniline derivatives of oxazolidin-2,4-diones and imidazolidin-2,4-diones were synthesized by *N*3 alkylation and screened for their anticonvulsant activity by the maximal electroshock (MES) test, and their neurotoxicity was evaluated by the rotarod test. Among all the synthesized derivatives, compounds **4b**, **6c**, **6d**, **10b**, **11a**, **11b**, and **11d** were found to exhibit maximum seizure protection in MES test and were devoid of any neurotoxic effects. Furthermore, the functional activity of these compounds were evaluated in vivo for 5-HT_{1A} receptor affinity by using rectal body temperature and lower lip retraction in rats, while head twitch response in mice was performed for the determination of probable affinity toward 5-HT_{2A} receptor. The results of these tests demonstrated that compounds **4b**, **6c**, **6d**, **10b**, **11a**, **11b**, and **11d** exhibited 5-HT_{1A} (pre- and postsynaptic) agonist/antagonist features whereas compounds **11a** and **11b** exhibited antagonist action for 5-HT_{2A} receptor. From the in vivo studies it was observed that a majority of aniline derivatives (**6c**, **6d**, **11a**, **11b**, **11d**) were found to be more active as compared to their bulky piperazine congeners (**4b**, **10b**). Thus, the overall reduction in the bulkiness of the derivatives without compromising the lipophilicity is well appreciated for providing insights into the structural requirements necessary for development of new effective molecules having anticonvulsant effect.

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Keywords Anticonvulsants · Heteroaryl · Piperazine derivative · Aniline derivative · MES · Neurotoxicity

Introduction

The term epilepsy is derived from the Greek word *epilepsia*, meaning "falling sickness". Epilepsy is one of the most common neurological disorders, affecting around 50 million people worldwide (http://www.who.int/mediacentre/factsheets/fs999/en/index.html, Accessed 25 March 2011). In the past decade, several new anticonvulsant drugs such as felbamate, lamotrigine, gabapentin, tiagabine, topiramate have been approved by US-FDA for the treatment of epilepsy (Pastalos, 1999). However to-date, antiepileptic drug therapy is marred by a number of limitations (Baulac, 2003) as available drugs are effective only in 60–80% of epileptic patients. Hence, there is a need for the development of newer anticonvulsants with enhanced therapeutic profile.

Oxazolidinedione and imidazolidinedione are the key structural element of many biologically active compounds. Oxazolidine-2,4-diones have been reported to be clinically evaluated as a hypnotic and antiepileptic agent, e.g., tridione, paradione, dimedione, and malidone which have been employed for the treatment of epilepsy (Livingston and Boks, 1955). Apart from this they have also been reported to possess antimicrobial (Shankarananth *et al.*, 2010) and antihyperglycemic properties (Dow *et al.*, 1991; Momose *et al.*, 2002).

Similarly, imidazolidinedione (glycolylurea), the core moiety of phenytoin is effective against most type of partial seizures. A number of 5,5-disubstituted imidazolidinediones have found use in medicine as hypnotics and for the

treatment of chorea (Maryland, 1943). Apart from this, imidazolidines have been reported to possess a wide array of pharmacological properties such as antidiabetic, (Cheng *et al.*, 2010) antitumor, (Rodgers *et al.*, 1977) microbicidal, (Mulwad *et al.* 2011; Albuquerque *et al.*, 1999) HIV protease inhibitors, (Flosi *et al.*, 2006) antiarrhythmic, (Pekala *et al.*, 2005; Matsukura *et al.*, 1992) antifungal, (Dolezel *et al.*, 2009) antibacterial and anti-inflammatory (Menezes *et al.*, 1992).

Serotonin (5-HT) plays a crucial role in many of the physiological and pathophysiological processes in the brain. Presently, there has been a growing evidence suggesting the involvement of serotoninergic neurotransmission in the modulation of a wide variety of experimentally induced seizures along with enhanced seizure susceptibility as observed in some genetically prone rats (Salgado-Commissariat *et al.*, 1996); (Filakovszky *et al.*, 1999); (Graf *et al.*, 2004). Modulation of 5-HT_{1A}/$_{2A}$ receptors plays an important aspect in mediating the anticonvulsant action through these receptors.

It is well reported that aryl-piperazines exhibits good affinity with 5-$HT_{1A/2A}$ receptors. This specificity depends critically on the nature of the specific heterocyclic nuclei (A), on the aromatic substitution (B) and on the length (n) of the poly-methylene chain usually ($n = 2$) (Fig. 1). In addition to piperazine, several aniline derivatives were also developed as anticonvulsants in this study. The piperazine ring is replaced by a linear secondary amine followed by an aryl nucleus. The purpose of this replacement was to evaluate the effect of reduction of the bulkiness of the pharmacophoric part on the anticonvulsant activity. Thus the final structure of the synthesized derivatives constituted of the oxazolidin-2,4-diones and disubstituted hydantoins designed so as to include the common pharmacophoric features such as specific heterocyclic nuclei (A), a poly-methylene chain (with the length kept constant as $n = 2$) and various piperazine and aniline derivatives forming the aromatic substitution (B) (Fig. 1).

Thus, in the course of developing new potential anti-convulsant agents mediating their action through 5-HT_{1A}/5-HT_{2A} receptor we focused our attention on the synthesis of a new series of 3-[(4-arylpiperazin-1-yl)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**4a–f**); 3-[(*p*-aniline)-ethyl]-5,5-diphenyl imidazolidine-2,4-dione (**6a–e**); 3-[(4-arylpiperazin-1-yl)-ethyl]-5 phenyl-oxazolidine-2,4-dione (**10a–f**); 3-[(*p*-aniline)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11a–e**) derivatives with an ethyl spacer between imide nitrogen atom and 4-arylpiperazine or *p*-aniline derivative moiety (Schemes 1, 2; Table 1).

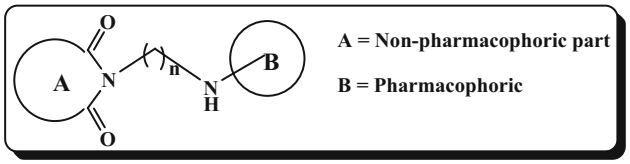


Fig. 1 Proposed pharmacophore

Experimental

All the chemicals were purchased from Sigma Aldrich and solvents from Merck and were used without further purification. All reactions were monitored by thin-layer chromatography (TLC) performed on Merck silica gel 60 F254 aluminum sheets (Merck; Darmstadt, Germany). Spots were detected by their absorption under UV light ($\lambda = 254$ nm) or were visualized with iodine vapors.

The spectroscopic analyses (IR, NMR, and MS) besides the C, H, N, O analyses were used for structural confirmation of the synthesized derivatives. Melting points (m. p.) were determined in open capillary tubes by using STUART (SMP10, UK) and are uncorrected. The Infra-Red (IR) spectra were recordrd on a Shimadzu 8300 FT-IR spectrophotometer using KBr pellets and solid run in solution.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX (300 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm) units relative to Tetra Methyl Silane (TMS) which was used as an internal standard. Splitting patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. A mass spectrum was obtained on a Hewlett Packard model GCD-1800A Electron Impact Mass Spectrometer (EIMS) at 70 eV ionizing beam using direct insertion probe. Elemental analyses (C, H, N, O) of the compounds were performed using Exeter CE-440 Elemental Analyzer instrument and results obtained were within ±0.4% of the theoretical values.

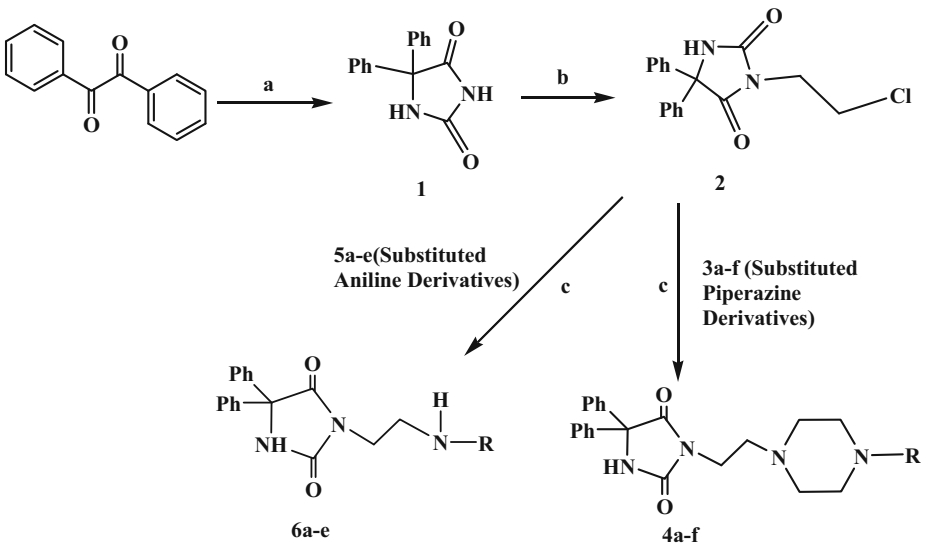
Chemistry

General procedure for the preparation of 3-[(4-arylpiperazin-1-yl)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**4a–f**)

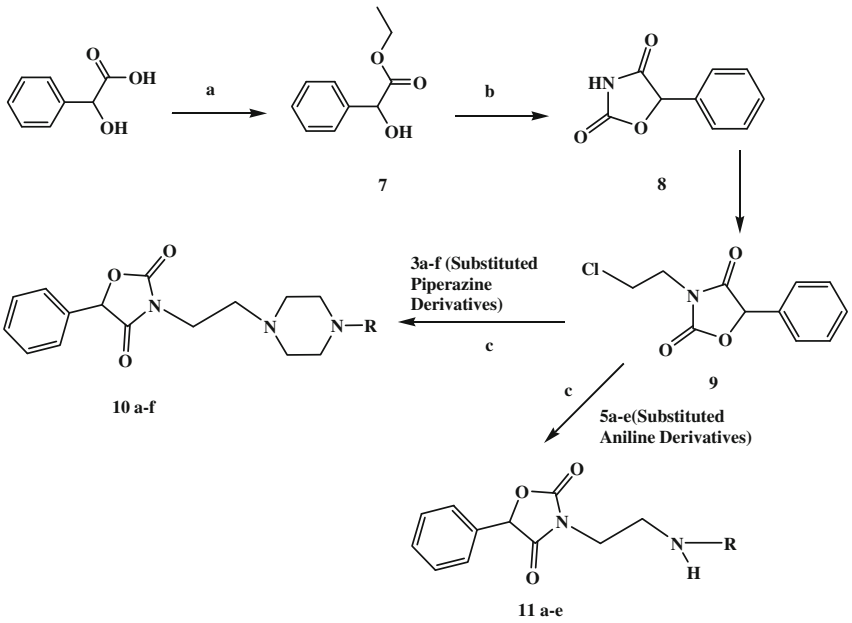
*Step 1: Procedure for the synthesis of 5,5-diphenylhydantoin (**1**)*

Synthesis of 5,5-diphenylhydantoin **1** was carried out using Biltz synthesis (1908) reported by Schmidt (2008) and Dunnavant and James (1956).

*5,5-Diphenyl-imidazolidine-2,4-dione (**1**)* Melting point: 298–300°C; yield: quantitative; IR (KBr, ν_{max} cm^{-1}): 3270



Scheme 1 Synthetic procedures (*a*) KOH, NH_2CONH_2, (*b*) KOH, DMF, 1-bromo-2-chloro ethane/RT, 1–2 h, (*c*) DMSO, RT/reflux, 2–3 h



Scheme 2 Synthetic procedures (*a*) dry ethanol, conc. H_2SO_4, reflux, (*b*) urea, NaH, NaOEt, ice bath—3.5 h reflux, (*c*) KOH, DMSO, 1-bromo-2-chloro ethane/RT, 1–2 h, (*d*) DMSO, RT/Reflux, 2–3 h

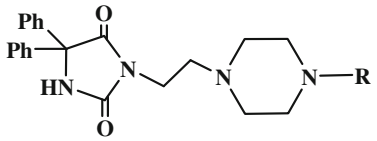
(N–H), 3000 (C=CH, aromatic), 1633 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.7 (s, 1H, N_3), δ 8.9 (s, 1H, N_1), 7.2 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$): 170.7, 160, 143, 129, 128.4, 126, 75.5; MS (*m/z*): 253.27 (M + 1); Anal. calcd. For $C_{15}H_{12}N_2O_2$ C, 71.42; H, 4.79; N, 11.10; O, 12.68 Found C, 71.68; H, 4.75; N, 11.08; O, 12.65.

*Step 2: Procedure for the synthesis of 3-(2-chloro-ethyl)-5,5-diphenyl-imidazolidine-2,4-dione (**2**)*

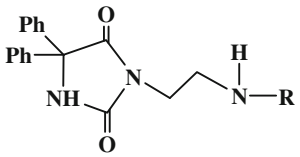
To a solution of the 5,5-diphenylhydantoin (4.75 mmol) in DMSO (dimethyl sulphoxide), KOH (10 ml; 14.4 mmol) was added (14.3 mmol), along with 1-bromo-2-chloroethane (11.9 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. The completion of reaction was monitored by TLC (EtOAc: Hexane 1:4) The reaction mixture was subsequently washed with ethyl acetate (100 ml), water (3 × 30 ml), brine (2 × 50 ml), dried over (Na_2SO_4), and evaporated to dryness. The crude product **2** obtained, was purified by column chromatography.

*3-(2-Chloro-ethyl)-5,5-diphenyl-imidazolidine-2,4-dione (**2**)* Melting point: 267–269°C; yield: 76% IR (KBr, ν_{max} cm^{-1}): 3306 (N–H), 1650 (C=O), 1437 (aromatic C=C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3–7.2 (m, 10H, 2Ph), 6.1 (s, 1H, NH), 3.9 (t, 2H, CH_2Cl), 3.8-3.7 (t, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 174.5, 156.8, 137.5, 128.9, 128.5, 125.4, 67.9, 40.0, 31.9; MS (m/z): 315.77 (M + 1); Anal. Calc for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.26;

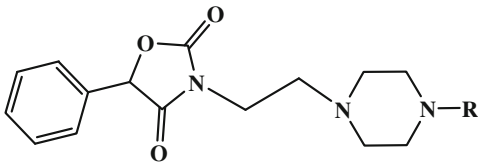
Table 1 Structures and physicochemical data of compounds



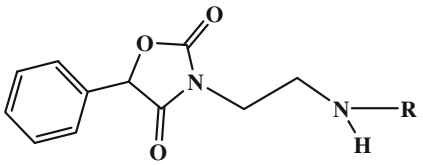
4a-f



6a-e



10a-f



11a-e

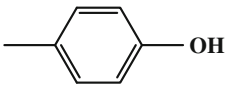
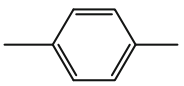
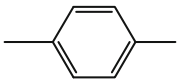
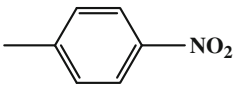
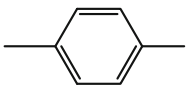
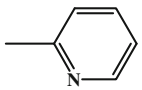
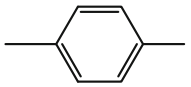
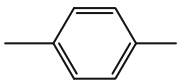
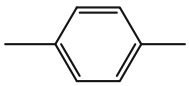
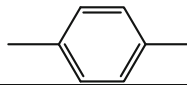
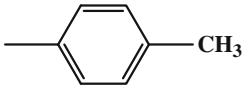
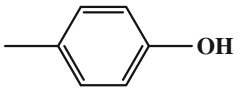
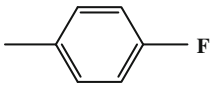
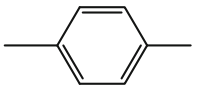
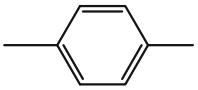
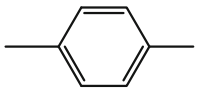
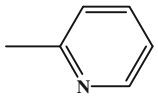
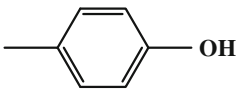
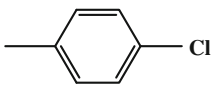
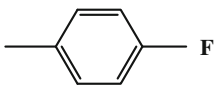
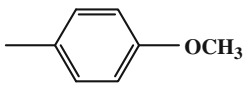
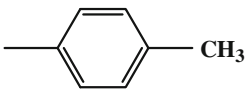
Compd no.	R	Formulae	Yield (%)	Mol. Wt (calc.)
4a		$C_{27}H_{28}N_4O_3$	55	456.54
4b		$C_{27}H_{27}FN_4O_2$	60	458.53
4c		$C_{27}H_{27}ClN_4O_2$	57	474.98
4d		$C_{27}H_{27}N_5O_4$	62	485.53
4e		$C_{28}H_{30}N_4O_2$	58	454.56
4f		$C_{26}H_{27}N_5O_2$	67	441.52
6a		$C_{23}H_{21}N_3O_3$	65	387.43
6b		$C_{23}H_{20}ClN_3O_2$	55	405.88
6c		$C_{23}H_{20}FN_3O_2$	70	389.42
6d		$C_{24}H_{23}N_3O_3$	65	401.46

Table 1 continued

Compd no.	R	Formulae	Yield (%)	Mol. Wt (calc.)
6e		$C_{24}H_{23}N_3O_2$	55	385.46
10a		$C_{21}H_{23}N_3O_4$	65	381.43
10b		$C_{21}H_{22}FN_3O_3$	67	383.42
10c		$C_{21}H_{22}ClN_3O_3$	60	399.87
10d		$C_{21}H_{22}N_4O_5$	55	410.42
10e		$C_{22}H_{25}N_3O_3$	67	379.45
10f		$C_{20}H_{22}N_4O_3$	56	366.41
11a		$C_{17}H_{16}N_2O_4$	62	312.32
11b		$C_{17}H_{15}ClN_2O_3$	60	330.77
11c		$C_{17}H_{15}FN_2O_3$	58	314.31
11d		$C_{18}H_{18}N_2O_4$	65	326.35
11e		$C_{18}H_{18}N_2O_3$	55	310.35

N, 8.90; O, 10.17; Found: C, 65.12; H, 4.75; N, 8.1; O, 10.14.

*Step 3: General procedure for the synthesis of compound (**4a–f**)*

3-(2-Chloro-ethyl)-5,5-diphenylhydantoin **2** (0.005 mol), appropriate 4-phenylpiperazine derivatives (**3a–f**) (0.001 mol) and DMSO were refluxed for 4 h. The completion of reaction was monitored by TLC (MeOH: DCM 1:9). The solvent was evaporated and the residue was treated with water (50 ml) and the precipitate was filtered off, washed with water. The crude product obtained was purified by column chromatography to afford the products **(4a–f)**.

*3-{2-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (**4a**)* Semisolid mass; yield: 55%; IR (solid run in solution, ν_{max} cm^{-1}): 3444 (OH),

3294 (N–H), 2821 (C–H), 1666 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.3–7.1 (m, 10H, 2Ph), 6.9–6.8 (m, 4H, Ph), 5.2 (s, 1H, N–H, phenytoin), 5.1 (s, 1H, OH) 3.2 (t, 2H, NCH_2–NCH_2), 3.1 (m, 4H, piperazine), 2.6 (t, 2H, NCH_2–NCH_2), 2.5 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 129, 128, 126, 116.4, 114.7, 73.3, 58.6, 52.6, 51.8, 43.2; MS (*m/z*): 457.54 (M + 1); Anal. calcd for $C_{27}H_{28}N_4O_3$ C, 71.03; H, 6.18; N, 12.27; O, 10.51 Found: C, 71.24; H, 6.20; N, 12.30; O, 10.46.

*3-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (**4b**)* Melting point: 263–265°C; yield: 60%; IR (KBr, ν_{max} cm^{-1}): 3306 (N–H), 2825 (C–H), 1685 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.3–7.2 (m, 10H, 2Ph), 6.9–6.8 (m, 4H, Ph), 5.2 (s, 1H, N–H, phenytoin), 3.9 (t, 2H, NCH_2–NCH_2), 3.8 (m, 4H, piperazine), 3.1 (t, 2H, NCH_2–NCH_2), 2.7 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 129, 128, 126, 116.4, 114.7, 73.3, 58.6, 52.6, 51.8, 43.2; MS (*m/z*): 459.43 (M + 1); Anal.calcd. for $C_{27}H_{27}FN_4O_2$: C, 70.72; H, 5.94; N, 12.22; O, 6.98; Found: C, 71.89; H, 5.93; N, 12.26; O, 6.97.

*3-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (**4c**)* Melting point: 263-265°C; yield: 57% IR (KBr, ν_{max} cm^{-1}): 3286 (N–H), 2827 (C–H), 1657 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.3–7.2 (m, 10H, 2Ph), 6.9–6.8 (m, 4H, Ph), 5.3 (s, 1H, N–H, phenytoin), 3.9 (t, 2H, NCH_2–NCH_2), 3.7 (m, 4H, piperazine), 3.1 (t, 2H, NCH_2–NCH_2), 3.0 (s, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 129, 128, 126, 116.4, 114.7, 73.3, 58.6, 52.6, 51.8, 43.2; MS (*m/z*): 475.98 (M + 1); Anal. calcd. for $C_{27}H_{27}ClN_4O_2$; C, 68.27; H, 5.73; Cl, 7.46; N, 11.80; O, 6.74; Found: C, 68.54; H, 5.75; Cl, 7.48; N, 11.84; O, 6.76.

*3-{2-[4-(4-Nitro-phenyl)-piperazin-1-yl]-ethyl}-5,5-diphenyl-imidazolidine-2,4-dione (**4d**)* Melting point 265-267°C; yield 62%; IR (KBr, ν_{max} cm^{-1}): 3315 (N–H), 2848 (C–H), 1667 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.2–8.1 (d, 2H, Ph), 7.4–6.9 (m, 10H, 2Ph), 6.7–6.6 (s, 2H, Ph) 6.2 (s, 1H, N–H, phenytoin), 3.9 (t, 2H, NCH_2–NCH_2), 3.8 (m, 4H, piperazine) 3.4 (t, 2H, NCH_2–NCH_2,), 3.0 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 166.9, 160.2, 141, 125, 122, 121, 116.4, 114.7, 70.3, 54.6, 50.6, 50.8, 42.2; MS (*m/z*): 486.53(M + 1): Anal. calcd. for $C_{27}H_{27}N5O_4$; C, 66.79; H, 5.61; N, 14.42; O, 13.18 Found: C, 67.05; H, 5.63, N, 14.47; O, 13.23.

*5,5-Diphenyl-3-[2-(4-p-tolyl-piperazin-1-yl)-ethyl]-imidazolidine-2,4-dione (**4e**)* Semisolid mass; yield: 58%; IR (solid run in solution, ν_{max} cm^{-1}): 3387 (N–H), 2918 (C–H), 1666 (C=O), 1315 (C–N); ^{1}H NMR ($CDCl_3$, 300 MHz): 7.6–7.4 (m, 10H, 2Ph), 6.9–6.4 (m, 4H, Ph), 5.3 (s, 1H, N–H, phenytoin), 3.9 (t, 2H, NCH_2–NCH_2), 3.7 (m, 4H, piperazine), 2.6 (t, 2H, NCH_2–NCH_2), 2.4 (m, 4H, piperazine), 2.2 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 129, 128.4, 126, 116.4, 114.7, 73.3, 58.6, 52.6, 51.8, 43.2, 38.7; MS (*m/z*): 455.56 (M + 1); Anal. calcd. for $C_{27}H_{27}N_5O_4$ C, 73.98; H, 6.65; N, 12.33; O, 7.04 calculated: C, 74.27; H, 6.67; N, 12.37; O, 7.06.

*5,5-Diphenyl-3-[2-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-imidazolidine-2,4-dione (**4f**)* Melting point: 264–266°C; yield: 67%; IR (KBr, ν_{max} cm^{-1}): 3290, 1599 (N–H), 2831 (C–H), 1315 (C–N); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.2 (d, 1H, H-1, pyridyl), 7.5–7.3 (m, 10H, 2Ph), 6.6–6.5 (m, 3H, H-2, H-3, H-4, pyridyl), 5.3 (s, 1H, N–H, phenytoin), 3.1 (t, 2H, NCH_2–NCH_2), 3.0 (m, 4H, piperazine), 2.6 (t, 2H, NCH_2–NCH_2) 2.3 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 161.1, 148.9, 143, 138, 129, 128, 126, 113, 108, 73.3, 57.9, 55.1, 51.8, 43.2 (1C); MS (*m/z*): 442.52 (M + 1); Anal. calcd. for $C_{26}H_{27}N_5O_2$; C, 70.73; H, 6.16; N, 15.86; O, 7.25 Found: C, 70.65; H, 6.15; N, 15.83; O, 7.23%.

General procedure for the preparation of 3-[(*p*-aniline)-ethyl]-5,5-diphenyl imidazolidine-2,4-dione (**6**)

Steps 1 and 2 are same as described under the preparation of 3-[(4-arylpiperazin-1-yl)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**4**).

*Step 3: General procedure for the synthesis of compound (**6a–e**)*

3-(2-Chloro-ethyl)-5,5-diphenylhydantoin **2** (0.005 mol) along with various *para* substituted anilines (**5a–f**) (0.001 mol) and DMSO were refluxed for appropriate time till the completion of reaction monitored by TLC (EtOAc:Hexane 2:1). The solvent was evaporated and the residue was treated with water (50 ml). The precipitate was filtered off, washed with water and the crude product obtained was purified by column chromatography to afford the products (**6a–e**).

*3-[2-(4-Hydroxy-phenylamino)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**6a**)* Semisolid mass; yield: 65%; IR (solid run in solution, ν_{max} cm^{-1}): 3456 (OH), 3323 (N–H), 2918 (C–H), 1655 (C=O), 1315 (C–N); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.1 (m, 10H, 2Ph), 7.3 (m, 4H, 1Ph), 6.1 (s, 1H, N–H, phenytoin), 5.1 (s 1H, OH), 3.9 (s, 1H, N–H, aniline), 2.9 (t, 2H, NCH_2), 2.6 (t, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 145.7, 143, 136.1, 129, 128.4, 126, 116.5, 113.7, 73.3, 49.8, 45; MS (*m/z*): 388.43 (M + 1):

Anal.calcd. for $C_{23}H_{21}N_3O_3$; C, 71.30; H, 5.46; N, 10.85; O, 12.39; Found: C, 71.25; H, 5.48; N, 10.83; O, 12.41.

*3-[2-(4-Chloro-phenylamino)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**6b**)* Melting point: 265–267°C; yield: 55%; IR (KBr, ν_{max} cm^{-1}): 3380 (N–H), 2818 (C–H), 1645 (C=O), 1300 (C–N); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.1 (m, 10H, 2Ph), 6.6 (m, 4H, 1Ph), 5.3 (s, 1H, N–H, phenytoin), 4.2 (s, 1H, N–H, aniline), 3.9 (t, 2H, NCH_2), 3.7 (t, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 141.6, 129.7, 129, 128, 126, 122, 113, 73.3, 49.8, 45; MS (*m/z*): 406.88 (M + 1); Anal.calcd. for $C_{23}H_{20}ClN_3O_2$; C, 68.06; H, 4.97; N, 10.35; O, 7.88 Found: C, 68.22; H, 4.95; N, 10.39; O, 7.85.

*3-[2-(4-Fluoro-phenylamino)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**6c**)* Melting point: 269–271°C; yield: 70%; IR (KBr, ν_{max} cm^{-1}): 3367 (N–H), 2900 (C–H), 1673 (C=O), 1313 (C–N); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.3 (m, 10H, 2Ph), 6.8–6.5 (m, 4H, 1Ph), 6.3 (s, 1H, N–H, phenytoin), 4.1 (s, 1H, N–H, aniline), 3.2 (t, 2H, NCH_2), 3.1 (t, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 150.5, 143, 139.1, 129, 128.4, 126, 116, 113, 73.3, 49.8, 45MS (*m/z*): 390.42 (M + 1); Anal. calcd. for $C_{23}H_{20}FN_3O_2$; C, 70.94; H, 5.18; N, 10.79; O, 8.22; Found: C, 71.10; H, 5.17; N, 10.76; O, 8.19.

*3-[2-(4-Methoxy-phenylamino)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**6d**)* Melting point: 268–270°C; yield: 65%; IR (KBr, ν_{max} cm^{-1}): 3207 (N–H), 2907 (C–H), 1666 (C=O), 1298 (C–N); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.3–7.2 (m, 10H, 2Ph), 6.7–6.6 (m, 4H, 1Ph), 6.1 (s, 1H, N–H, phenytoin), 5.9 (d, 1H, N–H, aniline), 3.7 (m, 3H, OCH_3), 3.9 (t, 2H, NCH_2), 3.8 (t, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 150.4, 143, 135.8, 129, 128.4, 126, 114.9, 113.3, 73.3, 56, 49.8, 45; MS (*m/z*): 402.46 (M + 1); Anal.calcd. for $C_{24}H_{23}N_3O_3$; C, 71.80; H, 5.77; N, 10.47; O, 11.96 Found; C, 72.01; H, 5.79; N, 10.50; O, 11.94.

*5,5-Diphenyl-3-(2-p-tolylamino-ethyl)-imidazolidine-2,4-dione (**6e**)* Melting point: 266–268°C; yield: 55%; IR (KBr, ν_{max} cm^{-1}): 3284 (N–H), 2989 (C–H), 1639 (C=O), 1301 (C–N); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.3–7.2 (m, 10H, 2Ph), 6.7–6.6 (m, 4H, 1Ph), 6.246 (s, 1H, N–H, phenytoin), 4.2 (d, 1H, N–H, aniline), 3.9 (t, 2H, NCH_2), 3.7 (t, 2H, NCH_2), 2.6 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 168.9, 161.2, 143, 140, 130, 129, 128.4, 126, 112.5, 73.3, 49.8, 45, 20.9; MS (*m/z*): 386.46 (M + 1); Anal.calcd. for $C_{24}H_{23}N_3O_2$; C, 74.78; H, 6.01; N, 10.90; O, 8.30 Found: C, 75.02; H, 6.02; N, 10.89; O, 8.28.

General procedure for the preparation of 3-[(4-arylpiperazin-1-yl)-ethyl]-5 phenyl-oxazolidine-2,4-dione (**10**)

*Step 1: Procedure for the synthesis of ethyl mandelate (**7**)*

A solution of DL-mandelic acid (hydroxyphenyl acetic acid) (2.63 mmol) in ethanol (150 ml) containing concentrated sulfuric acid (0.25 ml) was refluxed for 1.5 h. After cooling, the solution was diluted with ice-water, neutralized by saturated aqueous sodium carbonate and the mixture was extracted with ether. The combined ethereal extracts were dried and evaporated to yield the final compound **7**.

*Hydroxy-phenyl-acetic acid ethyl ester (**7**)* Melting point: 93–95°C; yield: quantitative; IR (KBr, ν_{max} cm^{-1}): 2983, 1454, 732 (–CH_2–CH_3), 1720 (Ester C=O); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (5H, m, Ph), 5.17 (1H, s, PhCH), 4.28 and 4.20 (2d, 2H, CH_2Me), 3.65 (1 H, br s, OH) and 1.22 (t, 3H, Me); ^{13}C NMR ($CDCl_3$): 173.6, 138.4, 128.5, 128.3, 126.5 (Ph-C3, C5), 72.9 (CH), 62.1 (CH_2) 14.0; MS (*m/z*): 181.20(M + 1); Anal.calcd. for $C_{10}H_{12}O_3$; C, 66.65; H, 6.71; O, 26.64; Found: C, 66.70; H, 6.73; O, 26.59.

*Step 2: Procedure for the synthesis of 5-phenyl-oxazolidin-2,4-dione (**8**)*

To a solution of ethoxide (prepared by dissolving 0.6 mol of sodium in absolute ethanol) urea was added in one portion. To this stirred solution, an ice-cold solution of ester **7** (0.6 mol) in absolute ethanol was added gradually over a period of 10 min at 0°C. The pasty mass obtained was allowed to attain room temperature by allowing it to stand for 20 min and then refluxed for 2 h. Excess of solvent was removed by distillation and the resulting slurry was stored at 5°C for 2 h. The disodium salt thus obtained was washed with small portions of cold ethanol to afford the final product **8**.

*5-Phenyl-oxazolidine-2,4-dione (**8**)* Melting point: 123–125°C; yield: quantitative; IR (KBr, ν_{max} cm^{-1}): 3373 (NH), 1606 (C=O); ^1H NMR ($CDCl_3$, 300 MHz): δ 10.2 (s, 1H, N–H), 7.4-7.2 (m, 5H, 1Ph), 5.2 (s, 1H, methine); ^{13}C NMR ($CDCl_3$): 170.7, 157.3, 135.9, 129.8, 129, 127.4, 92.4; MS (*m/z*): 178.16(M + 1); Anal. calcd. for $C_9H_7NO_3$ C, 61.02; H, 3.98; N, 7.91; O, 27.09 F Found: C, 61.12; H, 3.97; N, 7.88; O, 26.95.

*Step 3: Procedure for synthesis of (**9**)*

A mixture of 5-phenyl-oxazolidin-2,4-dione (1 mmol), K_2CO_3 (1.3 mmol), alkyl halide (1.1 mmol) and DMF (Dimethylformamide) were stirred at room temperature for 1.5–2 h. The completion of reaction was monitored by TLC (100% EtOAc). After completion, the reaction mixture was poured into ice-water. The crystallized product **9** thus obtained was filtered and washed with water.

*3-(2-Chloro-ethyl)-5-phenyl-oxazolidine-2,4-dione (**9**)* Melting point: 127-129°C; yield: 84%; IR (KBr, ν_{max} cm^{-1}) 2924 (C–H), 2854, 1456 (-CH_2-), 1647 (C = O), 1732 (Ar C–C) 759 (C–Cl); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4-7.2 (m, 5H, 1Ph), 5.2 (s, 1H, methine), 4.2 (d, 2H, CH_2Cl), 3.7-3.4 (s, 2H, NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 155.5, 135.9, 129.8, 129, 127, 90, 45.4, 43.6; MS (m/z): 240.34(M + 1); Anal.calcd. for $C_{11}H_{10}ClNO_3$; C, 55.13; H, 4.21; N, 5.84; O, 20.03 Found: C, 55.10; H, 4.20; N, 5.82; O, 20.06.

*Step 4: General procedure for the synthesis of (**10a–f**)*

To a solution of *N*3 alkylated 5-phenyl-oxazolidine-2, 4-dione **9** (3.32 mmol) in DMF, different piperazine derivatives (**3a–f**) (8.06 mmol) were added. The reaction mixture was allowed to stir at room temperature. TLC (DCM: MeOH, 5%) was performed to confirm the completion of reaction. After complete removal of the solvent, the reaction mixture was poured into water (20 ml) and the aqueous phase extracted with ethyl acetate (3 × 20 ml). The combined ethyl acetate layer was dried over anhydrous sodium sulpfate (Na_2SO_4). The solvent was removed under vacuum to give the crude compounds. The crude products were purified by column chromatography to afford the final products (**10a–f**).

*3-{2-[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-ethyl}-5-phenyl-oxazolidine-2,4-dione (**10a**)* Melting point: 145–147°C; yield: 65%; IR (KBr, ν_{max} cm^{-1}): 3252 (OH), 2821 (C–H), 1642 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2 (m, 5H, 1Ph), 6.5–6.4 (m, 4H, Ph), 6.2 (1H, methine), 5.1 (s, 1H, –OH) 3.8 (t, 2H, NCH_2–NCH_2), 3.7 (m, 4H, piperazine), 3.5 (t, 2H, NCH_2–NCH_2), 3.4 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 155.9, 142.6, 135.9, 129.8, 129.0, 127.4, 123.3, 114.5, 90.2, 57.9, 55.1, 52.3, 42.3; MS (*m/z*): 382.43(M + 1); Anal. calcd. for $C_{21}H_{23}N_3O_4$; C, 66.13; H, 6.08; N, 11.02; O, 16.78 found: C, 66.39; H, 6.10; N, 11.06; O, 16.84.

*3-{2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-ethyl}-5-phenyl-oxazolidine-2,4-dione (**10b**)* Melting point: 146–148°C; yield: 67%; IR (KBr, ν_{max} cm^{-1}): 2825 (C–H), 1662 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2 (m, 5H, 1Ph), 6.7–6.6 (m, 4H, Ph), 5.8 (s, 1H, methine), 3.6 (t, 2H, NCH_2–NCH_2), 3.4 (m, 4H, piperazine), 3.1 (t, 2H, NCH_2–NCH_2), 2.6 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 155.9, 151.6, 140.1, 135.9, 129.8, 129.0, 129.8, 127.4, 116.4, 114.7, 90.2, 57.9, 55.1, 52.3, 42.3; MS (*m/z*): 384.42(M + 1) Anal.calcd. for $C_{21}H_{22}FN_3O_3$; C, 65.78; H, 5.78; N, 10.96; O, 12.52 Found: C, 66.04; H, 5.80; N, 10.98; O, 12.57.

*3-{2-[4-(4-Chloro-phenyl)-piperazin-1-yl]-ethyl}-5-phenyl-oxazolidine-2,4-dione (**10c**)* Melting point: 152–154°C; yield: 60%; IR (KBr, ν_{max} cm^{-1}): 2827 (C–H), 1658 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2 (m, 5H, 1Ph), 7.0-6.5 (m, 4H, Ph), 6.0 (1H, methine), 3.4 (t, 2H, NCH_2–NCH_2), 3.1 (m, 4H, piperazine), 2.8 (t, 2H, NCH_2–NCH_2), 2.6 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 155.9, 142.6, 135.9, 129.8, 129.0, 127.4, 123.3, 114.5, 90.2, 57.9, 55.1, 52.3, 42.3; MS (*m/z*): 400.87(M + 1); Anal. calcd. for $C_{21}H_{22}ClN_3O_3$; C, 63.08; H, 5.55; N, 10.51; O, 12.00 Found: C, 63.15; H, 5.52; N, 10.52; O, 12.02.

*3-{2-[4-(4-Nitro-phenyl)-piperazin-1-yl]-ethyl}-5-phenyl-oxazolidine-2,4-dione (**10d**)* Melting point: 149–151°C; yield: 55%; IR (KBr, ν_{max} cm^{-1}): 2848 (C–H), 1632 (C=O), 1599 (NO_2), 1377 (NO_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.0 (s, 2H, Ph–NO_2), 7.2 (m, 5H, 1Ph), 6.8-6.6 (m, 2H, Ph), 6.7 (1H, methine), 3.6 (t, 2H, NCH_2–NCH_2), 3.4 (m, 4H, piperazine), 2.8 (t, 2H, NCH_2–NCH_2), 2.7 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$):168.9, 155.9, 142.6, 135.9, 129.8, 129.0, 127.4, 123.3, 114.5, 90.2, 57.9, 55.1, 52.3, 42.3; MS (*m/z*): (M + 1) 411.42 (M + 1); Anal. calcd. for $C_{21}H_{22}N_4O_5$; C, 61.45; H, 5.40; N, 13.65; O, 19.49 Found: C, 61.35; H, 5.42, N, 13.62; O, 19.40.

*5-Phenyl-3-[2-(4-p-tolyl-piperazin-1-yl)-ethyl]-oxazolidine-2,4-dione (**10e**)* Melting point: 150–152°C; yield: 67%; IR (KBr, ν_{max} cm^{-1}): 2918 (C–H), 1666 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.2 (m, 5H, 1Ph), 6.8–6.4 (m, 4H, Ph), 6.2 (1H, methine), 3.6 (t, 2H, NCH_2–NCH_2), 3.2 (m, 4H, piperazine), 3.0 (t, 2H, NCH_2–NCH_2), 2.9 (m, 4H, piperazine) 1.25 (s, 3H, –CH_3); ^{13}C NMR ($CDCl_3$): 168.9, 155.9, 142.6, 135.9, 129.8, 129.0, 127.4, 123.3, 114.5, 90.2, 57.9, 55.1, 52.3, 42.3; MS (*m/z*): 380.45(M + 1); Anal.calcd. for $C_{22}H_{25}N_3O_3$; C, 69.64; H, 6.64; N, 11.07; O, 12.65 Found: C, 70.01; H, 6.66; N, 11.11; O, 12.60.

*5-Phenyl-3-[2-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-oxazolidine-2,4-dione (**10f**)* Melting point: 147–149°C; yield: 56%; IR (KBr, ν_{max} cm^{-1}): 2831 (C–H), 1683 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.1 (d, 1H, H-1, pyridyl), 7.1 (m, 5H, 1Ph), 6.6–6.5 (m, 3H, H-2, H-3, H-4, pyridyl), 6.4 (1H, methine), 3.0 (t, 2H, NCH_2–NCH_2), 2.9 (m, 4H, piperazine),

2.8 (t, 2H, NCH_2–NCH_2), 2.6 (m, 4H, piperazine); ^{13}C NMR ($CDCl_3$): 168.9, 155.5, 135.9, 129.8, 129.0, 127.4, 161.1, 148.9, 138.0, 113.0, 108.9, 90.2, 57.9, 55.1, 52.2, 42.3; MS (*m/z*): 367.41 M + 1); Anal. calcd. for $C_{20}H_{22}N_4O_3$; C, 65.56; H, 6.05; N, 15.29; O, 13.10 Found: C, 65.82; H, 6.07; N, 15.35; O, 13.15.

General procedure for the preparation of 3-[(*p*-aniline)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11**)

Steps 1, 2 and 3 are same as described under the preparation of 3-[(4-arylpiperazin-1-yl)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**10**)

*Step 4: General procedure for the synthesis of (**11a–e**)*

To a solution of aniline derivatives (**5a–f**) (8.06 mmol) in DMSO (3.32 mmol) of *N*3 alkylated oxazolidin-2,4-dione was added. After 2–4 h, depending upon completion of reaction which was monitored by TLC (MeOH:DCM 0.5:9.5), the reaction was terminated followed by evaporation of solvent. Compounds obtained were purified by column chromatography to afford the final compounds (**11a–e**).

*3-[2-(4-Hydroxy-phenylamino)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11a**)* Melting point: 128–130°C; yield: 62%; IR (KBr, ν_{max} cm^{-1}): 3486 (–OH), 3308 (N–H), 2790 (C–H), 1649 (C=O), 1257 (C–O, Str), 1312 (C–N); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.1–7.0 (m, 5H, 1Ph), 6.5–6.3 (m, 4H, 1Ph), 6.1 (1H, methine), 5.2 (s, 1H, –OH) 4.1 (s, 1H, N–H, aniline), 2.9–2.6 (2t, 4H, NCH_2–NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 155.5, 145.7, 136.1, 135.9, 129.8, 129.0, 127.4, 116.5, 113.7, 90.2, 56.0, 50.2, 44.1; MS (*m/z*): 312.32 (M + 1); Anal. calcd. for $C_{17}H_{16}N_2O_4$; Actual C, 65.38; H, 5.16; N, 8.97; O, 20.49 Found: C, 65.34; H, 5.18, N, 9.00; O, 20.57.

*3-[2-(4-Chloro-phenylamino)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11b**)* Melting point: 130–132°C; yield: 60%; IR (KBr, ν_{max} cm^{-1}): 3308 (N–H), 2790 (C–H), 1639 (C=O); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.3 (m, 5H, 1Ph), 7.2 (m, 4H, 1Ph), 6.3 (1H, methine), 4.0 (s, 1H, N–H, aniline), 3.6-3.2 (2t, 4H, NCH_2–NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.1, 155.5, 150.5, 139.1, 135.9, 129.8, 129.0, 127.4, 116.3, 113.9, 50.2, 44.1; MS (*m/z*): 331.77 (M + 1); Anal. calcd. for $C_{17}H_{15}ClN_2O_3$; Actual C, 61.73; H, 4.57; N, 8.47; O, 14.51 Found: C, 61.65; H, 4.58; N, 8.45; O, 14.49.

*3-[2-(4-Fluoro-phenylamino)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11c**)* Melting point: 132–134°C; yield: 58%; IR (KBr, ν_{max} cm^{-1}): 3290 (N–H), 2831 (C–H), 1663 (C=O), 1498 (–CH_2–); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.8-7.3 (m, 5H, 1Ph), 7.2-7.0 (m, 4H, 1Ph), 6.1 (1H, methine), 4.2 (s, 1H, N–H, aniline), 3.6 (t, 2H, NCH_2–NCH_2), 2.9 (t, 2H, NCH_2–NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 161.1, 155.5, 150.5, 139.1, 135.9, 129.8, 129.0, 127.4, 116.3, 113.9, 50.2, 44.1; MS (*m/z*): 315.31 (M + 1); Anal. calcd. for $C_{17}H_{15}FN_2O_3$; C, 64.96; H, 4.81; N, 8.91; O, 15.27 Found: C, 65.90; H, 4.82; N, 8.90; O, 15.25.

*3-[2-(4-Methoxy-phenylamino)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11d**)* Melting point: 133–135°C; yield: 65%; IR (KBr, ν_{max} cm^{-1}): 3308 (N–H), 2790 (C–H), 2835 (–OCH_3), 1679 (C=O); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.3 (m, 5H, 1Ph), 7.2–7.1 (m, 4H, 1Ph), 6.1 (1H, methine), 4.9 (s, 1H, N–H, aniline), 4.2 (s, 3H, –OCH_3), 3.6 (t, 2H, NCH_2–NCH_2), 2.6 (t, 2H, NCH_2–NCH_2); ^{13}C NMR ($CDCl_3$): 168.9, 155.5, 150.4, 135.9, 135.8, 129.8, 129.0, 127.4, 114.9, 113.3, 90.2, 56.0, 50.2, 44.1; MS (*m/z*): 327.35 (M + 1); Anal. calcd. for $C_{18}H_{18}N_2O_4$; Actual C, 66.25; H, 5.56; N, 8.58; O, 19.61 Found: C, 66.45; H, 5.55; N, 8.60; O, 19.57.

*5-Phenyl-3-(2-p-tolylamino-ethyl)-oxazolidine-2,4-dione (**11e**)* Melting point: 140–142°C; yield: 55%; IR (KBr, ν_{max} cm^{-1}): 3308 (N–H), 2790 (C–H), 1654 (C=O), ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4–7.2 (m, 5H, 1Ph), 6.8-6.7 (m, 4H, 1Ph), 6.2 (1H, methine), 4.2 (s, 1H, N–H, aniline), 3.1-3.0 (2t, 4H, NCH_2–NCH_2), 1.9 (m, 3H, –CH_3); ^{13}C NMR ($CDCl_3$): 168.9, 155.5, 140.5, 135.9, 129.8, 130.0, 129.0, 127.4, 126.1, 112.2, 90.2, 56.0, 50.2, 44.1, 20.9; MS (*m/z*): 311.35 (M + 1); Anal. calcd. for $C_{18}H_{18}N_2O_3$; C, 69.66; H, 5.85; N, 9.03; O, 15.47 Found: C, 69.55; H, 5.83; N, 9.01; O, 15.45.

Pharmacology

Pharmacological experiments were carried out on Albino Swiss mice (20–25 g) and Wistar rats (200–250 g) (procured from Central Animal Breeding House, Institute of Medical Sciences, Banaras Hindu University) were used. The animals were housed in plastic cages at an ambient temperature of 25 ± 2°C and 45–55% relative humidity and maintained on a 12:12 h (7:00 a.m. to 7:00 p.m.) light–dark cycle with free access to standard pellet diet and water ad libitum. Animals were allowed to acclimatize to their environment for at least 7 days before experimentation. The animals were randomly distributed into different groups of six animals each. Each animal was weighed, caged separately, and had identification marks cryptically encoding the dose level and group. All experimental protocols were approved by Institutional Animal Ethical Committee (IAEC) [Approval No. Dean/10-11/155]

Institute of Medical Sciences, Banaras Hindu University. Experiments were conducted as per the Guidelines issued for the Care and Use of Laboratory Animals as promulgated by the National Institutes of Health (NIH).

Initially, all the synthesized derivatives were subjected to evaluation for preliminary anticonvulsant screening in mice. Seizure assay was carried out according to the Phase I tests of the antiepileptic drug development (ADD) protocol developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Krall *et al.*, 1978; Stables and Kupferberg, 1997a, b; Kupferberg and Stables, 1997).

Phase I involved the intraperitonial administration of the compounds in mice as a suspension in 0.5% methylcellulose. Phase I is a qualitative assay involving a small number of mice (1–4) at dose levels of 30, 100, and 300 mg/kg. Compounds found active in Phase I evaluation were advanced to Phase VIa of anticonvulsant drug development protocol wherein the compounds were orally administered into rats at a dose of 30 mg/kg. The anticonvulsant screening of synthesized derivatives were performed using the maximal electroshock (MES) test whereas their neurotoxicity liability was evaluated using the rotarod method.

In vivo anticonvulsant screening

Maximal electroshock (MES) test

In this test, seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice and rats. The current was applied through corneal electrodes for 0.2 s duration. Abolition of the hind-leg tonic-extensor component of the seizure indicated protection against the spread of MES induced seizures. The synthesized compounds were suspended in 0.5% methylcellulose and were administered in a standard volume of 0.5 ml/20 g body weight at 30, 100, 300 mg kg^{-1}. Control animals received 0.5% suspension of methylcellulose and phenytoin was used as a reference drug (30 mg kg^{-1}). From this test, one can readily preselect compounds that are effective in suppression of tonic–clonic seizures and to a certain extent, of partial seizures with or without secondary generalization in humans (Rogawski, 2006; Ucar *et al.* 1998; Stables and Kupferberg, 1997a, b).

Rotarod performance test

Rotarod test was carried to measure the minimal motor impairment in mice and rats. The animals were trained to balance on the knurled rotating rod (3.2 cm diameter) that rotates at 6 rpm. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the three trials (Krall *et al.*, 1978; Stables and Kupferberg, 1997a, b).

In vivo 5-HT_{1A} and 5-HT_{2A} bioassay

N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)-cyclohexane carboxamide trihydrochloride (WAY 100635), 8-Hydroxy-2-(di-*n*-propylamino) tetralin hydrobromide (8-OH-DPAT), and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (±)-(DOI) in aqueous solutions were used for the abovementioned studies.

The investigated compounds (**4b**, **6c**, **6d**, **10b**, **11a**, **11b**, **11d**) were suspended in 1% aqueous solution of Tween 80. The suspensions were neutralized using a few drops of 0.1 M NaOH. 8-OH-DPAT and WAY 100635 were injected subcutaneously (sc). The compounds **4b**, **6c**, **6d**, **10b**, **11a**, **11b**, **11d** and (±)-DOI were administered intraperitoneally (ip) in a volume of 2 ml/kg for rats and 10 ml/kg for mice. The data obtained were analyzed by one-way analysis of variance followed by Dunnett's test. (Berendsen *et al.*, 1989; Jurczyk *et al.*, 2004; Dursun and Handley, 1996; Schreiber *et al.*, 1995).

Rectal body temperature of rats

Effects of the tested compounds given alone on the rectal body temperature of rats were recorded 30, 60, 90, and 120 min after administration. In a separate study, the effect of WAY 100635 (0.1 mg/kg) on hypothermia induced by the tested compounds was evaluated. WAY 100635 was administered 15 min before the tested compounds and the rectal body temperature was recorded 30 and 60 min after their injection. The results were expressed as a change in body temperature (Δt) with respect to basal body temperature, as measured at the beginning of the experiment.

Lower lip retraction (LLR)

The lower lip retraction (LLR) was assessed as per the method described by Berendsen et al. (1989). The rats were placed individually in cages and were scored for LLR for three times (15, 30, and 45 min) after the administration of the tested compounds or 8-OH-DPAT. The scoring of the results were done as follows (0 = lower incisors not visible, 0.5 = partly visible, 1 = clearly visible).

The total maximum score amounted to three per 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 compounds to be investigated or WAY 100635 were administered 45 min and 15 min, respectively, prior to 8-OH-DPAT and the animals were scored 15, 30, and 45 min after 8-OH-DPAT administration.

Table 2 Evaluation of all synthesized compounds in MES and rotarod test after intraperitoneal injection (30, 100, 300 mg/kg) in mice (Phase I)

Intraperitoneal injection in mice				
	MES (h)[a]		NT (h)[b]	
	0.5	4	*0.5*	*4*
4a	–	300	–	300
4b	–	30	–	–
4c	–	–	–	–
4d	–	300	–	300
4e	–	300	100	300
4f	–	–	–	–
6a	–	–	–	–
6b	–	–	–	–
6c	100	30	–	–
6d	300	100	–	–
6e	–	–	–	–
10a	–	–	–	–
10b	–	100	–	–
10c	–	–	–	–
10d	–	300	–	300
10e	–	–	–	–
10f	–	–	–	–
11a	100	30	–	–
11b	100	30	–	–
11c	–	300	–	300
11d	–	100	–	–
11e	–	–	–	–
Phenytoin	30	30	100	100

[a] MES test (number of animals protected/number of animals tested)

[b] Neurotoxicity assessed by rotarod (number of animals exhibiting toxicity/number of animals tested)

Table 3 Evaluation of compounds in MES and rotarod test after oral administration (30 mg/kg) in rats (Phase VI a)

	Oral drug administration in rat			
	MES (h)[a]		NT (h)[b]	
	0.5	4	0.5	4
4b	1/6	3/6	0/6	0/6
6c	3/6	4/6	0/6	0/6
6d	2/6	2/6	0/6	0/6
10b	2/6	2/6	0/6	0/6
11a	3/6	3/6	0/6	0/6
11b	3/6	4/6	0/6	0/6
11d	0/6	2/6	0/6	0/6
Phenytoin	6/6	5/6	–	–

[a] MES test (number of animals protected/number of animals tested)

[b] Neurotoxicity assessed by rotarod (number of animals exhibiting toxicity/number of animals tested)

Head twitch method

In order to acclimatize the mice to the experimental environment, each animal was transferred to a cage, 30 min before treatment. Head twitches were induced in mice by (±)-DOI (2.5 mg/kg). Immediately after the treatment, the head twitches (rapid right and left movements of the head with little or no involvement of the trunk) were counted for 20 min (Darmani *et al.*, 1990). 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-known5-HT_{2A} receptor antagonist (Byrtus *et al.*, 2005).

In silico ADME studies

The QikProp 3.1 (Schrodinger; LLC, USA) program was used to predict the ADME properties of the synthesized analogs. Ligands were build using Maestro 8.5 build panel and prepared by Ligprep 2.2 version v22208 (Schrödinger, LLC, USA) application that used OPLS 2005 force field. The best-fit ligands were neutralized before being used by QikProp. The program was processed in normal mode, and predicted properties for the best-fit molecules, consisting of principal descriptors and physiochemical properties with analyses of the log *P* (octanol/water), % human oral absorption, Lipinski's rule of five violation, CNS activity.

Results and discussion

Chemistry

In this study we report the synthesis of a new series of 3-[(4-arylpiperazin-1-yl)-ethyl]-5,5-diphenyl-imidazolidine-2,4-dione (**4a–f**); 3-[(*p*-aniline)-ethyl]-5,5-diphenyl imidazolidine-2,4-dione (**6a–e**); 3-[(4-arylpiperazin-1-yl)-ethyl]-5 phenyl-oxazolidine-2,4-dione (**10a–f**); 3-[(*p*-aniline)-ethyl]-5-phenyl-oxazolidine-2,4-dione (**11a–e**) derivatives with an ethyl spacer between imide nitrogen atom and 4-arylpiperazine or *p*-aniline derivative moiety.

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2, respectively. The ^{1}H-NMR spectra of the investigated compounds revealed characteristic chemical shifts agreed with their proposed structures. All compounds were isolated in their pure form and molecular formulae were established on the basis of elemental (C, H, N, O) analyses.

5,5-diphenylhydantoin **1** was selectively alkylated at *N*3 position with 1-bromo-2-chloro-ethane to afford the 2-chloroethyl derivative **2**. The IR spectra of both **1** and **2** showed the presence of N–H peaks at 3270 and

Table 4 Effect of the investigated compounds and WAY 100635 on the rectal 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
4b	10	−0.9 ± 0.2	−0.7 ± 0.1	−0.7 ± 0.2	−0.8 ± 0.2
	20	−1.7 ± 0.3	−1.6 ± 0.3	−1.6 ± 0.2	−1.7 ± 0.2
6c	10	−0.5 ± 0.1	−0.7 ± 0.1	−0.9 ± 0.3	−0.7 ± 0.2
	20	−2.5 ± 0.1	−2.7 ± 0.2	−2.9 ± 0.1	−1.5 ± 0.1
6d	10	−0.5 ± 0.1	−0.6 ± 0.2	−0.8 ± 0.1	−0.6 ± 0.1
	20	−1.2 ± 0.3	−1.5 ± 0.2	−1.8 ± 0.2	−1.3 ± 0.1
10b	10	−0.6 ± 0.2	−0.4 ± 0.1	−0.5 ± 0.2	−0.5 ± 0.3
	20	−1.5 ± 0.3	−1.4 ± 0.1	−1.4 ± 0.1	−1.4 ± 0.1
11a	10	−0.4 ± 0.1	−0.6 ± 0.2	−0.7 ± 0.1	−0.6 ± 0.1
	20	−1.0 ± 0.1	−1.2 ± 0.1	−1.6 ± 0.1	−1.1 ± 0.1
11b	10	−0.2 ± 0.1	−0.5 ± 0.1	−0.7 ± 0.2	−0.5 ± 0.1
	20	−1.2 ± 0.2	−1.3 ± 0.3	−1.5 ± 0.1	−1.3 ± 0.1
11d	10	−0.5 ± 0.1	−0.8 ± 0.1	−0.8 ± 0.3	−0.7 ± 0.2
	20	−1.1 ± 0.1	−1.5 ± 0.2	−1.5 ± 0.2	−1.3 ± 0.1
WAY100635	0.1	0.2 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1

The investigated compounds (ip) and WAY 100635 (sc) were administered 30 min before the test. The absolute mean initial body temperatures were within a range of 36.3 ± 0.5 C. $P < 0.001$ versus vehicle

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

Treatment	Dose mg/kg	Mean SEM LLR score	
		A	B
Vehicle	–	0.1 ± 0.1	2.8 ± 0.2
4b	10	1.0 ± 0.1	2.2 ± 0.2
	20	1.8 ± 0.3	2.5 ± 0.2
6c	10	1.5 ± 0.2	2.8 ± 0.2
	20	2.3 ± 0.1	NT
6d	10	1.0 ± 0.2	2.3 ± 0.1
	20	1.4 ± 0.1	2.5 ± 0.1
10b	10	0.1 ± 0.1	0.4 ± 0.1
	20	0.9 ± 0.3	0.7 ± 0.2
11a	10	0.2 ± 0.1	0.8 ± 0.1
	20	0.5 ± 0.2	0.8 ± 0.1
11b	10	0.1 ± 0.1	0.4 ± 0.2
	20	0.3 ± 0.2	0.6 ± 0.3
11d	10	0.1 ± 0.4	0.8 ± 0.1
	20	0.8 ± 0.2	0.9 ± 0.2
WAY 100635	0.1	0.1 ± 0.1	0.3 ± 0.2

The investigated compounds (ip) and WAY 100635 (sc) were administrated 15 min before the test (A), or 45 min before 8-OH-DPAT (1 mg/kg, sc) (B) $p < 0.01$ versus vehicle (A) or versus vehicle + 8-OH-DPAT (B) NT-not tested

Table 6 Effect of compounds **11a**, **11b**, and ketanserin on the (±)-DOI* induced head twitch response in mice (*((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane)

Treatment	ID_{50} (mg/kg, ip)[a]
11a	11 (7.9–15.4)
11b	8 (6.1–11.5)
Ketanserine	0.12 (0.07–0.20)

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

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

Compound	$5HT_{1A}$ activity		$5HT_{2A}$ activity
	Presynaptic	Postsynaptic	
4b	Agonist	Agonist	NA
6c	Agonist	Agonist	NA
6d	Agonist	Agonist	NA
10b	Agonist	Antagonist	NA
11a	Agonist	Antagonist	Antagonist
11b	Agonist	Antagonist	Antagonist
11d	Agonist	Antagonist	NA

Table 8 ADME screening by QikProp 3.1 (Schrödinger; LLC, USA)

Comp no	Ligand no.	CNS	FOSA	FISA	Q Plog P o/w	Q Plog HERG	Q Plog BB	Q Plog Khsa	% Human oral absorption	Lipinski's rule of five	#Stars	#rtvFG
4a	S1Lig1	1	189.95	127.57	3.3	−6.668	−0.669	0.394	79.529	0	2	0
4b	S1Lig2	1	190	72.847	4.254	−6.674	0.105	0.576	94.405	0	1	0
4c	S1Lig3	1	189.98	72.855	4.512	−6.704	0.156	0.65	95.91	0	1	0
4d	S1Lig4	−2	176.95	173.57	3.111	−6.316	−1.116	0.415	70.393	0	0	0
4e	S1Lig5	1	279.58	73.644	4.322	−6.729	−0.038	0.691	95.555	0	2	0
4f	S1Lig6	1	193.71	82.376	3.68	−6.892	−0.125	0.405	89.424	0	1	0
6a	S1Lig7	−2	59.59	136.1	2.975	−5.126	−1.053	0.09	88.045	0	2	0
6b	S1Lig8	0	55.971	86.807	4.324	−5.755	−0.409	0.411	100	0	2	0
6c	S1Lig9	0	55.965	86.797	4.069	−5.715	−0.457	0.34	100	0	1	0
6d	S1Lig10	0	148.77	86.941	3.933	−5.743	−0.65	0.313	100	0	2	0
6e	S1Lig11	0	144.19	86.984	4.139	−5.757	−0.593	0.452	100	0	2	0
10a	S2Lig1	0	201	147.17	2.42	−6.77	−0.75	0.19	76.87	0	1	0
10b	S2Lig2	0	205.3	88.14	3.14	−6.96	0	0.1	91.12	0	0	0
10c	S2Lig3	0	201.03	92.49	3.36	−6.82	−0.02	0.18	91.64	0	0	0
10d	S2Lig4	0	201.03	190.79	2.11	−6.89	−1.24	−0.05	67.64	0	0	0
10e	S2Lig5	0	289.21	92.5	3.18	−6.82	−0.16	0.22	90.58	0	0	0
10f	S2Lig6	0	204.28	106.14	2.44	−6.86	−0.28	−0.11	83.96	0	0	0
11a	S2Lig7	0	76.17	157.62	2.35	−5.81	−1.24	0.01	85.48	0	1	0
11b	S2Lig8	0	76.16	102.94	3.52	−5.87	−0.49	0.26	100	0	0	0
11c	S2Lig9	0	76.16	102.94	3.24	−5.81	−0.54	0.19	100	0	0	0
11d	S2Lig10	0	168.95	102.94	3.07	−5.85	−0.73	0.15	100	0	1	0
11e	S2Lig11	0	164.36	102.96	3.33	−5.87	−0.68	0.3	100	0	0	0

3306 cm^{-1}, respectively. The subsequent condensation of **2** with the various different piperazine and aniline derivatives was carried out by *N*-alkylation affording products **4a–f** and **6a–e**, respectively. The IR spectrum of **4a–f**, **6a–e** exhibited N–H peaks at (3387–3207 cm^{-1}), CH_2 peak at (2818–2918 cm^{-1}), and C=O peak at (1639–1645 cm^{-1}). ^{1}H-NMR spectrum of **4a–f**, **6a–e** showed aromatic peaks from 7.4 to 6.9 ppm followed by signals for piperazine protons between 3.8–3.1 ppm and 3.0–2.4 ppm (**4a–f)** and at 5.9–3.9 ppm for aniline N–H protons of (**6a–e**) confirming the formation of the desired products.

Similarly DL-mandelic acid was used for the synthesis of ethyl mandelate **7**. IR spectra of ethyl mandelate **7** shows the absence of COOH group in the IR spectra and presence of an ester linkage (1720 cm^{-1}) which was subsequently confirmed by ^{1}H-NMR showing the disappearance of acidic proton along with appearance of $–CH_2–CH_3$ protons. Condensation of **7** with urea in the presence of sodium ethoxide yielded 5-phenyl-oxazolidine-2,4-dione **8** exhibiting N–H peaks at (3373 cm^{-1}), and C=O peaks at (1606 cm^{-1}), respectively. Intermediate **8** was further selectively alkylated at *N*3 position with 1-bromo-2-chloroethane resulting in the formation of **9** which was confirmed by disappearance of *N*3 protons and presence of peaks for $N–CH_2–CH_2$ protons at 4.2 ppm (d, 2H, CH_2Cl), 3.7-3.4 ppm (s, 2H, $N–CH_2$) and IR peaks at 2924 cm^{-1} (C–H), 2854 cm^{-1}, 1456 cm^{-1} ($–CH_2–$), 1647 cm^{-1} (C=O), 1732 cm^{-1} (Ar C–C) 759 cm^{-1} (C–Cl). The subsequent condensation of intermediate **9** with various piperazine and aniline derivatives afforded products **10a–f** and **11a–f**, respectively. The IR spectrum of **10a–f**, **11a–e** exhibited C–H and C=O peaks at 2821–2918 cm^{-1} and 1632–1683 cm^{-1}, respectively, whereas in **11a–e** N–H peaks were observed at (3308–3390 cm^{-1}). The ^{1}H-NMR spectrum of **10a–f** and **11a–e** shows aromatic peaks at 7.2–7.1 and 7.8–7.0 ppm, followed by the presence of piperazine protons at 3.7–2.9 and 3.4–2.6 ppm (**10a–f**) and 4.0–4.9 ppm for aniline N–H protons (**11a–e**).

The series of synthesized derivatives were characterized by physical and spectral analyses. A wide range of both *para*-substituted piperazine and aniline derivatives consisting of both electron donating as well as electron withdrawing groups were employed for the reaction with equal ease.

Pharmacology

In vivo animal studies

The choice of appropriate animal models for the initial in vivo testing of potential anticonvulsant compounds is one of the most important steps in the successful search for new

Table 9 Details of descriptors (Schrodinger; LLC, USA)

S. no	Descriptor	Description	Recommended range
1.	CNS	Predictive central nervous activity	−2 (inactive) to +2 (active)
2.	FOSA	Hydrophobic component of the SASA (saturated carbon and attached hydrogen)	0.0–750.0
3.	FISA	Hydrophilic components of SASA (SASA on N, O, and H on heteroatoms)	7.0–330.0
4.	QPlog Po/w	Predicted octanol/water coefficient	−2.0–6.5
5.	QPlog HERG	Predicted IC_{50} value for blockage of HERG K^+ channels	<−5
6.	QPlog BB	Predicted brain/blood partition coefficient	−3.0–1.2
7.	QPlogKhsa	Prediction of human serum albumin	−1.5–1.5
8.	% Human oral absorption	It predicts human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model. This property usually correlates well with human oral-absorption.	>80% is high < 25% is poor
9.	Lipinski's rule of five	Lipinski's rules of five are: mol_MW < 500, QPlogPo/w < 5, donorHB ≤ 5, accptHB ≤ 10. Compounds that satisfy these rules are considered druglike. (The "five" refers to the limits, which are multiples of 5	Maximum is 4
10.	#stars	Number of property or descriptor values that fall outside the 95% range of similar values for known drugs. A large number of stars suggest that a molecule is less drug-like than molecules with few stars. The following are some of properties and descriptors are included in the determination of #stars: Molecular weight, dipole, QPlogPw, QPlogPo/w, QlogS, solvent accessible surface area (SASA) etc.	0–5
11.	#rtvFG	This particular descriptor indicates the number of reactive functional groups. The presence of these groups can lead to decomposition, reactivity, or toxicity problems in vivo.	0–2

antiepileptic drugs. Among the various chemo-convulsants and physical stimuli used to induce experimental seizures, MES is recognized as a valid and reliable means of studying seizure mechanisms in the development of anti-convulsant drugs. Rotarod performance test is used to ascertain the impairment of motor performance, ataxia, loss of skeletal muscular strength and acute neurotoxicity produced by drugs in preclinical studies.

After the initial assessment for anti-MES activity in Phase I, compounds **4b**, **6c**, **6d**, **10b**, **11a**, **11b**, **11d** were found to be active against epileptic seizures (Table 2) and were devoid of any neurotoxicity. Preliminary results from Phase I rotarod test demonstrated that compounds **4c**, **4f**, **6a**, **6b**, **6e**, **10a**, **10c**, **10e**, **10f**, **11a**, and **11e** though did not exibit any visible signs of neurotoxicity at the maximum administered dose of 300 mg/kg, (Table 2) but were unable to elicit any protection against the MES assay. As a result compounds **4b**, **6c**, **6d**, **10b**, **11a**, **11b**, **11d** were advanced to phase VIa of anticonvulsant drug development protocol. The results of the phase VIa studies are shown in Table 3

For the synthesized series of compounds, it was observed that the anticonvulsant activity depends mainly on the length of alkyl spacer between imide nitrogen atom (here kept constant at $n = 2$, most active), 4-arylpiperazine and aniline moiety, as well as on mode of substitution (all *para* substituted) of the latter and the type of substituents (electro positive and electro negative). With respect to part C in the pharmacophore (Fig. 1), a majority of aniline derivatives **(6c**, **6d**, **11a**, **11b**, **11d)** were found to be active than the piperazine ones **(4b**, **10b)**. Amongst all the evaluated compounds in Phase VIa, the chloro derivative **11b** and fluoro derivative **6c** of aniline were found to be highly active in comparison to others.

The anticonvulsant action of these molecules was found to be comparable to that of phenytoin, which was used as a standard anticonvulsant drug. Overall, the aniline derivatives were found to be more active as compared to their piperazine congeners against MES (Tables 2, 3).

In vivo receptor binding studies

The compounds found active in MES (**4b**, **6c**, **6d**, **10b**, **11a**, **11b**, **11d**) without any neurotoxic effects were further taken up for in vivo receptor binding studies (Tables 4, 5, 6, 7). All the above-mentioned compounds tested, like 8-OH-DPAT, induced hypothermia in mice. Thus, the results obtained from the hypothermia model are an indicative that **4b**, **6c**, **6d**, **10b**, **11a**, **11b** and **11d** behave like presynaptic 5-HT_{1A} receptor agonists.

Postsynaptic 5-HT_{1A} affinity was assessed by LLR test. Like 8-OH-DPAT, compounds **4b**, **6c**, and **6d** evoked LLR in rats, whereas **10b**, **11a**, **11b**, and **11d** like WAY100635, inhibited LLR induced by 8-OH-DPAT (Table 5). The above results demonstrated that **4b**, **6c**, and **6d** exhibit

features of post synaptic 5-HT_{1A} receptor agonist, while **10b**, **11a**, **11b**, and **11d** behave like antagonists of these receptors.

To estimate the affinity toward 5-HT_{2A} receptor, head twitch method was used. Like ketanserin, a reference 5-HT_{2A} receptor antagonist, compounds **11a** and **11b** inhibited the head twitches induced by (±)-DOI, a 5-HT_{2A} receptor agonist, in mice (Table 6). In comparison to **11a** and **11b** all other tested compounds elicited very less affinity for the 5-HT_{2A} receptor and were assigned as non actives (NA) (Table 7). Hence, compounds **11a** and **11b** may be classified as 5-HT_{2A} receptor antagonists.

From the results obtained by in vivo receptor studies, it is evident that the tested compounds are characterized by diverse activity at 5-HT_{1A} receptors. Thus, we can finally conclude that the compounds **4b**, **6c**, **6d** showed characteristics of pre- and post-synaptic $5HT_{1A}$ receptor agonists; compounds **10b**, **11a**, **11b**, **11d** exhibited characteristics of 5-HT_{1A} agonist at both pre- and post-synaptic sites. Moreover, compounds **11a** and **11b** exhibited properties of potential 5-HT_{2A} receptor antagonists (Table 7).

In silico ADME studies

One of the main goals in drug discovery is the identification of innovative small molecular scaffolds exhibiting high binding affinity and selectivity for the target together with a reasonable absorption, distribution, metabolism and excretion (ADME) profile, lead and/or drug likeness. Such chemical entities are likely to be able to enter higher phases of the drug development process. This has resulted in a paradigm shift in identifying the drug likeness properties of lead molecules early in the drug discovery process. Thus, in vitro approaches are now widely used to investigate the ADME properties of new chemical entities and, more recently, computational modeling has been investigated as a tool to optimize selection of the most suitable candidates for drug development (Sengupta *et al.*, 2007).

QikProp (Schrödinger, LLC, USA) programme was used to predict the ADME properties of the synthesized compounds. QikProp 3.1(Schrödinger; LLC, USA) predicts both physically significant descriptors and pharmaceutically relevant properties. It also evaluates the acceptability of the analogues based on Lipinski's rule of 5, (Lipinski *et al.*, 2001) an important parameter essential for rational drug design.

It was observed that apart from compounds **4d** and **6a** all other derivatives are predicted to be active for CNS activity which is in agreement with the results obtained from the in vivo studies. Apart from this, a majority of compounds are being predicted to possess significant oral absorption. None of the compounds violated the Lipinski rule of five nor do they possess any reactive groups which may lead to decomposition, reactivity or toxicity related problems in vivo (Tables 8, 9).

Conclusion

In conclusion, a new series of substituted piperazine and aniline derivatives of 5-phenyl oxazolidin-2,4-diones and 5,5-diphenylimidazolidin-2,4 diones which were synthesized by selective *N*3 alkylation can be graded as potential ligands of 5-HT_{1A} receptors. Thus from the in vivo animal as well as receptor studies, it is evident that the aniline derivatives of phenytoin and oxazolidine exhibit more promising action than the more bulky piperazine derivatives. This reduction in the overall bulkiness of the pharmacophore without compromising the lipophilicity which will be of further help for these molecules in crossing the blood brain barrier so as to reach the target receptors for eliciting the anticonvulsant effects.

At this stage, we can conclude that reduction in bulkiness has a positive impact on the anticonvulsant activity of the compounds. Moreover, compounds showing affinity toward 5-$HT_{1A/2A}$ receptors can be further quantified (in vitro) by radio ligand binding assays. Thus, this study helps to provide a useful insight into the structural requirements necessary for carrying out rationally based pharmacophoric manipulations in order to obtain promising compounds with anticonvulsant effects.

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