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DESIGN SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NOVEL BENZHYDRYL PIPERAZINE DERIVATIVES AS A NEW CLASS OF ANTI-CONVULSANT AGENTS

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Keywords:

Anti convulsant activity, Neurotoxicity, Benzhydryl piperazine

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ABSTRACT: A novel series 3(a–d) 1-(4-benzhydryl piperazin-1-yl)-3-(di substituted) propan-1-one &1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e) & 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) compounds have been synthesized and screened for its anticonvulsant and neurotoxic activity, After i.p. injection to rat at doses of 30, 100, and 300 mg/kg body weight. Synthesized compounds were examined in the maximal electroshock-induced seizures (MES). Spectroscopic data were consistent with the structure of newly synthesized compounds. The neurotoxicity was assessed using the rotarod method. In the prepared series, 3f was found to be active in the MES screen at 0.5 h, and 4 h.

INTRODUCTION: Epilepsy is a chronic disease differentiated by the paroxysmal and reoccurring incidences of uncontrolled excitation of neurons of the brain. Since the currently used drugs include the drugs effective currently for 60-80% efficacy in epileptic patients, the combination therapy with antiepileptic drugs is indicated clinically over the monotherapy. In the world currently, 50 million individuals are affected by epilepsy [1, 2]. The recently discovered antiepileptic drugs have been reported for different types of seizures, including Phenytoin, carbamazepine, Lamotrigine, sulfamate and topiramate (Thiry *et al.*, 2007). The SAR for these kinds of agents is well reported in the literature, suggesting the need for two aryl binding sites at both ends and an important hydrogen binding site at the middle for potent activity. The evidence suggests that the diphenyl methyl attached to piperazine increases the anti-convulsant activity by providing hydrophobicity to the molecule. The compounds prioritized for the anti-convulsant properties should have a C=O group required for hydrogen bonding interactions at the active site.

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The hydrophobic diphenyl moiety showed higher activity than other groups. The insertion of the –CH_2-CH_2-N at one end with the donor and acceptor group retained the activity. The compound 3(a-f) containing the carbonyl and amide linkage, may play an important role in the hydrogen bonding domain, enhancing the anti-convulsant activity [3, 4, 5]. With these reports in this study, we also tried to

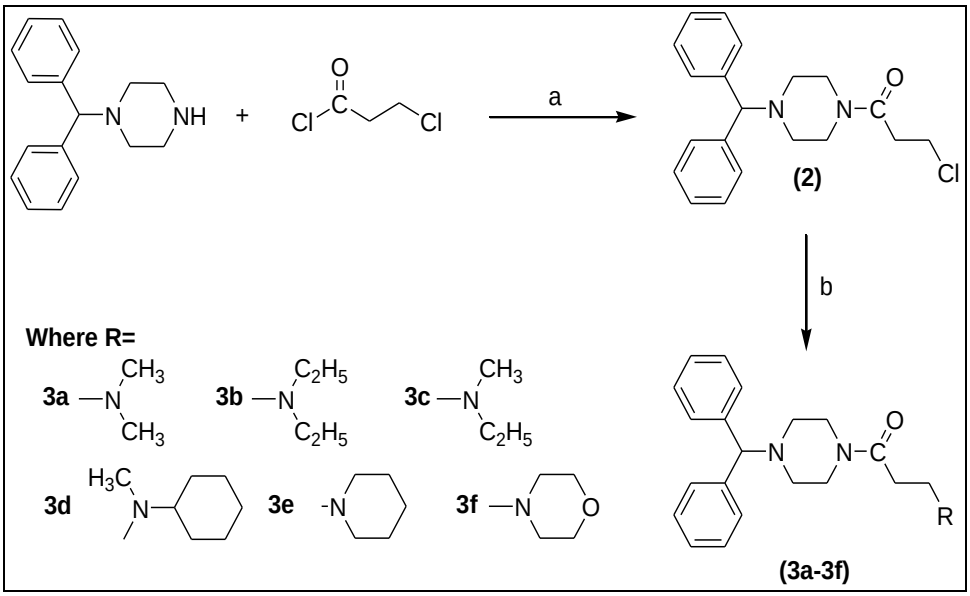
further elucidate the requirement of the essential groups or features in the 3D space with a pharmacophore modeling tool. We have successfully implemented and reported the pharmacophore modeling using both HipHop and HypoGen modules for drug discovery and research in diabetes, cancer, tuberculosis and Alzheimer's disease [6].

The pharmacophore module implemented in this study can be used to explain the important features of the predefined dataset qualitatively (HipHop) or quantitatively (HypoGen) to correlate between biological activity and important groups or features in 3D space. These hypotheses can be used as a query for LBVS [Ligand-based virtual screening] to identify or design new chemical entities for the concerned target enzyme. This protocol has been reported in the literature for a large no. of targets in modern drug discovery [7]. We have implemented the same protocol for identifying and comparing the features required for anti-convulsant drugs in the current work. The manuscript also reveals in detail the SAR and the comparison of the features with clinically available anti-convulsant agents.

MATERIAL & METHODS

Synthesis & Characterization: The melting points were determined in an open glass capillary using melting point apparatus (Veego, Bombay, India) and are uncorrected. The reactions were monitored using the TLC. IR, and NMR were recorded in SAIF, CDRI, Lucknow using the Perkin Elmer FTIR model and Bruker DRX-300, respectively and chemical shifts were calculated in ppm relative to TMS as an internal standard. DART-MS was used for mass spectroscopic analysis and recorded on a JEOL-Accu TOF JMS-T100 LC mass spectrometer.

Reaction Scheme



Reaction Conditions: (a) Dioxane, cooling at 0-5°C, stirred at RT for 4-6 h **(b)** Dry K_2CO_3, 12 h at 25°C.

Synthesis of Benzhydryl Piperazine (1): Benzhydrol (0.29 mol, 53.36 g) [1] was dissolved in dichloromethane (100 mL). Thionyl chloride (50 mL, 0.69 mol) was added to the reaction mixture, and reaction mixture was stirred at 40°C for 3 h. The dried residue after solvent evaporation was dissolved in the acetonitrile (20 mL) yield was 90%. Benzhydryl chloride (0.29 mol, 58.58g) was refluxed for 12h with piperazine (1.44g, 0.29 mol). The solvent was evaporated under vacuum and the residue dissolved in ethyl acetate with occasional washing with water (100ml) and 1N HCl, respectively (100ml). The organic layer was discarded, and the aq. The layer was neutralized with 2N NaOH to pH > 10, and the layer was extracted with DCM. The DCM was washed with brine and dried over sodium sulphate followed by evaporation under vacuum to obtain the compound as a yellow oil (Yield was 80%).

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one (2): A stirred solution of benzhydryl piperazine (10 mmol, 2.52g) in dioxane was heated for 10 min followed by cooling at 0-5°C in ice bath in which chloro propanoyl chloride was added and stirred at room temperature for 4-6 hrs. The aqueous layer was extracted with ethyl acetate and washed with 10% ammonium chloride solution and water. The organic layer was dried, and solvent was removed under reduced pressure. The yield of pure compound was (80%) [8, 9, 10].

IR (ATR): 3026, 2974, 1705, 1643, 1520, 1087,785, 671.

Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one (3a): A mixture of compound (2), diethylamine and dry K_2CO_3 in benzene was stirred for 12 h at 25°C. The ethyl acetate or DCM layer was distilled water three times approximately and solvent was removed under reduced pressure. The yield of compound was 75%.

^{1}H NMR: (300 MHz, $CDCl_3$): δ ,7.13-7.40 (m, 10H, Ar-H), 5.28 (s, 1H, of benzhydryl moiety) 3.78-3.82 (t, 2H, *J*= 6 Hz –$COCH_2(CH_2)$, 3.57-3.61 (t, 2H, *J*=6 Hz, pip), 3.40-3.44 (t, 2H, *J*=6 Hz pip), 2.71-2.77 (q, 4H, of –N-(CH_2)-CH_3), 2.46-2.51 (t, 6H, *J*= 7.5 Hz in which 4H of pip, 2H of –$COCH_2$), 1.11-1.16 (t, 6H, *J*= 7.5 Hz of –N-CH_2-(CH_3). IR (KBr):- 3021, 2977, 2822, 1631, 1545, 1482, 1422, 1343, 1215, 670. Found: C, 75.91; H, 8.75; N, 11.06. $C_{24}H_{33}N_3O$, Required: C, 75.95; H, 8.76; N, 11.07. The same procedure was used for the synthesis of compound 3b, 3c and 3d the dimethyl amine, ethyl methyl amine and N-Methyl cyclohexyl amine was preferred base over diethyl amine. The yield of final compounds 3a, 3c and 3d was 70%, 54% & 58% respectively.

2.16 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethyl amino) propan-1-one (3b) [9]:
^{1}H NMR: (300 MHz, $CDCl_3$): δ,7.15-7.41 (m,10H, Ar-H), 5.27 (s, 1H, of benzhydryl moiety) 3.55-3.60 (t, 2H,*J*= 7.5 Hz piperazine), 3.45-3.48 (t, 2H, *J*=4.8 Hz, pip), 2.76-2.81 (t, 4H, *J*=7.5 Hz pip), 2.55-2.60 (t, 2H, *J*= 7.5 Hz of –$COCH_2$), 2.28 (s, 6H, N-CH_3).

IR (KBr): 3065, 2941, 2914, 2809, 1684, 1540, 1509, 1465, 1421, 1394, 1371, 684.

Found: C, 75.13; H, 8.35; N, 11.95. $C_{22}H_{29}N_3O$, Required: C, 75.18; H, 8.32; N, 11.96.

2.17 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino) propan-1-one (3c) [9]:
^{1}H NMR: (300 MHz, $CDCl_3$): δ, 7.16-7.42(m, 10H, Ar-H), 4.22 (s, 1H, of benzhydryl moiety) 3.59-3.62 (t, 2H, *J*= 4.65 Hz piperazine), 3.45-3.48 (t, 2H, *J*=4.65 Hz, pip), 2.66-2.72 (t, 2H, *J*=7.65 Hz, CO-CH_2-(CH_2), 2.42-2.50 (q, br, 2H, of –N-(CH_2)-CH_3), 2.36-2.39 (t, 8H, in which 4H of pip, 2H of –$COCH_2$ and 2H of –N-CH_2-(CH_3), 2.22 (s, 3H, N-CH_3).

2.18 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(cyclohexyl (methyl) amino) propan-1-one (3d): ^{1}H NMR :-(300 MHz, $CDCl_3$): δ, 7.16-7.41(m, 10H, Ar-H), 5.27 (s, 1H, of benzhydryl moiety) 3.58-3.62 (t, 2H, *J*= 6 Hz -CO-CH_2-(CH_2), 3.46-3.49 (t, 4H, *J*=4.5 Hz, pip), 2.83 (t, 2H,*J*=7.5Hz, CO-CH_2), 2.57 (m, 1H, of cyclohexane), 1.47-1.79 (m, 10H of cyclohexane).

2.19 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e) [10]: The similar procedure was implemented for the synthesis of compound 3e while the $K_2CO_3$was used as a base. The solvent was evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with water, and dried over sodium sulphate. The product was obtained in the 80% yield (R_f = 0.85).

^{1}H NMR:-(300 MHz, $CDCl_3$): δ ,7.16-7.41 (m,10H, Ar-H), 5.27 (s, 1H, of benzhydryl moiety) 3.58-3.62 (t, 2H, *J*= 4.65 Hz pip), 3.45-3.48 (t, 2H, *J*=4.8 Hz, pip) 2.66 (t, 4H, *J*=9 Hz, pip), 2.49-2.51 (t, 2H, *J*= 15 Hz of –$COCH_2$), 2.37 (t, 2H, *J*= 9 Hz –$COCH_2(CH_2)$, 2.35 (m, 4H, piperidine), 1.55 (m, 6H, piperidine).

2.20 Synthesis of 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f): The product was synthesized with the same procedure as described above for other compounds in this case, the morpholine was preferred over piperidine. The yield of pure compound was (65%). R_f = 0.65.

^{1}H NMR:-(300 MHz, $CDCl_3$): δ,7.13-7.41 (m, 10H, Ar-H), 5.17 (s, 1H, of benzhydryl moiety) 3.77-3.82 (t,2H, *J*=7.05 Hz –$COCH_2(CH_2)$, 3.67-3.70 (t, 4H, *J*=4.5 Hz, morpholine), 3.59-3.62 (t,

2H, *J*=4.65 Hz pip), 3.44-3.47 (t, 2H, *J*=4.65 Hz pip), 2.47-2.51 (t, 6H, *J*= 6 Hz in which 4H of pip, 2H of $–COCH_2$), 2.41-2.45 (t, 4H, *J*= 6.9 Hz of morpholine).

Pharmacology: The MES pattern test used the initial anti-convulsant evaluation of the target compounds undertaken by anti-convulsant drug development. Minimal motor impairment was measured by the rotarod (neurotoxicity, NT) test. (ADD) the program, NIH protocol. The profile of anti-convulsant activity was established after i.p. injections by electrical method.

Anti-convulsant Activity [11, 12, 13, 14]: The anti-convulsant activity was carried out using the MES pattern test. Neurotoxicity was measured by Rotarod. The activity profile was established by IP injections using the electrical method. Animals have maintained an adequate diet and are allowed free access to required food and water. Initial screening of the animals was carried out for 24 h before the experiment. For 0.25 sec, 150 mA current was given to the pinna of the animals by using Medicraft® Electro-Convulsometer (Lucknow, India). The normal saline solution is used as the conducting medium between electrode and pinna. The selection of animals was based on the production of tonic convulsion. A short phase of the tonic extension of the hind limbs indicates the maximal seizure. After selection, animals were divided into groups, all compounds were administered intra-peritoneally at different doses as 30, 100, 300 mg/kg. After 30 min and 4 h of drug administration, electroshock was applied. The disappearance of the hind limb tonic extensor phase of convulsion was considered a positive criterion for anti-convulsant activity. For neurotoxicity screening, the Rotarod performance test was used [5].

The minimal impairment was measured in by the reported protocol using Rotarod. The knurled rod of diameter 3.2 cm rotates at 6 revolutions per min. Only those animals, which have demonstrated their capability to stay on the revolving rod for at least 1 min, were considered for the test. The normal rats were able to remain on the rotating rod. The treated animals at the doses of i.p. in doses of 30, 100, and 300 mg/kg were placed on the rotating rod (half an hour after drug administration) and observed for neurotoxicity test for at least 1 min in each repeated three trials. The results were represented in the table indicating the minimum doses for the optimum bioavailability. The animals were observed for the activity after dosing at 0.5 and 4 h.

TABLE 1: EFFECT OF TESTED COMPOUNDS AND PHENYTOIN ON MES INDUCED CONVULSIONS IN RATS (N=6)

Compd. code.	Dose (mg/kg i.p.)	MES (number of animals protected)		NT (number of animals showed neurotoxicity)		ED_{50}** (mg/kg)	ED_{50} (mmol/kg)	Activity in comparison to Phenytoin
		½ h	4 h	½ h	4h			
(3a)	30	3	1	0	0	31.5	0.0831	0.49
	100	4	3	3	1			
	300	6	6	4	3			
(3b)	30	1	1	0	0	504.7	1.437	0.03
	100	1	2	3	3			
	300	2	2	4	4			
(3c)	30	3	2	0	0	21.7	0.059	0.69
	100	4	3	3	1			
	300	4	4	4	3			
(3d)	30	3	3	0	0	30	0.071	0.58
	100	5	5	3	3			
	300	6	6	4	4			
(3e)	30	5	5	0	0	-	-	-
	100	5	6	1	1			
	300	6	6	2	1			
	30	3	2	0	0	23.3	0.0517	0.79
(3f)	100	5	4	3	3			
	300	5	5	4	4			
	30	3	3	0	0	10.3	0.041	1.0
Phenytoin	100	5	4	3	3			
	300	6	6	4	4			

* ED50 is calculated using XLSOFT (Version 2012.2.01) on the basis of maximum effect Observed at ½ h. ** ED50 (Choi, *et al*., 1996) 15 Doses of 30, 100 and 300 mg/kg were administered i.p. The figures in the table indicate.

RESULT AND DISCUSSION:

Chemistry: The synthesis of compounds (3a, 3b, 3c, 3d, 3e & 3f) has been carried out as presented in the scheme. These compounds were synthesized by the reaction of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one with the various disubstituted amines, piperidine and morpholine.

The title compound 1-(4-benzhydrylpiperazin-1-yl)-3-(diethyl amino) propan-1-one **(**3a) was synthesized by the refluxing of 1-(4-benzhydrylpiperazin-1-yl)-3-chloropropan-1-one and diethyl amine in the presence of dry K_2CO_3 and dichloromethane. The compound 1-(4-benzhydryl-piperazin-1-yl)-3-(dimethylamino) propan-1-one (3b) was synthesized as same as of compound (3a). At the place of diethylamine we take dimethyl amine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino) propan-1-one (3c) was synthesized as same as of compound (3a). At the place of diethylamine we take Ethyl methylamine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one(3e) was also synthesized as same as of compound (3a). At the place of diethyl amine we take piperidine. The compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) was synthesized as same as of compound (3a). At the place of diethylamine we take morpholine.

Structure of the prepared compounds was confirmed with the help of spectral analysis. In the prepared series, 1-(4-benzhydrylpiperazin-1-yl)-3-(cyclohexyl (methyl) amino) propan-1-one **(**3d) and 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino) propan-1-one (3c) showed average activity. Compound 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e) was not shown any activity. Out of six compounds one compound 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethyl amino) propan-1-one (3b) exhibited very poor activity and compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) showed excellent activity. All compounds exhibited neurotoxicity at a 300 mg/kg maximum dose level. None of the compounds showed neurotoxicity at a dose of 30 mg/kg.

Result and Discussion of Computational:

Common Feature Pharmacophore Development: Hip Hop algorithm was used in this study to extract the common feature for the series because of the small difference in the biological activity of 3 log units. The most active Ligand from this series was assigned a maximum weight as the remaining compounds may bind similarly at the receptor site. The seven molecules from the series were used to develop a pharmacophore model using the Hip Hop module. Training set molecules for pharmacophore development.

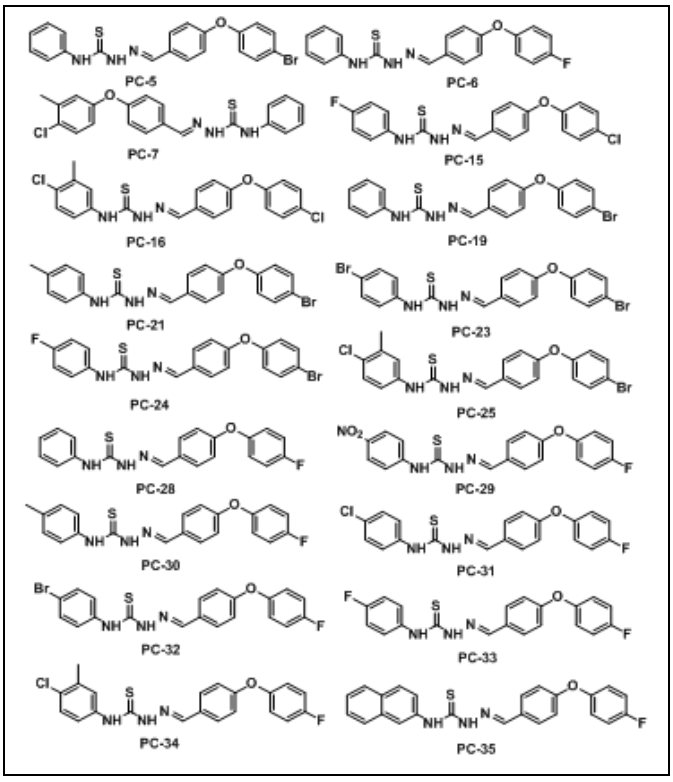


FIG. 1: STRUCTURES OF THE 18 TRAINING SETS OF MOLECULES THE PHARMACOPHORE DEVELOPMENT

Pharmacophore Modeling [16, 17]:

3D Pharmacophore Generation: The most active compound was differentiated from the rest of the compounds by assigning the highest weight 2 and 0 where it signifies that all features of this compound were essential for modeling and must be mapped respectively. All other compounds were assigned a value of 1 and 1 in principle and maximum omit feat column, which means at least one mapping and one feature must map. Remaining all parameters was kept default. The ten hypotheses generated had the scores ranging from 360.378-354.65. The entire ten hypotheses contain seven features *viz*. The two acceptor (H_2) aromatic ring (R, 3) and donor features were common for all hypotheses.

The first hypotheses were selected for further studies as it passed the internal validation. The two H functions maps the on one oxygen from phenoxybenzamine part PC-23 from the series **Fig. 2B**, while the C=S group mapped the other H function from the N-(4-bromophenyl)-2-methylene hydrazine carbothioamide. The three benzene ring from PC-23 was mapped for the R function of this pharmacophore model. The two N-H functions compiled the remaining two D functions from the N-(4-bromophenyl)-2-methylene hydrazine carbothioamide part at one end of this molecule. All the studies were carried out using the best conformation search within the 20kcal/mol threshold energy.

TABLE 2: THE CHARACTERISTICS OF THE GENERATED PHARMACOPHORE MODEL

Hypo.	Features	Rank	Direct Hit	Partial Hit	Max Fit
1	RRRDDHH	360.378	11111111111111111	000000000000000000	7
2	RRRDDHH	360.378	11111111111111111	000000000000000000	7
3	RRRDDHH	360.378	11111111111111111	000000000000000000	7
4	RRRDDHH	360.378	11111111111111111	000000000000000000	7
5	RRRDDHH	354.65	11111111111111111	000000000000000000	7
6	RRRDDHH	354.65	11111111111111111	000000000000000000	7
7	RRRDDHH	354.65	11111111111111111	000000000000000000	7
8	RRRDDHH	354.65	11111111111111111	000000000000000000	7
9	RRRDDHH	354.65	11111111111111111	000000000000000000	7
10	RRRDDHH	354.65	11111111111111111	000000000000000000	7

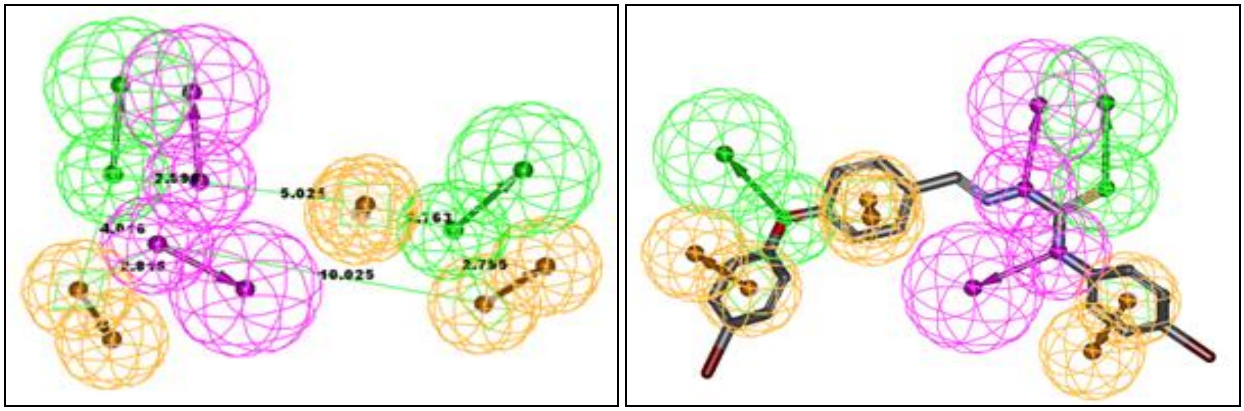


FIG. 2: (A) PHARMACOPHORE MODEL B) LIGAND PHARMACOPHORE MAPPING OF PC-23

Pharmacophore Validation [8, 16, 17]: The Hip Hop model developed was validated by six external test set compounds using the flexible fit method of the Ligand pharmacophore mapping protocol.

The **Table 1** and the figure showed the fit values for the mapping and the alignments for the hypo-1. A library of 20 compounds was designed, and top 5 were selected for further synthesis and evaluation. Figures (iii c) and D show the alignments for the PC-23. The designed compound maps 5 out of the required seven features.

The analysis showed these compounds have potential anti-convulsant agents. **Fig. 3**. Clinically used progabide and ramacemide on Hypo-1. C and D mapping of the top-ranked designed compounds on the Hypo-1.

TABLE 3: THE PHARMACOPHORE MAPPING OF THE ISOLATED COMPOUNDS ON THE BEST HYPOTHESIS (HYPO-1)

Comp.	Fit Value	Comp.	Fit Value
Progabide	3.69965	Lamotigrine	2.4722
Ramacemide	3.68569	3F	2.80726
Phenytoin	3.23739	3C	2.38453
Zonisamide	2.98457	3D	2.35067
Ralotolin	2.96309	3A	2.32678
Carbamazepine	2.94395	3E	2.29198
Mephobarbital	2.72951	3B	2.25101

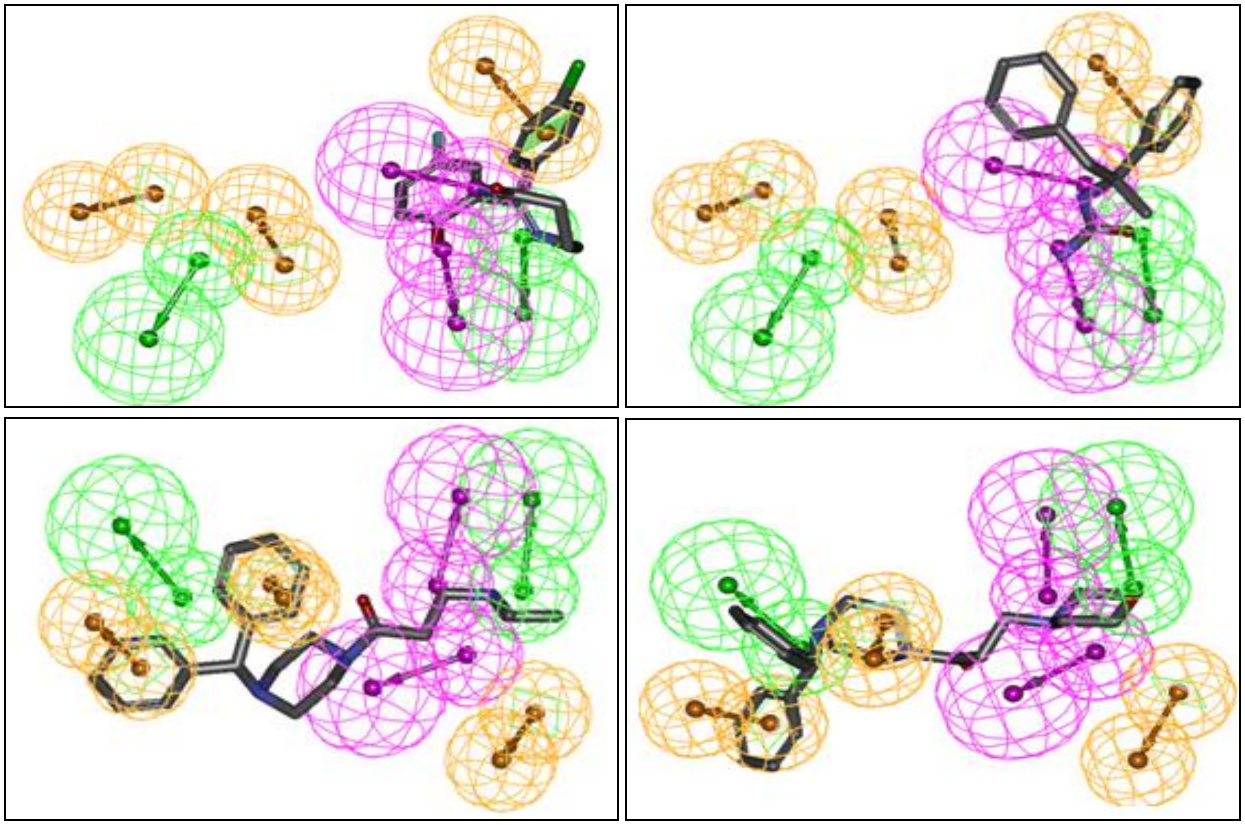


FIG. 3: A AND B MAPPING OF THE CLINICALLY USED COMPOUNDS PROGABIDE AND RAMACEMIDE ON HYPO-1. C AND D MAPPING OF THE TOP-RANKED DESIGNED COMPOUNDS ON THE HYPO-1

Material and methods

HipHop Pharmacophore Model Generation [8, 16, 17, 18]: The reported series of anti-convulsant compounds were used for the generation of the HipHop pharmacophore model. The HipHop was preferred over Hypogen as the selected series lacks the required 3 log unit variation necessary for the development of a quantitative pharmacophore model. The training set of 18 diverse compounds **Fig. 1** showing maximum activity at 250 mm was used for his model generation. The pharmacophore generation was carried out using the discovery studio 2.0 in the Windows operating system. The well-reported protocol for the pharmacophore generation as reported by our group was used for this study. The preprocessing of these compounds was also carried out using the CharmM force field and the default parameters using the best fit conformational generation protocol. In the common feature pharmacophore generation protocol of DS 2.0 the principal and maximum omit features were assigned as 2 and 0 for most active compounds and 1 and 0 for all other less active compounds, as reported earlier, with default interfeature distance of 2.97Å to find the closely related functional groups from training set compounds with default features *viz*. hydrogen bond acceptor (1-5), ring aromatic (1-5), donor (1-5). The Hypo-1 generated from this study was used as a query to validate the model using the internal training and external test set prediction to use this model for further computational experiments as pharmacophore-based virtual screening.

Validation of Pharmacophore Model: In this validation process the complete strategy was followed to ensure that the acceptability of the pharmacophore model for further studies. For this purpose Hypo-1 was used to predict the training set and some standard compounds from literature (Supplemental Data **Fig. 2** [5-25]. The ligand pharmacophore mapping protocol of DS 2.0 was used to map all the hit compounds with the best flexible search option.

CONCLUSION: The present study reports the molecular modeling, synthesis and anti-convulsant activity of 1-(4-benzhydrylpiperazin-1-yl)-3-(disubstituted) propan-1-one (3a-d) and 1-(4-benzhydrylpiperazin-1-yl)-3-(substituted) propan-1-one (3e-f). The pharmacological evaluation showed that 1-(4-benzhydrylpiperazin-1-yl)-3-

(cyclohexyl (methyl) amino) propan-1-one (3d) and 1-(4-benzhydrylpiperazin-1-yl)-3-(ethyl (methyl) amino) propan-1-one (3c) showed average activity. Compound 1-(4-benzhydrylpiperazin-1-yl)-3-(piperidin-1-yl) propan-1-one (3e) was not shown any activity. Out of six compounds one compound 1-(4-benzhydrylpiperazin-1-yl)-3-(dimethyl amino) propan-1-one (3b) exhibited very poor activity and compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one(3f) showed excellent activity. Molecular modeling also supports that compound 1-(4-benzhydrylpiperazin-1-yl)-3-morpholinopropan-1-one (3f) have excellent activity.

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CONFLICTS OF INTEREST: The authors declare that there is no conflict of interest regarding the publication of this paper.

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