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Synthesis, molecular docking, and pharmacological evaluation of some new triphenyl imidazole derivatives as anxiolytic agents

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In the present investigation, the docking of triphenyl imidazole derivatives have been done following which synthesis of the compounds have been carried out and the compounds have been characterized by TLC, IR, and ^{1}H NMR. The compounds have been assessed *in vivo* for antianxiety activity by two different methods. Other parameters have also been assessed including similarity index and Log P values which is found to be in the range which indicate that drug penetration to CNS is good. Among the synthesized derivatives, the compounds NS-3 and NS-4 give remarkable anxiolytic activity. The studies of molecular docking studies display that the compounds appropriately docked into binding pocket of the $GABA_A$ receptor and bioavailability/drug-likeness has also been predicted to be satisfactory warranting forthcoming exploration. The further prospect is to optimize the synthesized derivatives to engender new moieties for treatment of anxiety.

Keywords: Triphenyl imidazole derivatives, Benzil, Benzaldehyde, Antianxiety activity, CNS agents, Docking score

Imidazole ($(CH)_3N$) is a versatile heterocyclic aromatic compound characterized by a five-membered ring containing two non-adjacent nitrogen atoms and have employed an exclusive place in the field of medicinal chemistry. This compound is found in numerous biological molecules, including histidine, histamine, or in natural nucleotides. Due to the versatility of this pharmacophore, it was found to possess extensive range of biological activities other than microbial activities such as analgesic, anti-Alzheimer, anticonvulsant, anti-depressant**,** anti-epileptic, anti-inflammatory, antihypertensive, platelet aggregation inhibitors, antioxidant, anti-cancer[1–8]. Many known drugs such as dacarbazine, metronidazole, cimetidine, flumazenil, thyroliberin, methimazole, and pilocarpine contains imidazole moiety in its structure. Anxiety is one of the most recurrent neurological disorders. Anxiolytics can be highly effective in managing symptoms of anxiety and improving overall mental well-being. It's essential to use these medications under the guidance of a healthcare professional to ensure they are appropriate for your specific situation and to monitor for any potential side effects or interactions with other medications. Proper medical supervision helps to maximize the benefits while minimizing risks, contributing to better health and quality of life[9]. These drugs slow down the process of central nervous system (CNS) by increasing gamma-aminobutyric acid (GABA) activity which may result in depression. The drugs include benzodiazepines, ethanol, opiates, and barbiturates. Benzodiazepines, also exhibit calming effects, potentiate GABA neurotransmission by increasing the affinity of GABA receptors and so increase the inhibitory effects on the CNS[10-15]. Moreover, heterocyclic compounds like imidazole and aniline, distinguished for their diverse pharmacological properties including anti-convulsant, anticancer, antihypertensive, and antiepileptic and have gathered attention for potential drug development[16–20]. The current study synthesizes novel tri-phenylimidazole derivatives linked with aniline and the drugs were evaluated for their anxiolytic property.

Experimental Section

Chemicals for the synthesis were procured from Sigma-Aldrich and were used in the same form. Melting points of the synthesized derivatives were obtained by open capillary tubes on Electrothermal capillary apparatus and were uncorrected. The docking simulations were performed by using Argus Lab software whereas Swiss ADME and Molinspiration software were used for prediction of the pharmacokinetic properties of the compounds. The statistical analysis of biological activity

performed was done by using GraphPad Prism 5 software. For forecasting the biological activities PASS online software was used. The Infrared spectra (IR) were developed on potassium bromide plates Shimadzu FTIR Spectrophotometer 8300. Proton resonance magnetic spectra (^{1}H NMR) were verified on a Bruker DRX-300 spectrophotometer and spectra were confirmed on a Bruker NMR spectrometer (100 MHz) and chemical shifts were expressed in "δ ppm". The signals are cited as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet and are expressed in d ppm.

General Procedure for synthesis of Compound 2,4,5-triphenyl-1*H*-imidazole (1)

Benzil (10 gm), ammonium acetate (10 gm), benzaldehyde (20 ml), and glacial acetic acid (20 ml), were taken in a round bottom flask and the mixture was refluxed for 3 hours. The reaction mixture was allowed to stay at room temperature to attain the room temperature. 1500 ml of distilled water was added and the mixture was filtered. The solid mass was washed with toluene and recrystallized from methanol.

General Procedure for Synthesis of 2-chloro-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl) ethenone (2)

Mixtures of 0.1 moles of 2,4,5-triphenyl-1H-imidazole (1) dissolved in toluene and 0.01 mole of chloro acetyl chloride in toluene was prepared. The solution of chloro acetyl chloride was added dropwise in 2,4,5-triphenyl-1H-imidazole solution with continuous stirring in ice bath by maintaining temperature in the range of 0-5ºC. After continuous stirring for 2-4 hours, the white precipitate was obtained which was filtered, dried, and recrystallized with methanol.

General Procedure for the Synthesis of 1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)-2- (substituted phenylamino) ethenone (NS1-NS5)

1.8 gm of compound (2) was dissolved in 10 ml of DMF (Dimethyl formamide) and equivalent molar of different anilines were dissolved in a minimum amount of DMF and the mixture was stirred at 20-50°C for 24 hr with a pinch of potassium Iodide. After completion of the reaction monitored by TLC, the mixture was allowed to cool. The product was precipitated from the cold solution. The precipitate was filtered off and recrystallized with methanol.

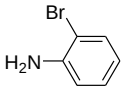
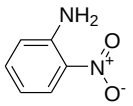
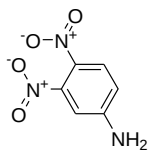
The synthesis scheme was represented in Fig. 1 and the synthesized structure and their physical characterization data was represented in Table 1.

NS1: Structure of 2-(2-bromophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl) ethanone is shown in (Fig. 2):

Characterization

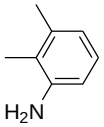
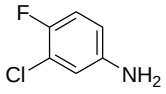
IR (KBr, cm^{-1}): 3060 (str, C-H arom), 2921 (str, CH alip), 1230 (str, C-N arom), 1236 (str, C-N alip), 740 (str, C-C arom), 1510 (str, C=C arom). ^{1}H NMR (300 MHz; DMSO) δ ppm: 7.0-7.6 (Ar-H); 4.02 (s, 1H, CH2), 3.397 (s, 1H, NH).

Table 1 — Substituent of Compounds with Code and Physical characterization of compounds

S. No.	Compound Code	Structure of substituents	M. P (ºC)	Molecular Formula	Molecular Weight	% Yield	Rf value	Elemental Analysis			
								C	H	N	O
1.	NS-1	 2-bromoaniline	179-181	$C_{29}H_{22}BrN_3O$	508.41	53.19	0.73	68.51	4.36	8.27	3.15
2.	NS-2	 o-nitroaniline	84-86	$C_{29}H_{22}N_4O_3$	474.51	68.92	0.68	73.40	4.67	11.81	10.12
3.	NS-3	 3,4--dinitroaniline	89-91	$C_{29}H_{21}N_5O_5$	519.51	61.35	0.77	67.05	4.07	13.48	15.40

(*Contd*.)

Table 1 — Substituent of Compounds with Code and Physical characterization of compounds (*Contd*.)

S. No.	Compound Code	Structure of substituents	M. P (ºC)	Molecular Formula	Molecular Weight	% Yield	Rf value	Elemental Analysis			
								C	H	N	O
4.	NS-4	 2,3-dimethylaniline	96-98	$C_{31}H_{27}N_3O$	457.57	71.84	0.56	81.37	5.95	9.18	3.50
5.	NS-5	 3-chloro-4-fluoroaniline	175-178	$C_{29}H_{21}ClFN_3O$	481.95	73.17	0.63	72.27	4.39	7.36	3.32

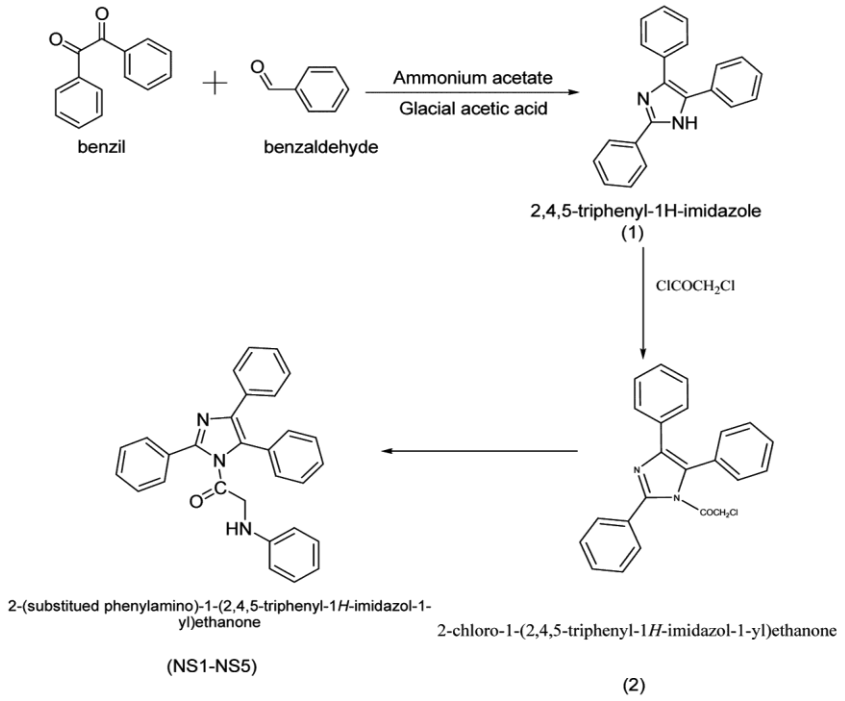


Fig. 1 — Synthesis scheme for the preparation of the target compound. Reagent and conditions (a) chloroacetyl chloride, solvent, Base (b) different anilines, DMF, K_2CO_3

NS2: Structure of 2-(2-nitrophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl) ethanone is shown in (Fig. 3):

Characterization

IR (KBr, cm^{-1}): 3062 (str, CH arom), 2917 (str, CH alip), 1231 (str, C-N arom), 1233 (str, C-N alip), 741 (str, C-C arom), 1510 (str, C=C arom). ^{1}H NMR(300 MHz; DMSO) δ ppm: 6.69-7.43 (Ar-H); 3.87 (s, 1H, CH2), 3.80 (s, 1H, NH).

NS3: Structure of 2-(3,4-dinitrophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl) ethanone is shown in (Fig. 4)

Characterization

IR (KBr, cm^{-1}): 3063 (str, CH arom), 2919 (str, CH alip), 1238 (str, C-N arom), 1235 (str, C-N alip), 745 (str, C-C arom), 1512 (str, C=C arom). ^{1}H NMR (300 MHz; DMSO) δ ppm: 7.08-8.23 (Ar-H); 4.22 (s, 1H, CH2), 3.81 (s, 1H, NH).

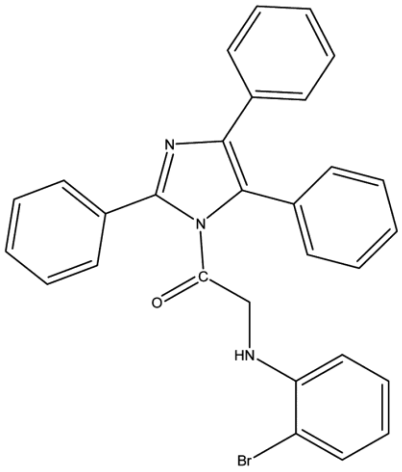


Fig. 2 — Structure of 2-(2-bromophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethanone

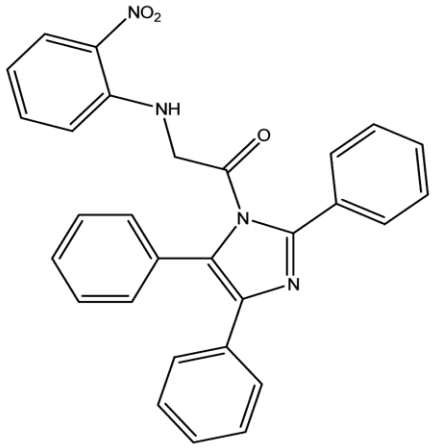


Fig. 3 — Structure of 2-(2-nitrophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethanone

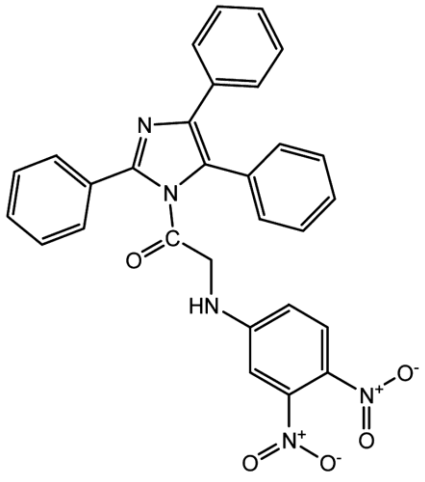


Fig. 4 — Structure of 2-(2- dinitrophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethanone

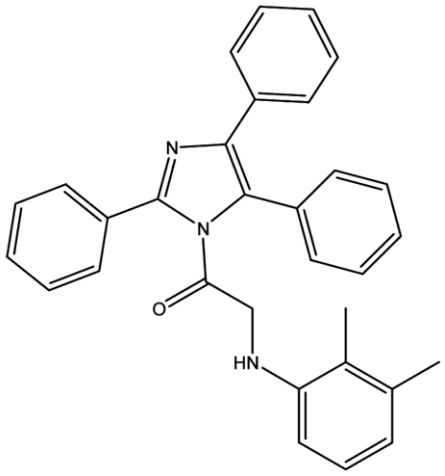


Fig. 5 — Structure of 2-(2- dimethylphenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethanone

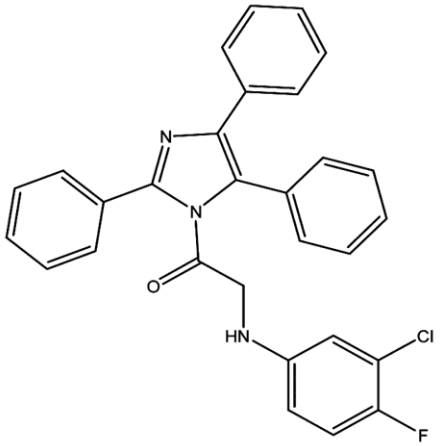


Fig. 6 — Structure of 2-(2- fluorophenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethanone

NS4: Structure of 2-(2,3-dimethylphenylamino)-1-(2,4,5-triphenyl-1*H*-imidazol-1-yl) ethanone is shown in (Fig. 5):

Characterization

IR (KBr, cm^{-1}): 3065 (str, CH arom), 2911 (str, CH alip), 1232 (str, C-N arom), 1237 (str, C-N alip), 743 (str, C-C arom), 1512 (str, C=C arom). ^{1}H NMR (300 MHz; DMSO) δ ppm: 6.79-7.48 (Ar-H); 4.28 (s, 1H, CH2), 3.9 (s, 1H, NH), 2.86 (1H, CH3), 2.72 (1H, CH3).

NS5: Structure of 2-(3-chloro-4-fluorophenylamino)-1-(2,4,5-triphenyl-1*H*-iimidazole1-yl) ethanone is shown in (Fig. 6):

Characterization

IR (KBr, cm–1): 3065 (str, CH arom), 2911 (str, CH alip), 1232 (str, C-N arom), 1237 (str, C-N alip),

743 (str,C-C arom), 1512 (str, C=C arom). ^{1}H NMR (300 MHz; DMSO) δ ppm: 6.69-7.45 (Ar-H); 4.17 (s, 1H, CH2), 4.0 (s, 1H, NH).

Pharmacological Evaluation

Animals and Treatment

The Elevated Plus Maze method and Hole board test method were used for the evaluation of antianxiety activity. Animal Ethics Committee permission was gained and the evaluations were performed as per the approved protocol. Diazepam was used as standard drug and the results obtained were compared with control group results. The statistical data was calculated by using one-way ANOVA and the significance level was fixed at $p<0.05$.

Anti-Anxiety Activity by Hole Board Test and Elevated Plus Maze method

The anti-Anxiety activity of the target compounds was carried out by the Elevated Plus Maze test and Hole Board Test. Prior permission of the Animal Ethics Committee was obtained and all experiments were conducted according to the approved protocol (837/PO/Re/S//04/CPCSEA). Albino rats, weighing 100–150 g each, were selected from the stock colony maintained in the central animal facility with free access to food and water. Animals were maintained in an air-conditioned room. The room was maintained at 25 ± 2°C with natural daytime. All solutions were prepared freshly on test day and given orally in a volume of 0.5% CMC to 100-150g body weight of rat. The experimental animals were treated PTZ with (60 mg/ kg, n = 6, i. p), or the compounds (200 mg/kg) 60 min before evaluation. The control group was given a saline solution. The results were expressed as mean ± SEM and were analysed using one-way analysis of variance (ANOVA) followed by Dunnett's t test. The probability of 0.05 or less was considered statistically significant. Statistical analysis was computed with the Graph Pad Prism software version 5.01, Graph Pad Software Inc. USA.

Hole Board Test

The apparatus consisted of a wooden platform measuring 40 cm × 40 cm, elevated 2 inches off the ground, with sixteen holes arranged symmetrically in a diamond shape. Groups of 5 mice were individually placed at one edge of the platform, and their exploratory behaviour (head pokes into the holes) was observed for 5 minutes. Diazepam (4 mg/kg, intraperitoneally) was administered 30 minutes before the test.

Elevated Plus Maze Test

The apparatus was a wooden structure raised 50 cm above the ground, following the design outlined by Lister[25,26]. It had two open arms (50×10 cm) and two closed arms (50×10×40 cm). Each group of 5 mice was placed in the centre of the maze, facing the closed arms, and the time spent in both the open and closed arms was recorded over 5 minutes.

Molecular docking and Prediction of ADME properties

The binding affinity and interactions of test compounds with the $GABA_A$ receptor were examined through molecular docking using the Argus Lab software. The crystal structure of the Human GABA-A receptor alpha1-beta2-gamma2 subtype, bound to GABA was attained from the Protein Data Bank in PDB format. The receptor's structure, including Diazepam as a bound ligand was used as a reference for docking[21]. The structure of protein was prepared using the "Protein Preparation Wizard" from the Schrodinger suite with default settings. The test compounds were designed, the energy was minimized using the MMFF94 force field, and subjected to a conformational search using the Low Mode MD method. Rigid receptor docking was then performed to fit the reference and test compounds into the GABAA receptor. The confirmation with minimum binding energy was analysed further to know and study its binding mode with the receptor.

Computational Calculation and other physicochemical parameters

The ADME parameters were forecasted using Chem 3D Ultra version 11.0 and Schrodinger software. Key parameters for CNS activity include blood-brain barrier (BBB) permeability, absorption level, Clog P, and topological polar surface area (TPSA). Additional parameters include molecular weight (MW), molar refractivity (MR), the number of rotatable bonds (RotB), hydrogen bond donors (nHBD), and hydrogen bond acceptors (nHBA). The analysis of these parameters suggests that the synthesized drugs can cross the blood brain barrier potentially leading to an effective therapeutic outcome. Various other factors like molecular weight, n ON value, n OHNH value, n-violations were determined through online software[22].

Similarity Calculation

Similarity of all the synthesized derivatives has been calculated and compared with respect to standard drug Diazepam[23].

$$di^2 = \sum_{j=1}^{n} \frac{\left(\frac{1 - X_{i,j}}{X_{i,std}}\right)^2}{n}$$

where, $X_{i,j}$is the approximation of atomic boundary 'I' for compound 'j', $X_{i,std}$ is the approximation of a similar subatomic boundary for the standard drug, Diazepam.

Table 2 represents the similarity index with respect to standard drug Diazepam.

Results and Discussion

Chemistry

A series of novel aniline-linked triphenyl imidazole analogues (NS1-NS5) were synthesized *via* a three-step synthetic pathway outlined in Fig. 1 and the substituents present are shown in Table 1. Initially, benzil, ammonium acetate and benzaldehyde were allowed to react in the presence of glacial acetic acid and the mixture was refluxed to get 2,4,5-triphenylimidazole (1). Subsequently, chloroacetylation was carried out by adding chloroacetyl chlorideto to obtain intermediate 2-chloro-1-(2,4,5-triphenyl-1H-imidazol-1-yl) ethenone (2). The aniline substituents **(NS1-NS5)** were gained by refluxing 2-chloro-1-(2,4,5-triphenyl-1H-imidazol-1-yl) ethenone with substituted anilines in the presence of DMF using a pinch of potassium iodide as catalyst. The precipitate obtained was filtered by using vacuum filtration and the product was recrystallized from ethanol. The final product was obtained. All the derivatives were characterized *via* infrared spectroscopy (IR), proton nuclear magnetic resonance spectroscopy (^{1}H NMR). IR spectra revealed characteristic bands at 3000–3200 cm^{-1} corresponding to the aromatic C–H bond, 1200-1350 cm^{-1} for the C–N aromatic, and 2900 cm^{-1} for aniline aliphatic C–H bond. In the ^{1}H NMR spectra, number of peaks of different protons were observed including 7.0-7.6 (Ar-H), singlet peak for CH_2 was observed at 4.02, and peaks corresponding to aniline NH was observed at 3.397.

Table 2 — Similarity values of target compounds (NS1-NS5) with respect to diazepam

Compound Code	Similarity[b] (in%) to Diazepam
NS1	72
NS2	55
NS3	67
NS4	83
NS5	59

Pharmacology

Hole Board Test

Albino rats, weighing 100–150 g each, were taken from their colony and maintained in animal facility. The food and water were provided to them and were kept in air-conditioned room. The apparatus consisted of a wooden platform measuring 40 cm × 40 cm, elevated 2 inches off the ground, with sixteen holes arranged symmetrically in a diamond shape. Groups of 5 mice were individually placed at one edge of the platform, and their exploratory behaviour (head pokes into the holes) was observed for 5 minutes given in Table 3 and the reading were logged in graph was enumerated in Fig. 7. Diazepam (4 mg/kg, intraperitoneally) was administered 30 minutes before the test.

Elevated Plus Maze Test

Albino rats (100-150 g) were taken for this activity. The apparatus was a wooden structure raised 50 cm above the ground, following the design outlined by Lister[25,26]. It had two open arms (50×10 cm) and two closed arms (50×10×40 cm). Each group of 5 mice was placed in the centre of the maze, facing the closed arms, and the time spent in both the open and closed arms was recorded over 5 minutes and given in Table 4 and the reading were recorded in graph was shown in Fig. 8.

Table 3 — Data for Hole Board Test (NS1-NS5)

Sr. No.	Treatment	No of Pocking	Duration of Pocking (s)
Group 1	Control	5.42±0.51	11.38±1.11
Group 2	Diazepam (4 mg/kg)	19.79±3.19***	165.19±6.31***
Group 3	NS-1	12.60±1.43*	136.8±4.32*
Group 4	NS-2	14.80±1.23**	149.56±2.4**
Group 5	NS-3	15.30±2.23**	150.23±4.9**
Group 6	NS-4	19.77±3.10***	160.67±3.4***
Group 7	NS-5	12.80±0.86*	118.2±2.43*

Docking Studies

The final derivatives NS1-NS5 were undergone docking studies to find the mechanism of drug interaction with receptor using Argus Lab software. The target protein structure was taken from the preceding works. The energy was minimized using MMFF94 forcefield and pdb files were generated to obtain stable 3D structures. The rigid receptor docking protocol was followed for docking and derivatives were docked into $GABA_A$ receptor. The procedure of ‘‘triangle matcher” was used for binding the molecule into the pocket and ranked by London dG scoring function. Various docking poses with negative binding affinity were obtained. The structure refinement was done with GBVI/WSA dG. The predicted interactions and the molecular docking images were given in Fig. 9, Fig. 10, Fig. 11, Fig. 12 and Fig. 13 and docking score were given in Table 5.

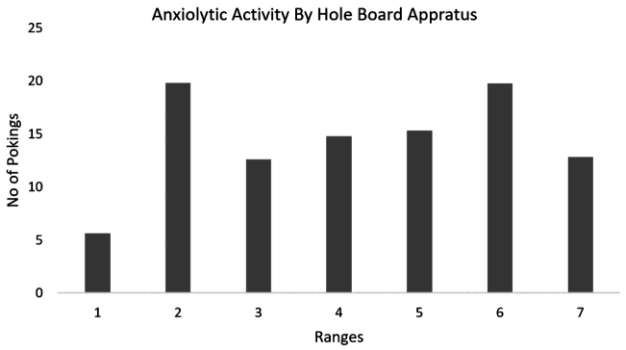


Fig. 7 — A graph representing anxiolytic activity by hole board test

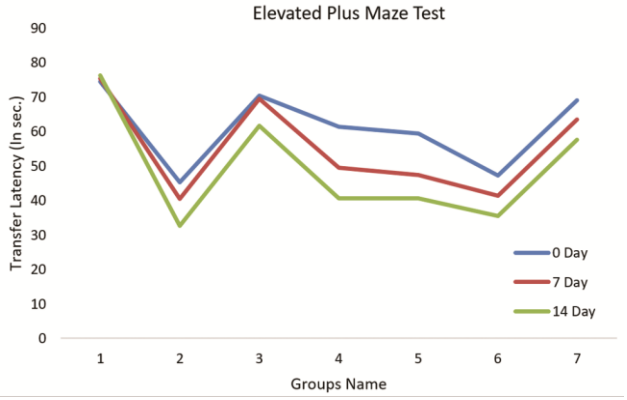


Fig. 8 — A graph representing Transfer Latency

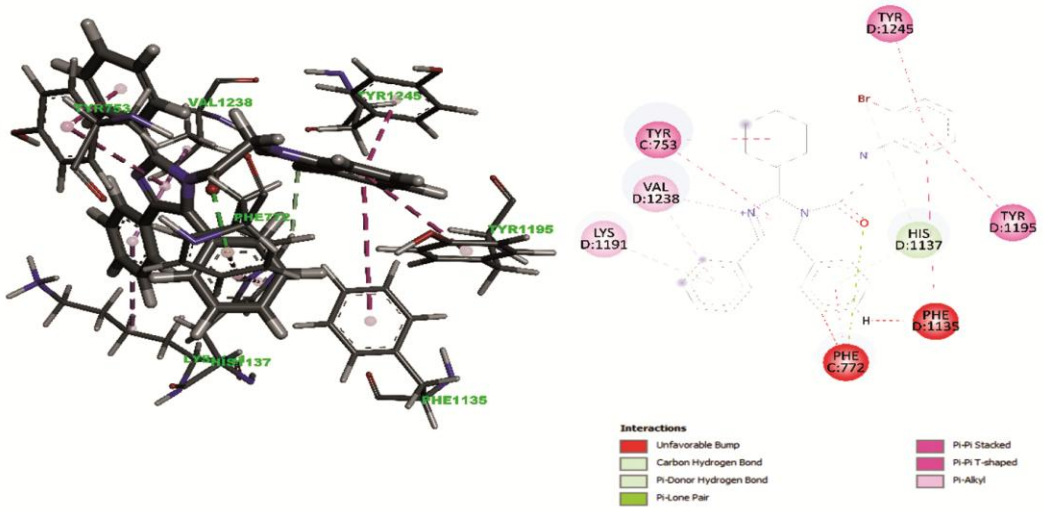


Fig. 9 — Docked structures of NS1

Table 4 — Data for EPM Test (NS1-NS5)

Sr. No.	Treatment	Transfer Latency (in seconds)		
		Day 0	Day 7	Day 14
Group 1	Control	74.35±0.30	75.4±0.45	76.2±0.70
Group 2	Diazepam (4mg/kg)	45.3±0.30**	40.5±0.30**	32.6±0.30***
Group 3	NS-1	70.45±0.20	69.5±0.50	61.6±0.30*
Group 4	NS-2	61.3±0.40	49.5±0.258	40.6±0.30**
Group 5	NS-3	59.40±0.60	47.4±0.20*	40.6±0.30**
Group 6	NS-4	47.2±0.15**	41.3±0.20**	35.5±0.60***
Group 7	NS-5	69.21±0.40	63.4±0.40	57.6±0.60*

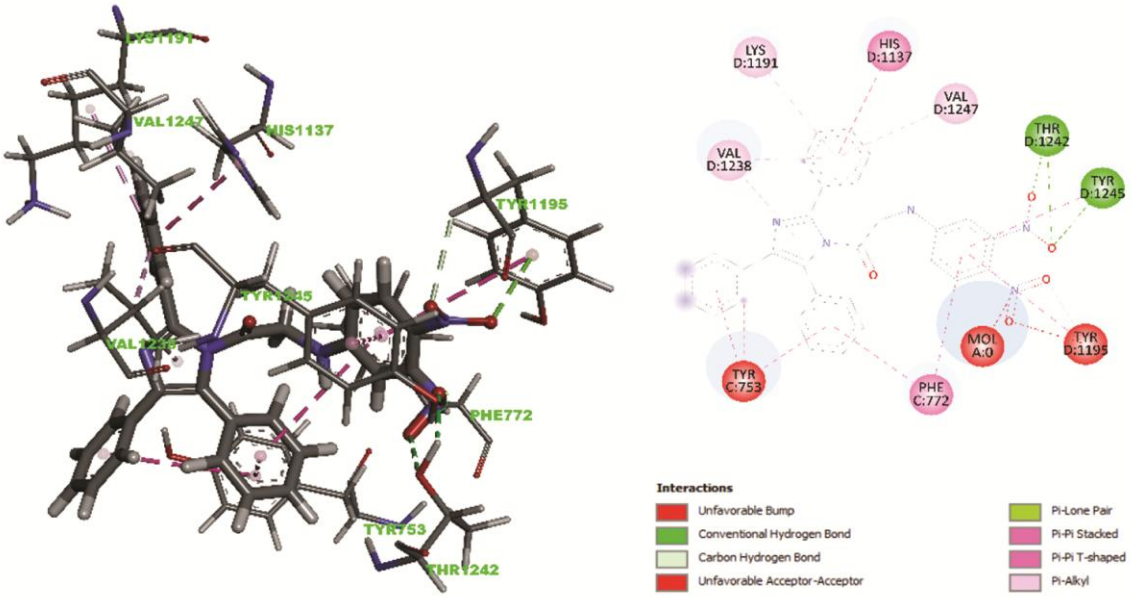


Fig. 10 — Docked structures of NS2

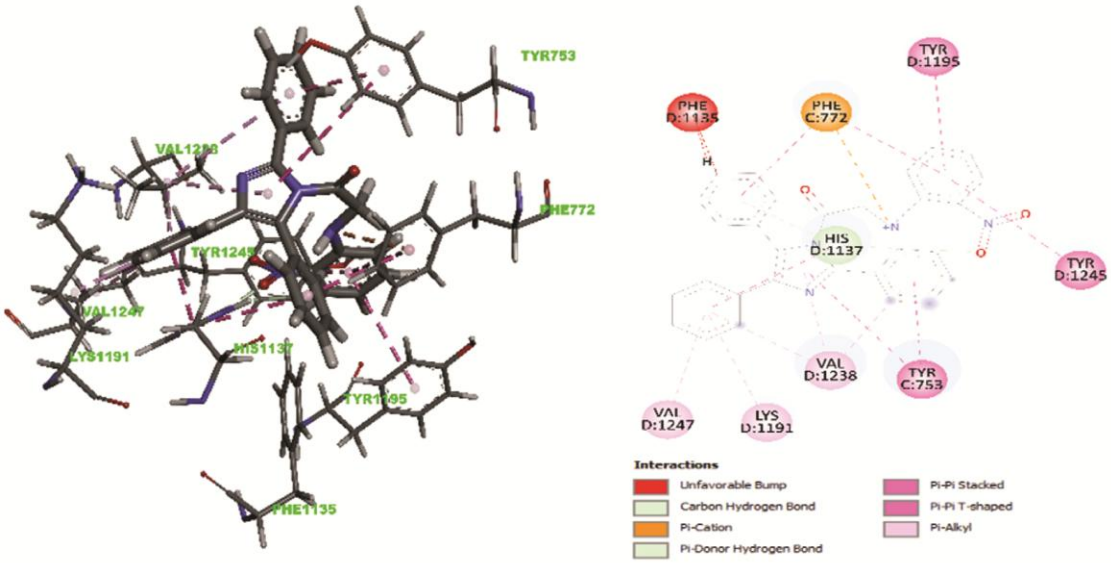


Fig. 11 — Docked structures of NS3

Computational calculation and Evaluation of Physicochemical parameters and Molinspiration values

The drugs were synthesized in such a way that they have the potency to cross the blood brain barrier (BBB) and found to be CNS active. To attain such behaviour, lipophilicity is an important parameter for distribution and active transport of drug in biological system. The partition coefficient is the first most and important parameter which defines the lipophilicity. Partition coefficient can be determined by shake-flask method and by different computational methods. The log P values of all the compounds were determined experimentally and through online software's and were calculated by Moriguchi method. Other parameters like molecular weight, n ON value, n OHNH value, n-violations and number of rotatable bonds are determined through online software's. The Table 6, Table 7 and Table 8 gives all the computational and other physicochemical studies.

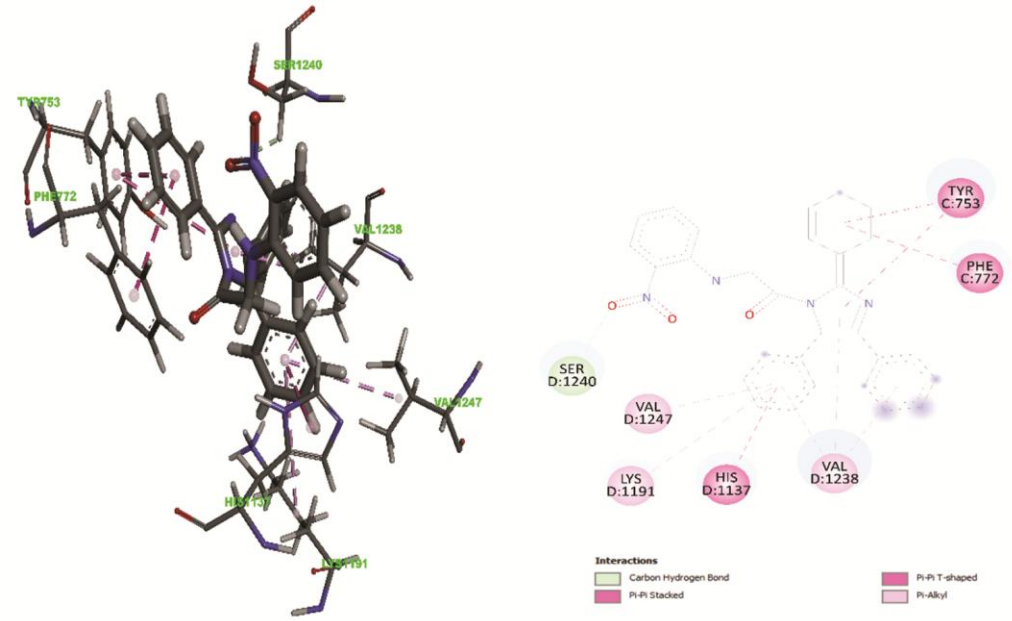


Fig. 12 — Docked structures of NS4

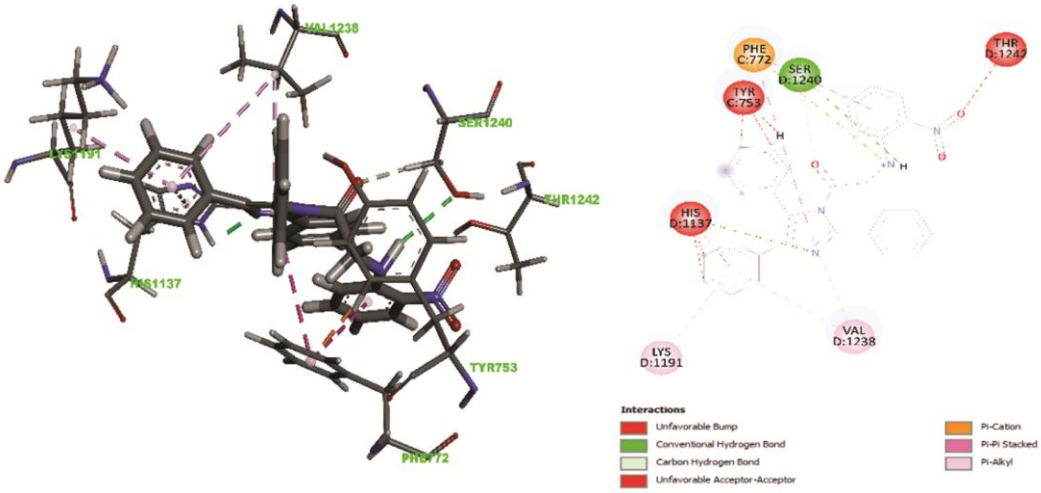


Fig. 13 — Docked structures of NS5

Table 5 — Docking Results of compounds NS1-NS5

Compound code	Amino acid residues involved within 5 Å	C-H bond interaction	π-π interaction	π-cation interaction	π-alkyl interaction	Binding Energy (Kcal/mol)
NS1	Tyr 753, Val 1238, Tyr 1245, Phe 772, Tyr 1195, His 1137, Phe 1135, Lys 1191	His 1137	Tyr 753, Tyr 1195, Tyr 1245		Val 1238, Lys 1191	–13.76
NS2	Tyr 753, Val 1247, Tyr 1245, Phe 772, Tyr 1195, His 1137, Thr 1242, Val 1238, Lys 1191		Phe 772, His 1137		Val 1238, Val 1247, Lys 1191	–11.89
NS3	Tyr 753, Val 1238, Tyr 1245, Phe 772, Tyr 1195, His 1137, Phe 1135, Val 1247, Lys 1191	His 1137	Tyr 753, Tyr 1195, Tyr 1245	Phe 772	Val 1238, Val 1247, Lys 1191	–13.25

(*Contd.*)

Table 5 — Docking Results of compounds NS1-NS5 (*Contd*.)

Compound code	Amino acid residues involved within 5 Å	C-H bond interaction	π-π interaction	π-cation interaction	π-alkyl interaction	Binding Energy (Kcal/mol)
NS4	Tyr 753, Val 1238, Phe 772, His 1137, Val 1247, Ser 1240 Lys 1191	Ser 1240	Tyr 753, His 1137, Phe 772		Val 1238, Val 1247, Lys 1191	–13.30
NS5	Tyr 753, Val 1238, Phe 772, His 1137, Ser 1240, Thr 1242, Lys 1191	Ser 1240		Phe 772	Val 1238, Lys 1191	–13.67

Table 6 — Drug-likeness properties of derivatives (NS1-NS5)

Compound code	miLogP	Mol wt	TPSA	MR	nON(HBA)	nOHNH(HBD)	CLogP
NS1	7.58	508.41	46.92	138.92	4	1	7.53
NS2	6.73	474.51	92.75	136.97	7	1	6.9
NS3	6.64	519.51	138.57	135.49	10	1	6.725
NS4	7. 64	457.57	46.92	143.02	4	1	7.62
NS5	7. 59	481.95	46.92	136.24	4	1	7.3

Comp compound, *miLogP* partition coefficient, *Mol wt* Molecular weight, *TPSA* topological polar surface area, *MR* molar refractivity, *HBA* hydrogen bond acceptor, *HBD* hydrogen bond donor.

Table 7 — Pharmacokinetic Parameters of derivatives (NS1-NS5)

Compd code	GIabs	BBB permeation	Pgp substrate	CYP2C19	CYP3A4	LipinskiViolation	Ghose Violation	Bioavailability Score
NS1	High	Yes	Yes	No	Yes	0	0	0.51
NS2	High	Yes	Yes	No	Yes	0	0	0.51
NS3	High	Yes	Yes	No	Yes	0	0	0.51
NS4	High	Yes	Yes	No	Yes	0	0	0.51
NS5	High	Yes	Yes	No	Yes	0	0	0.51

Table 8 — PASS-study of compounds (NS1-NS5)

Compound code	Pharmacological Activity	Activity Value
NS1	Anxiolytic	0.524
NS2	Anxiolytic	0.517
NS3	Anxiolytic	0.553
NS4	Anxiolytic	0.572
NS5	Anxiolytic	0.544

Similarity Calculation

The assessment of similarity between derivatives and standard were done by using 7 different physicochemical properties and was given in Table 2.

Conclusion

A series of triphenyl-imidazole derivatives (NS-1, NS-2, NS-3, NS-4, NS-5) were synthesized as represented in Fig 1. The compounds were obtained by reacting benzil with benzaldehyde in presence of ammonium acetate and glacial acetic acid and then the product was chloro acetylated with chloroacetyl chloride and finally, different substituted anilines were substituted in it to get the final product (NS1-NS5). The compounds were confirmed based on their m.p, TLC, IR, and ^{1}H-NMR data in which different peaks of different functional groups and number of protons was observed in the spectra's. All the derivatives were tested for antianxiety activity by the elevated plus maze method and hole board method some of which showed mild to good antianxiety activity in comparison to standard drug Diazepam. The compound NS-4 showed more potency in respect to all other synthesized derivatives. The synthesized compounds were also evaluated for similarity with standard drugs and various physicochemical parameters were also studied for it. The compounds shown to have drug like properties, and by virtual computational tools they have shown to possess good GIT absorption and bioavailability. Among all the synthesized compounds the compounds containing amino group (NS-4) shows better and promising activity when compared to standard drug Diazepam. All the results of the different models of activities were presented in table given above. Molecular docking studies of the target compounds were docked with GABAA receptor to find the likely mechanism of action. The compounds showed significant interaction at the BZD-binding site on the GABAA receptor. The similarity study was carried out which also displayed mild to moderate similarity with respect to standard drugs. The physicochemical parameters including pharmacokinetic and toxicity

studies confirmed with the standard compounds and suggested its possibility of being drug-like candidates and can cross the bloodbrain barrier. Therefore, it was depicted that the synthesis, computational studies, and evaluation of anticonvulsant, anti-anxiety, and skeletal muscle relaxant activity of new phenytoin derivatives were carried out. The compounds were successfully synthesized and well described by various physicochemical properties. Through studies, it was revealed that some of the compounds exhibit good CNS activity. The compounds also display mild to moderate similarity with respect to the standard drugs. The pharmacokinetic and toxicity studies confirmed with the standard compounds and suggested its possibility of being drug-like candidates. From the pharmacological activity, it was found that some of the target compounds have significant CNS activity. However, future optimization might be beneficial in the prospect research and expansion of the target compounds for the enhancement of the CNS activity.

Ethics approval and consent to participate

The experiments were approved by the Research Ethics Committee, IFTM University, Moradabad 244 001, India. Human and animal rights: No humans were used for the studies that are the base of this research. All animals used were in accordance with the US Public Health Service's "Policy on Humane Care and Use of Laboratory Animals", and "Guide for the Care and Use of Laboratory Animals".

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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