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"SYNTHESIS AND MOLECULAR DOCKING STUDIES OF NOVEL PYRROLYL BENZAIMIDAZOLE DERIVATIVES AS ANTICONVULSANT AGENTS

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ABSTRACT

The various novel pyrrolyl benzamide derivatives were synthesized and molecular docking studies were carried out further few compounds evaluated for anticonvulsant activity against MES and PTZ induced convulsions. Purity of the newly synthesized compounds confirmed by using TLC and structures were confirmed by using IR, NMR, ^{13}C and Mass spectra. Appropriate o-phenylene diamine(1) is treated with para amino-2-chloro benzoic acid (2) in ethanol and reaction mixture made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole-2-chloro aniline(3a-e) which is further stirred with 4-pyrrole-1-yl-benzoic acid(4) and 4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(6a-e) and (7a-e). and o-phenylene diamine (1) is treated with para-amino benzoic acid (8) in ethanol and reaction made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole aniline (9a-e) which is further stirred with4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(10a-e). Docking study was performed by Surflex-Dock program that is interfaced with Sybyl-X 2.0. Compounds 7e and 10d showed excellent consensus scoreat 7.17 & 7.26 respectively. Docking study reveals that all the compounds have showed very good docking score against the enzyme. The few newly synthesized compounds were screened for their anticonvulsant activity. Compounds 10a (9.8±0.34) and 10e (11.83±0.44) showed significantly decrease in hind limb extension against MES induced convulsions. Compound 6e (140±2.02) and 10e (160±2) showed protection against PTZ induced convulsions. Simultaneously activity is compared with control and standard group. The newly synthesized novel series of pyrrolyl benzamide derivatives may be developed into potential class of anticonvulsant agents in future.

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INTRODUCTION

Epilepsy is a neurological condition that makes people susceptible to seizures. Epilepsy is a group of chronic neurological disorders characterized by sporadic episodes of convulsive seizures, sensory disturbance, abnormal behaviour, loss of consciousness or all of these symptoms resulting from a brain dysfunction or an abnormal discharge of cerebral neurons. [1, 2] Seizures: A seizure is a sudden, uncontrolled disturbance of the central nervous system that is characterized by varying symptoms. In some patients, seizures are sometimes evoked by a specific stimulus. A seizure a change in sensation awareness, or behaviour brought about by a brief electrical disturbance in the brain. Seizures vary from momentary disruption of the senses, to short periods of unconsciousness or staring spells, to convulsions. The term "seizure" is widely used to describe an abnormal spasm or convulsions, generate by excessive electrical activity in the brain.[3]

About 2% of adults have a seizure at some time during their life time. Most commonly, seizures disorders begin in early childhood or in late adulthood. Seizures starting before age 2 are usually caused by high fevers or metabolic disorders, such as abnormal blood levels of sugar (glucose), calcium, magnesium, vitamin B6, or sodium. If the seizures recur, the cause is likely to be a hereditary brain disorder (such as nocturnal frontal lobe epilepsy).

Almost all seizures are relatively brief, lasting from a few seconds to a few minutes. Most seizures last 2 to 5 minutes. When a seizure stops, the person may have a headache, sore muscles, unusual sensations, confusion, and profound fatigue. These after-effects are called the postictal state. In some people, one side of the body is weak, and the weakness lasts longer than the seizure (a condition called Todd's paralysis).

Furthermore, repeated and increased excitation of neurons or increased duration of convulsions can lead to neuronal death and loss of memory.[4] The antiepileptic agents conventionally used in clinical settings, such as phenytoin, carbamazepine, and sodium valporate, produce many serious side effects and remarkable neurotoxicity.[5] As they provide only symptomatic relief and have to be consumed life long, simultaneous administration of other drugs predisposes the patient to the risk of drug interaction. Nevertheless, newer antiepileptics such as gabapentin, vigabatrin, lamotrigine, etc. are used as supplements to the conventional agents.[5] Moreover, the current drug therapy is associated with adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, gingival hyperplasia, hirsutism, and megaloblastic anaemia.[6] Hence, the search for curative antiepileptic agents that are effective as well as safe in terms of drug-related toxicity has been need of ours.

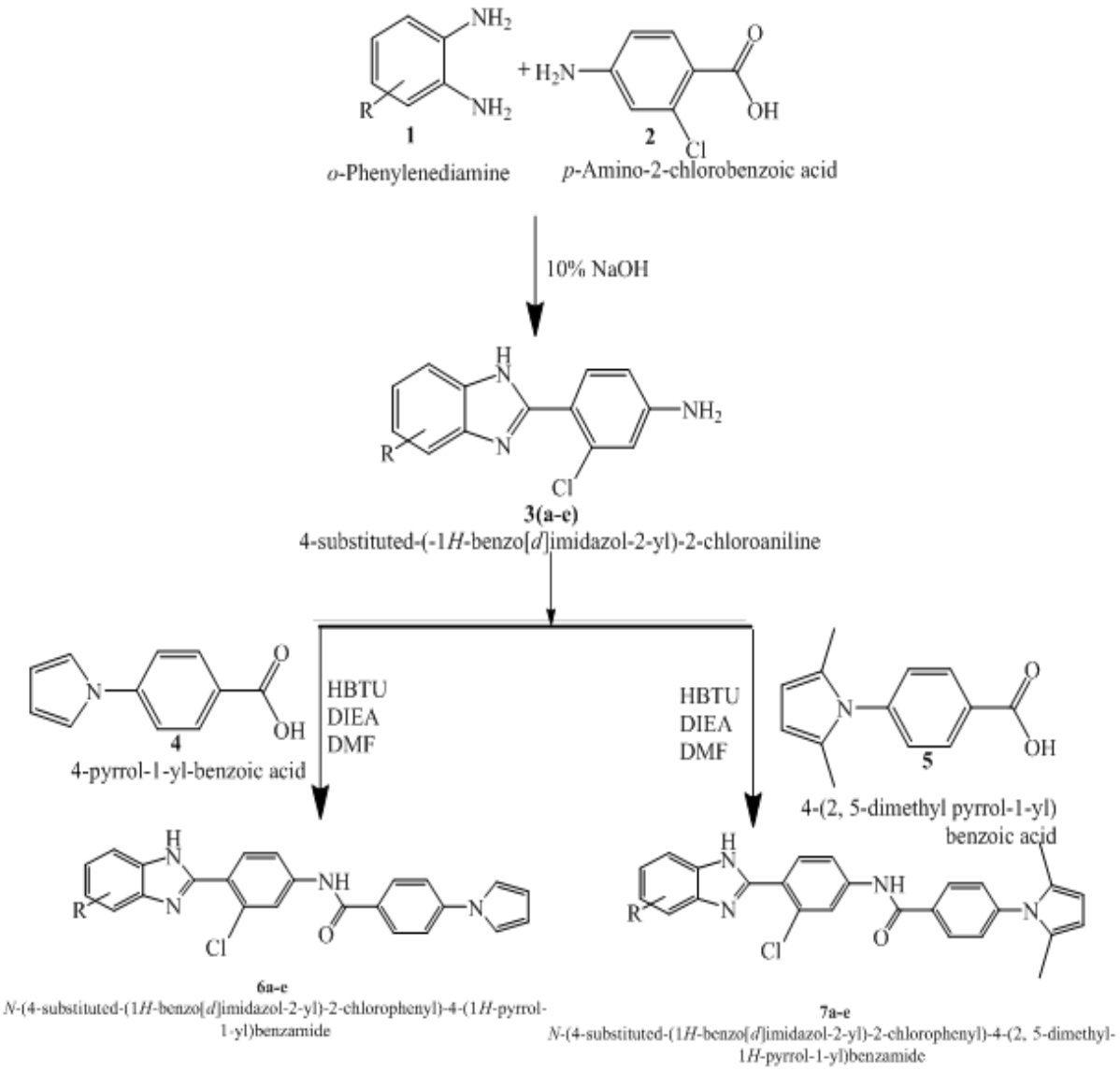
Pyrrole is one of the most ubiquitous heterocycles in the plant and animal kingdom because of its participation as a subunit of chlorophyll, haem and some bile pigments. Biosynthetically related vitamin B_{12} is a tetrapyrrole. A number of antibiotics are also derivatives of pyrrole. The indole ring system, in which pyrrole is fused to benzene ring, is widespread in nature and it is also present in the tryptophan, serotonin, many alkaloids and indigo [7]. Pyrrole and its derivatives have shown to possess biological activities such as antibacterial [8], analgesics [9], antitubercular [10,11], inflammatory, anticonvulsant [12] and antiallergic [13] Several macromolecular antibiotics having pyrrole structure were isolated from biological sources and their activities were defined.

Considering the above factors, it is pertinent to mention here that a drug, which can effectively treat the convulsions within a short duration of time, is most desirable and progress in this area is the need of the hour.

Experimental

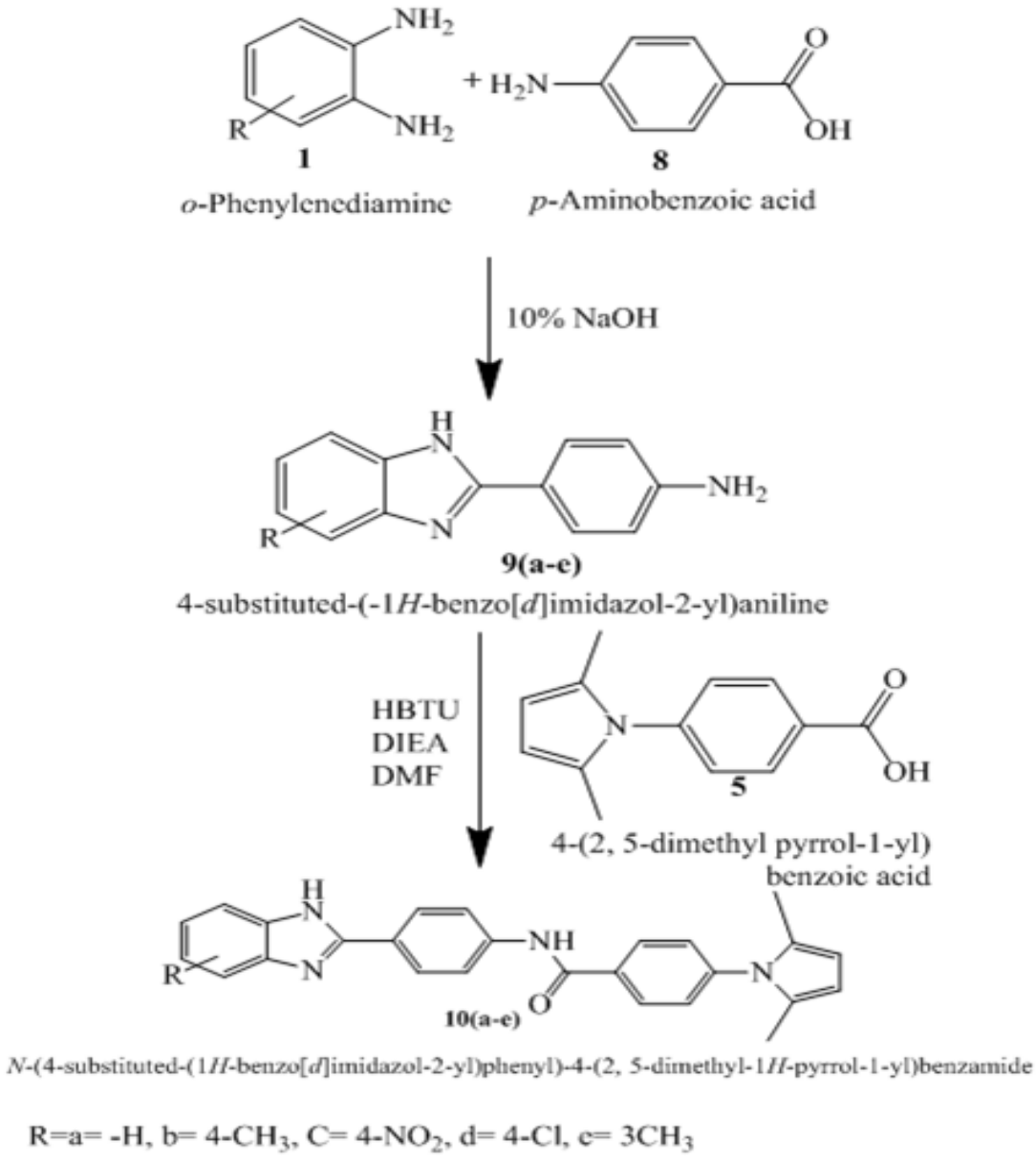
Melting points were determined using the Shital-digital programmable melting point apparatus and are uncorrected. FTIR spectra in KBr pellets were recorded on a Bruker FTIR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE II at 400 and 100 MHz, respectively; chemical shifts are expressed in parts per million (ppm) relative to TMS. The abbreviations used to describe the peak patterns are: (b) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, and (m) multiplate. Mass spectra (MS) were recorded in a JEOL GCMATE II GC-Mass spectrometer and Schimadzu QP 20105 GC-Mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany) visualized by long- and short- wavelength ultraviolet (UV) lamps.

SCHEME-IA



R=a= -H, b= 4-CH_3, C= 4-NO_2, d= 4-Cl, e= $3CH_3$

SCHEME-IB



Synthesis of 4-substituted (-1H- benzo (d) imidazole-2-yl)-2-chloroaniline (03a-e):

The mixture of o-phenylenediamine (0.1 mol) and 2-chloro para-amino benzoic acid (0.1 mol) were heated on a water bath for 6 h with solvent ethanol. It was cooled and 10% NaOH solution was added slowly with constant stirring until just alkaline. The crude product was filtered, washed with ice cold water, decolorized and washed repeatedly and dried. The product were then recrystallized from ethanol in HCl.

Synthesis of 4-(1H- pyrrol-1-yl) benzoic acid (4):

2,5-dimethoxy tetrahydrofuran (16 gm, 0.12 mol) was added to para-amino benzoic acid (13.72 gm, 0.1 mol) in glacial acetic acid (100 ml), and mixture were heated to reflux for 30 mins. The reaction mixture was poured into ice cold water, precipitated solid was filtered and dried. Solid crude product was recrystallized from ethanol and obtained as brown crystals. Melting point- 286 – 290°C.

Synthesis of 4- (2,5-dimethyl-1H-pyrrol-1-yl) benzoic acid (5):

Acetonyl acetone (13.69 gm, 0.12 mol) was added to para-amino benzoic acid (13.72 gm, 0.1 mol) in glacial acetic acid (100 ml) and the mixture was heated at reflux for 30 min. The reaction mixture was poured into ice cold water; precipitated solid was filtered and dried. Solid crude product was recrystallized from ethanol and obtained as brown crystals. Melting point- 204-208°C.

Synthesis of N-(4-substituted- (1H-benzo (d) imidazole-2-yl)-2-chlorophenyl)-4(1H-pyrrol-1-yl) benzamide (06a-e):

Appropriate 4-substituted (-1H- benzo (d) imidazole-2-yl)-2-chloroaniline (03a-e) (0.16 gm, 0.0018 mol) and 4-(1H-pyrrol-1-yl) benzoic acid (0.43 gm, 0.0023 mol) were dissolved in dry DMF, HBTU (0.87 gm, 0.0023 mol) and DIEA (0.93 ml, 0.0053 mol) were added and stirred for 5 h at 23°C. The reaction mixture was quenched by brine. The resulting mixture was extracted with ethyl acetate (3x50 ml). The ethyl acetate layer is washed with 1N HCl then with saturated $NaHCO_3$ solution followed by brine and then solvent was evaporated to dryness. The crude product was recrystallized with chloroform. The purity of the compound was confirmed by melting point and TLC.

Synthesis of N-(4-substituted- (1H-benzo (d) imidazole-2-yl)-2-chlorophenyl)-4(2, 5 dimethyl 1H-pyrrol-1-yl) benzamide (07a-e):

Appropriate 4-substituted (-1H- benzo (d) imidazole-2-yl)-2-chloroaniline (03a-e) (0.16 gm, 0.0018 mol) and 4-(2, 5 dimethyl 1H-pyrrol-1-yl) benzoic acid (0.43 gm, 0.0023 mol) were dissolved in dry DMF, HBTU (0.87 gm, 0.0023 mol) and DIEA (0.93 ml, 0.0053 mol) were added and stirred for 5 h at 23°C. The reaction mixture was quenched by brine. The resulting mixture was extracted with ethyl acetate (3x50 ml). The ethyl acetate layer is washed with 1N HCl then with saturated $NaHCO_3$ solution followed by brine and then solvent was evaporated to dryness. The crude product was recrystallized with chloroform. The purity of the compound was confirmed by melting point and TLC.

Synthesis of 4-substituted (-1H- benzo (d) imidazole-2-yl) aniline (9a-e):

The mixture of o-phenylenediamine (0.1 mol) and p-amino benzoic acid (0.1 mol) were heated on a water bath for 6 h with solvent ethanol. It was cooled and 10% NaOH solution was added slowly with constant stirring until just alkaline. The crude product was filtered, washed with ice cold water, decolorized and washed repeatedly and dried. The product was then recrystallized from ethanol in HCl.

Synthesis of N-(4-substituted- (1H-benzo (d) imidazole-2-yl) phenyl)-4-(2,5dimethyl-1H-pyrrol-1-yl) benzamide (10a-e):

Appropriate 4-substituted (-1H- benzo (d) imidazole-2-yl) aniline (3a-e) (0.16 gm, 0.0018 mol) and 4-(2,5-dimethyl-1H-pyrrol-1-yl) benzoic acid (0.43 gm, 0.0023 mol) were dissolved in dry DMF, HBTU (0.87gm, 0.0023 mol) and DIEA (0.93 ml, 0.0053 mol) were added and stirred for 5 h at 23°C. The reaction mixture was quenched by brine. The resulting mixture was extracted with ethyl acetate (3x50 ml). The ethyl acetate layer is washed with 1N HCl then with saturated $NaHCO_3$ solution followed by brine and then solvent was evaporated to dryness. The crude product was recrystallized with chloroform. The purity of the compound was confirmed by melting point and TLC.

The purity of the all newly synthesized compounds were confirmed by melting point and TLC. The structures of newly synthesized compound were confirmed by analytical and spectral data such as IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

N-(4-(1H-benzo[d]imidazol-2-yl)-3-chlorophenyl)-4-(1H-pyrrol-1-yl) benzamide(6a)

IR (KBr) νmax, cm-1:3423.05 (NH), 2924.37 (CH),1676.51 (C=O), 1637.61 (C=C), 1323.50(CN),1191.85 (C=N), 842.63 (C-Cl); ^{1}H NMR($CDCl_3$, 400MHz, δ): 9.44 (s, 1H, amide-NH), 8.08-8.10 (d, 4H, bridging phenyl-C_2, C_6, phenyl-C_2, C_6-H), 7.52-7.53 (m, 4H, benzimidazole-C_4, C_7, phenyl-C_3, C_5-H), 7.25 (m, 4H, pyrrole- C_2,C_5, benzimidazole- C_5,C_6- H), 6.39-6.40 (d, 2H, pyrrole-C_3, C_4- H;^{13}C NMR ($CDCl_3$, 100 MHz, δ):111.10 (pyrrole- C_3, C_4), 116.11 (benzimidazole- C_5, C_8), 118.36 (pyrroleC$_2$, C_5), 118.92 (phenyl-C_3, C_5), 125.29 (benzimidazole-C_6, C_7), 126.13 (phenyl- C_6, C_7), 129.31 (bridging phenyl- C_2, C_3, C_5, C_6), 130.28 (bridging phenyl-C_1)131.32 (phenyl- C_4), 142.17 (benzimidazole(C_4, C_9), 143.16 (bridging phenyl-C_4), 164.45 (C-amide).

***N-(3-chloro-4-(5-methyl-1H-benzo[d]imidazol-2-yl) phenyl)-4-(1H-pyrrol-1-yl) benzamide (6b)*:**

IR (KBr) νmax, cm-1:3326.58 (NH), 2921.61 (CH), 1606.78 (C=O), 1512.17 (C=C), 1319.86 (CN), 1121.62 (C=N), 722.40 (C-Cl); ^{1}H NMR ($CDCl_3$, 400MHz, δ): 9.6 (d, 1H, amide-NH), 8.10-8.13 (m, 4H, bridging phenyl- C_2, C_5, phenyl- C_2, C_6- H), 7.83-7.87 (m, 4H, bridging phenyl- C_3, C_5, phenyl- C_3, C_5- H), 7.43-7.52 (m, 2H, benzimidazole- C_4, C_6- H), 7.23-7.25 (d, 2H, pyrrole- C_2, C_5- H), 7.09-7.10 (t, H, benzimidazole-C_7-H), 6.4 (d, 2H, pyrrole- C_3, C_4- H), 2.79 (s, 3H, benzimidazole- C_5- H); ^{13}CNMR ($CDCl_3$, 100 MHz, δ): 111.52 (pyrrole-C_3, C_4), 114.21 (benzimidazole- C_4, C_8), 119.13 (phenyl- C_3, C_5), 120.67 (pyrrole-C_2, C_5), 125.65 (benzimidazole-C_7), 126.96 (phenyl- C_2, C_6), 128.80 (bridging phenyl- C_2, C_6), 129.39 (bridging phenyl- C_3, C_5), 131.56 (benzimidazole- C_6, C_9, bridging phenyl- C_1), 136.34 (benzimidazole- C_4, phenyl- C_4), 143.40 (bridging phenyl- C_4, benzimidazole-C_2), 165.55 (C- amide), 21.06 (C- methyl).

***N-(3-chloro-4-(5-nitro-1H-benzo[d]imidazol-2-yl) phenyl)-4-(1H-pyrrol-1-yl) benzamide (6c)*:**

IR (KBr) νmax, cm-1:3435.07 (NH), 2922 (CH), 1638.21 (C=O), 1605.79 (C=C),1287.91, (CN), 1157.02 (C=N), 726.93 (C-Cl); ^{1}H NMR ($CDCl_3$, 400MHz, δ):10.25 (d, 1H, amide NH), 8.09-8.14 (m, 5H,benzimidazole-C_6, bridging phenyl- C_2, C_6, phenyl-C_2 C_5- H), 7.8-7.9 (d,3H,benzimidazole-C_4, bridging phenyl- C_4, C_5- H), 7.71 (d, 2H, phenyl- C_3, C_5- H), 7.63 (d, 1H, benzimidazole-C_7-H), 7.37 (d, 2H, pyrrole- C_2, C_5- H), 6.35-6.39 (d, 2H, pyrrole- C_3, C_4- H); ^{13}CNMR ($CDCl_3$, 100 MHz, δ):110.98 (pyrrole- C_3, C_4), 112.51 (benzimidazole-C_5, C_9), 118.04, (benzimidazole-C_7 phenyl- C_3, C_5), 119.34 (pyrrole- C_2, C_5, phenyl- C_1), 127.63 (phenyl-C_2, bridging phenyl- C_2, C_6), 129.20 (bridging phenyl-C_1,C_3, C_5), 131.91(phenyl- C_4, benzimidazole- C_4), 132.98 (bridging phenyl- C_4, benzimidazole- C_2, C_6, C_9), 165.01 (C- amide).

***N-(3-chloro-4-(5-chloro-1H-benzo[d]imidazol-2-yl) phenyl)-4-(1H-pyrrol-1-yl) benzamide (6d)*:**
IR (KBr) νmax, cm-1:3434.0 (NH), 2923.31 (CH), 1718.35 (C=O), 1608.54 (C=C), 1268.31 (CN), 1180.56 (C=N), 847.08 (C-Cl).^{1}H NMR (CDCl$_3$, 400MHz, δ): 10.10 (d, 1H,amide- NH), 8.10-8.15 (m, 4H, bridging phenyl- C_2, C_5, phenyl- C_2, C_5- H), 7.87-7.96 (d, 4H, phenyl- C_3, C_5, bridging phenyl- C_3, C_5- H), 7.29-7.49 (m, 3H, benzimidazole- C_6, pyrrole- C_2, C_5- H), 7.10-7.14 (q, 1H, benzimidazole- C_6- H), 6.36-6.39 (d, 2H,pyrrole- C_3, C_4- H.

***N-(3-chloro-4-(4-methyl-1H-benzo[d]imidazol-2-yl) phenyl)-4-(1H-pyrrol-1-yl) benzamide (6e)*:**
IR (KBr) νmax, cm-1:2919.31 (NH), 2851.34 (CH), 1683.18 (C=O), 1604.27 (C=C), 1290.17 (CN), 1183.54 (C=N); ^{1}H NMR (CDCl$_3$, 400MHz, δ):10.25 (d, 1H, amide- NH), 8.15-8.17 (d, 4H, bridging phenyl- C_2, C_6, phenyl- C_2, C_6- H), 8.06-8.09 (t, 4H, phenyl- C_3, C_5, bridging phenyl- C_3, C_5- H), 7.53 (d, 1H, benzimidazole- C_5- H), 7.44 (d, 1H, benzimidazole- C_5- H), 7.25 (s, 2H, pyrrole- C_2, C_5- H), 7.17 (t, 1H, benzimidazole- C_6- H), 6.39-6.40 (t, 2H, pyrrole- C_3, C_4- H), 2.81 (s, 3H, benzimidazole-C_4- H); ^{13}CNMR (CDCl$_3$, 100 MHz, δ):14.12 (C-methyl), 111.26 (pyrrole- C_3, C_4, benzimidazole- C_8), 119.13 (phenyl- C_3, C_5), 120.98 (pyrrole- C_2, C_5). 122.89 (benzimidazole-C_7), 124.04(benzimidazole- C_6), 126.83 (benzimidazole- C_5), 127.59 (phenyl- C_2, C_6), 128.76 (bridging phenyl- C_2, C_6), 129.81 (bridging phenyl- C_3, C_5), 131.82 (bridging phenyl- C_1), 135.42 (phenyl- C_4, benzimidazole-C_4, C_9), 143.96 (bridging phenyl-C_4),144.25, (benzimidazole-C_2), 162.86 (C-amide).

N-(4-(1H-benzo[d]imidazol-2-yl)-3-chlorophenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (7a):
IR (KBr) νmax, cm-1: 3422.83 (NH), 1928.88 (CH), 1601.32 (C=O), 1545.90 (C=C), 1329.39 (CN), 1191.46 (C=N), 717.12(C-Cl);^{1}H NMR (CDCl$_3$, 400MHz, δ):10.11 (s, 1H, amide NH), 8.27 (s, 4H, bridging phenyl-C_2, C_6, phenyl-C_2, C_6-H), 7.92 (d, 3H, phenyl-C_3, bridging phenyl- C_3, C_5-H), 7.46 (d, 2H, benzimidazole- C_4,C_7- H), 7.35 (d, 2H, benzimidazole- C_5, C_6- H), 6.25 (d, 2H, pyrrole- C_3, C_4- H), 2.5 (m, 2H, pyrrole- C_2, C_5- H);MS (EI): m/z = found 442.00[M+]; calcd. 440.39.

***N-(3-chloro-4-(5-methyl-1H-benzo[d]imidazol-2-yl) phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (7b)*:**
IR (KBr) νmax, cm-1: 3432.71 (NH), 2922.47 (CH), 1608.51 (C=O), 1513.20 (C=C), 1324.92 (CN), 1187.18 (C=N), 843.67 (C-Cl);^{1}H NMR (CDCl$_3$, 400MHz, δ): 9.99 (S, 1H, amide-NH), 8.04-8.05(m, 4H, bridging phenyl- C_2, C_5, phenyl- C_2, C_6- H), 7.99 (m, 2H, bridging phenyl- C_3, C_5- H), 7.43-7.52 (m, 1H, phenyl- C_3- H), 7.51 (m, 2H, benzimidazole- C_6, C_4- H), 7.39 (m, 1H, benzimidazole- C_7-H), 2.52 (m, 3H, pyrrole- C_2, C_5, benzimidazole-C_5- H); MS (EI): m/z = found 455.00[M+]; calcd. 454.96.

***N-(3-chloro-4-(5-nitro-1H-benzo[d]imidazol-2-yl) phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (7c)*:**
IR (KBr) νmax, cm-1: 3438.79 (NH), 2923.91 (CH), 1637.62 (C=O), 1468.67 (C=C), 1331.23 (CN), 1098.92 (C=N) 805.30 (C-Cl);^{1}H NMR(CDCl$_3$, 400MHz, δ): 9.76 (s, 1H, amide-NH), 8.10(m, 5H, benzimidazole-C_6, bridging phenyl- C_2, C_6, phenyl- C_2 C_6-H), 7.5-7.77 (m, 4H, benzimidazole- C_4, bridging phenyl- C_3, C_5, pyrrole- C_3- H), 7.62-7.64(m, 1H, benzimidazole- C_7- H), 5.05 (s, 2H, pyrrole- C_3, C_4- H), 2.11 (m, 2H, pyrrole- C_2, C_5- H)

***N-(3-chloro-4-(5-chloro-1H-benzo[d]imidazol-2-yl) phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (7d)*:**
IR (KBr) νmax, cm-1:3408.58 (NH), 2925.08 (CH), 1608.22 (C=O), 1506.79 (C=C), 1326.38 (CN), 1187.24 (C=N), 724.85 (C-Cl);^{1}H NMR (CDCl$_3$, 400MHz, δ): 9.65 (s, 1H,amide- NH), 8.08 (m, 5H, phenyl- C_2, C_6, bridging phenyl- C_2, C_6, benzimidazole-C_4- H), 7.83 (m, 3H, phenyl- C_3, bridging phenyl- C_3, C_5- H), 7.48-7.51 (m, 1H, benzimidazole- C_7- H), 7.16-7.18 (d, 1H, benzimidazole- C_6- H), 6.28-6.30 (m, 2H, pyrrole- C_3, C_4- H), 2.11 (m, 2H, pyrrole- C_2, C_5-H).

***N-(3-chloro-4-(5-chloro-1H-benzo[d]imidazol-2-yl) phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (7e)*:**
IR (KBr) νmax, cm-1:3421.41 (NH), 2923.72 (CH), 1607.66 (C=O), 1517.82 (C=C), 1329.48 (CN),1181.88 (C=N), 731.74 (C-Cl);^{1}HNMR (CDCl$_3$, 400MHz, δ): 10.19 (s, 1H, amide- NH), 8.12 (s, 2H,bridging phenyl- C_2, C_6, phenyl- C_2, C_6- H), 7.96-7.99 (q, 4H, bridging phenyl- C_3, C_5, phenyl- C_2, C_6- H), 7.76 (m, 1H, phenyl- C_3- H), 7.53 (m, 1H, benzimidazole- C_5- H), 7.39-7.40 (m, 2H, benzimidazole- C_6, C_7- H), 6.28-6.30 (m, 2H, pyrrole-C_3, C_4- H), 2.50 (m, 3H, benzimidazole- C_4, pyrrole- C_2, C_5- H).

N-(4-(1H-benzo[d]imidazol-2-yl) phenyl)-4-(2,5-dimethyl-1H-pyrrol-1-yl) benzamide (10a):
IR (KBr) νmax, cm-1:3346.35 (NH), 2922.14 (CH), 1606.37 (C=O), 1511.30 (C=C), 1310.41 (CN), 1179.05 (C=N); ^{1}H NMR (CDCl$_3$, 400MHz, δ): 9.59 (d, 1H, amide-NH), 8.13-8.15 (m, 4H, bridging phenyl-C_2, C_6, phenyl-C_2, C_6-H), 7.91 (t, 2H, bridging phenyl- C_3, C_5-H), 7.81 (t, 2H, phenyl- C_3,C_5,- H), 7.71 (d, 2H, benzimidazole- C_4, C_7-H), 7.30 (m, 2H, benzimidazole- C_5, C_6- H), 5.93 (t, 2H, pyrrole- C_3, C_4- H), 1.98 (m, 2H, pyrrole- C_2, C_5- H); MS (EI): m/z = found 406.00[M+]; calcd. 406.49.

***4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(4-(5-methyl-1H-benzo[d]imidazol-2-yl) phenyl) benzamide (10b)*:**
IR (KBr) νmax, cm-1:3343.81 (NH), 2920.81 (CH), 1607.77 (C=O), 1512.41 (C=C), 1307.71 (CN), 1178.39 (C=N); ^{1}H NMR (CDCl$_3$, 400MHz, δ):10.19 (s, 1H, amideNH), 8.01 (d, 2H, bridging phenyl- C_3, C_5, - H), 7.83 (s, 2H, phenyl- C_3, C_5- H), 7.32-7.34 (d, 2H, benzimidazole- C_4, C_6- H), 7.19-7.20 (d, 1H, benzimidazole- C_7- H), 5.91-5.93 (d, 2H, pyrrole-C_3, C_4-H), 2.79 (d, 3H, benzimidazoleC_5- H), 2.05 (d, 2H, pyrrole- C_2, C_4- H).

***4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(4-(5-nitro-1H-benzo[d]imidazol-2-yl) phenyl) benzamide (10c)*:**

IR (KBr) νmax, cm-1: 3359.75 (NH), 2921.17 (CH), 1602.83 (C=O), 1513.85 (C=C);^{1}HNMR($CDCl_3$,400MHz,δ):10.17 (s, 1H, amide NH), 8.19 (d, 4H, bridging phenyl- C_2, C_6, phenyl- C_2 C_6- H), 8.05 (m, 1H, benzimidazole- C_6,- H), 7.91 (d, 3H, bridging phenyl- C_3, C_5, benzimidazole- C_4- H), 7.73 (m, 2H, phenyl- C_3, C_5- H), 7.62 (d, 1H, benzimidazole-C_7- H), 5.92-5.93 (q, 2H, pyrrole- C_3, C_4- H), 2.02 (t, 2H, pyrrole- C_2, C_5-H);MS (EI): m/z = found 452.00[M+]; calcd. 452.49.

***4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(4-(5-chloro-1H-benzo[d]imidazol-2-yl) phenyl) benzamide (10d)*:**

IR (KBr) νmax, cm-1:3367.01 (NH), 2921.19 (CH), 1603.84 (C=O), 1516.78 (C=C), 1266.65 (CN), 1172.82 (C=N), 771.39 (C-Cl); ^{1}H NMR ($CDCl_3$, 400MHz, δ):9.36 (d, 1H,amide- NH), 8.18-8.19 (m, 4H, bridging phenyl- C_2, C_5, phenyl- C_2, C_5- H), 8.08-8.10 (s, 2H, bridging phenyl- C_3, C_5- H), 7.71-7.73 (m, 2H, phenyl-C_3, C_5- H), 7.52-7.54 (m, 2H, benzimidazole- C_2- H),7.13 (d, 1H, benzimidazole-C_4-H), 4.11 (t, 2H, pyrrole- C_3, C_4- H), 2.12 9d, 2H, pyrrole- C_2, C_5- H).

***4-(2,5-dimethyl-1H-pyrrol-1-yl)-N-(4-(4-methyl-1H-benzo[d]imidazol-2-yl) phenyl) benzamide (10e)*:**

IR (KBr) νmax, cm-1:3441.26 (NH), 2924.58 (CH), 1609.28 (C=O), 1514.54 (C=C), 1267.45 (CN), 1169.46 (C=N).

Molecular docking

Molecular docking was used to clarify the binding mode of the compounds to provide straightforward information for further structural optimization.

It is reported that the anticonvulsant, antiepileptic and antiseizure drugs may account for hCA inhibition. The choice of consistent hCA enzyme was based on reported literature. Hence, X-ray coordinates of the hCA II isomer was taken from the RCSB data bank (PDB file with code 3F8E), in which, cis-2-hydroxy-4-(1S-3–methylbutyl)-3-methoxy-cinamic acid perfectly fits with the active site.

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Pharmacological activity

1) *In vivo* evaluation of anticonvulsant activity.

a) Maximal electroshock (MES) induced convulsion in rats [14]:

The anticonvulsant property of the drug in this model was assessed by its ability to protect against MES induced convulsions.

The animals are first weigh and are select for the experiment depending on weight. The rats are then divided into different groups of six rats in each. Control group will receive saline, standard group receive 25 mg/kg of phenytoin, other groups receive therapeutic dose of testing drugs respectively.

Maximal electroshock (Inco Electroconvulsiometer) of 150 mA current for 0.2 seconds will be administered through ear electrode to induce convulsions in the control and drug treated animals. The severity of convulsions will be assessed by duration of tonic flexion, tonic extensor, clonus, stupor and recovery phase for each animal. The duration of each phase for each animal (in sec) will be measured by using stopwatch.

b) Pentylenetetrazol (PTZ) induced Convulsion in rats [15]:

The anti-convulsant property of the drug in this model will be assessed by its ability to delay the onset of action and protection against PTZ induced convulsions.

Healthy albino Wister rats of either sex is used. The rats will be divided into different groups of six rats in each group. Control group receive saline; standard group receive 4mg/kg body weight of diazepam; other groups receive therapeutic dose of testing drugs respectively. Pentylenetetrazol (80mg/kg body weight) will be administered intraperitoneally to induce convulsions in the animals of all groups 45 min to 1 hr after administration of saline, standard drug and testing drugs.

The data will be expressed as mean ± standard error of mean (SEM). One-way analysis of variance (ANOVA) followed by Tukey multiple comparison test will be carried out with Graph Pad Prism software (version 3.0). Differences between means were considered significant at $p< 0.01$.

RESULTS AND DISCUSSION

Synthetic and spectral study

The synthetic scheme employed for preparation of the title compounds is depicted in scheme IA, IB and II.

Scheme-IA In this work appropriate o-phenylene diamine(1) is treated with para amino-2-chloro benzoic acid (2) in ethanol and reaction mixture made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole-2-chloro aniline(3a-e) which is further stirred with 4-pyrrole-1-yl-benzoic acid(4) and 4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(6a-e) and (7a-e).

Scheme-IB Appropriate o-phenylenediamine (1) is treated with para-amino benzoic acid (8) in ethanol and reaction mixture made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole aniline(10a-e) which is further stirred with 4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(10a-e). All the newly synthesized compounds were purified by passing through column chromatography. The purity of the compounds was confirmed by melting point and TLC. The structure of newly synthesized compound was established on the basis of analytical and spectral data.

The IR spectrum of 7**a**exhibitedbands at 3422 cm^{-1},1928 cm^{-1} which were due to (-NH), (-C-H) stretching frequencies respectively. The (C=O) absorption band displayed at 1601 cm^{-1}, (C-N), (C=N) and (C-Cl) absorption band displayed at 1329 cm^{-1}.1191 cm^{-1} and 717 cm^{-1}respectively. In the ^{1}H NMR spectrum of 7**a** showed singlet at δ 10.11 due to protons of (amide NH). Singlets at δ 8.27 due to four protons of bridging phenyl-C_2, C_6, phenyl-$C_2$and C_6, doublet at δ value 7.92 for three protons of phenyl-C_3, bridging phenyl- C_3 and C_5, double at δ value 7.46 for two protons of benzimidazole- C_4andC_7, doublet at δ value 7.35 for two protons benzimidazole- C_5 and C_6, doublet at δ value 6.25 for two protons of pyrrole- $C_3$and C_4 and multiplate at δ value 2.4 for six protons of pyrrole- C_2 and C_5.MS (EI): m/z = found 442.00[M+]; calcd. 440.39.

Docking study of pyrrolyl benzamide derivatives (Scheme-IA &1B):

To investigate the mechanism of anti-convulsant activity and detailed intermolecular interactions between the synthesized compounds, molecular docking studies were performed on the hCA II isomer which was taken from the RCSB data bank (PDB file with code 3F8E) using the surflex-dock programme of sybyl-X 2.0 software. All the inhibitors along with the ligand were docked into the active site of ENR as shown in Fig. 1A and B. The predicted binding energies of the compounds are listed in Table 1. The docking study revealed that all the compounds have showed very good docking score against the enzyme.

As depicted in the **fig. 2(A-C),** compound **10** makes two hydrogen bonding interactions at the active site of the enzyme (PDB ID: 3F8E), among those an interaction was of oxygen atom carbonyl group with hydrogen atom of THR200 (C=O------H-THR200, 1.95 Å), and remaining another hydrogen bonding interaction raised from the hydrogen atom of CONH group with nitrogen atom of HIS64 (CONH-----N-HIS64, 2.69 Å).

As depicted in **fig. 3(A-C)**, compound **4** makes three hydrogen bonding interactions at the active site of the enzyme (PDB ID: 3F8E), among those two interactions were of nitrogen atom present in the 3rd position of benzimidazole ring with hydrogen atoms of GLN92 (N------H-GLN92, 2.30 Å; 2.88 Å), and remaining another hydrogen bonding interaction raised from the hydrogen atom of NH present on the 1st position of benzimidazole ring with nitrogen atom of HIS64 (NH-----N-HIS64, 2.29 Å).

The binding interaction of 3F8E_ligand with enzyme active sites shows four bonding interactions and the docked view of the same has been depicted in Fig. **4(A-C)**.

Figure5 (A&B) represents the hydrophobic and hydrophilic amino acids surrounded to the studied compound **10** & **4.**

All the compounds showed consensus score in the range 7.48-2.54, indicating the summary of all forces of interaction between ligands and the enzyme and also, we saw that the studied compounds have showed same type of interaction with amino acid residue (HIS64) as that of reference 3F8E_ligand. This indicates that molecules preferentially bind to enzyme in comparison to the reference 3F8E_ligand (Table 1).

Table 1.Surflex Docking score (kcal/mol) of the Schiff bases.

Compounds	C Score[a]	Crash Score[b]	Polar Score[c]	D Score[d]	PMF Score[e]	G Score[f]	Chem Score[g]
3F8E_ligand	7.54	-0.50	4.80	-103.838	-61.785	-135.025	-23.851
3	7.48	-1.75	5.06	-151.744	-71.480	-175.558	-32.690
13	7.26	-1.10	3.74	-141.702	-87.403	-174.421	-30.084
8	7.15	-1.06	3.41	-156.937	-91.793	-194.490	-29.873
11	6.04	-0.91	1.15	-129.498	-56.938	-173.757	-26.742
5	5.43	-0.97	1.01	-128.732	-35.274	-151.599	-24.536
10	5.29	-0.99	1.06	-135.725	-50.212	-171.479	-25.583
4	5.20	-0.87	1.45	-125.212	-50.552	-163.138	-25.103
14	5.13	-0.91	1.52	-132.750	-57.163	-185.260	-26.423
15	4.76	-1.05	0.73	-123.626	-62.353	-167.775	-25.257
2	4.70	-0.85	1.53	-127.971	-37.689	-181.425	-22.067
6	4.69	-1.57	0.00	-125.450	-74.347	-178.296	-26.190
12	4.43	-1.26	0.02	-162.588	-72.400	-188.768	-28.513
7	4.23	-0.74	0.00	-145.099	-36.384	-140.747	-22.290
1	3.86	-0.78	1.36	-116.178	-29.783	-145.284	-21.363
9	2.54	-1.06	0.00	-109.527	-47.563	-147.655	-20.647

[a]CScore (Consensus Score) integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and reports the output of total score.

[b] Crash-score revealing the inappropriate penetration into the binding site. Crash scores close to 0 are favorable. Negative numbers indicate enetration.

[c] Polar indicating the contribution of the polar interactions to the total score. The polar score may be useful for excluding docking results that make no hydrogen bonds.
[d] D-score for charge and van der Waals interactions between the protein and the ligand.
[e] PMF-score indicating the Helmholtz free energies of interactions for protein-ligand atom pairs (Potential of Mean Force, PMF).
[f] G-score showing hydrogen bonding, complex (ligand-protein), and internal (ligand-ligand) energies.
[g] Chem-score points for H-bonding, lipophilic contact, and rotational entropy, along with an intercept term.

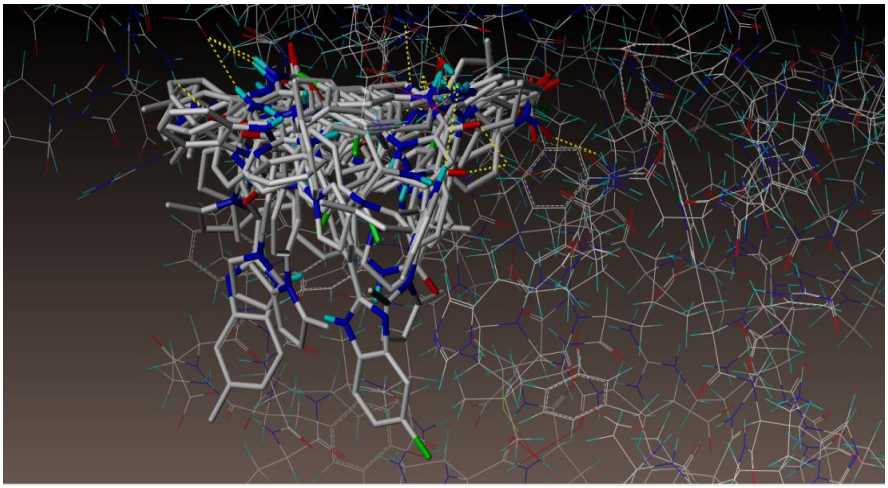


Figure 1. Docked view of all the compounds at the active site of the enzyme PDB ID: 3F8E.

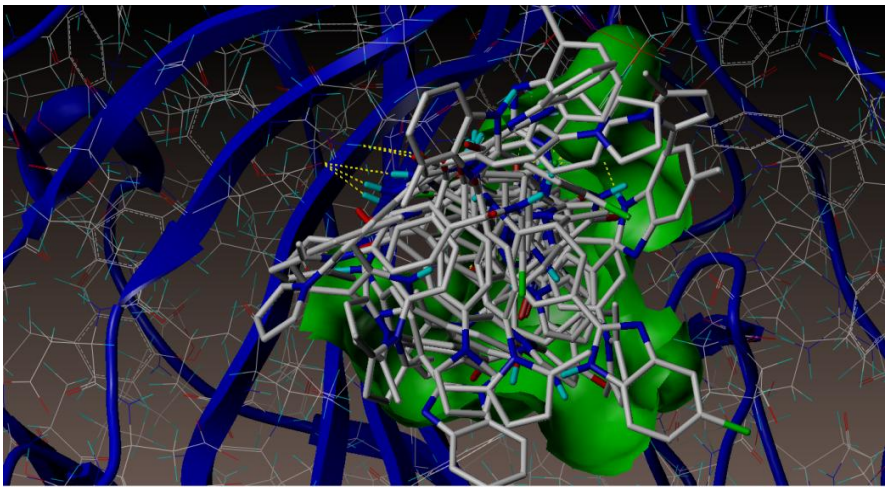
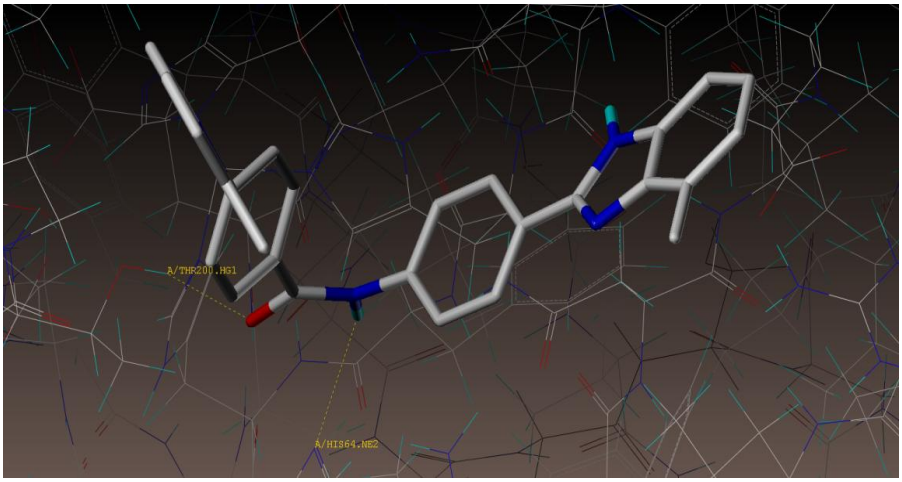
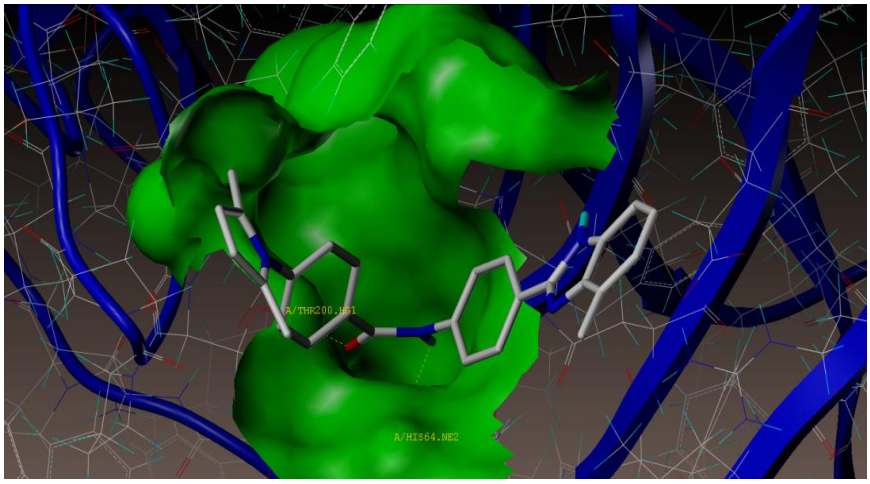


Figure 2. Docked view of compound 10 at the active site of the enzyme PDB: 3F8E.

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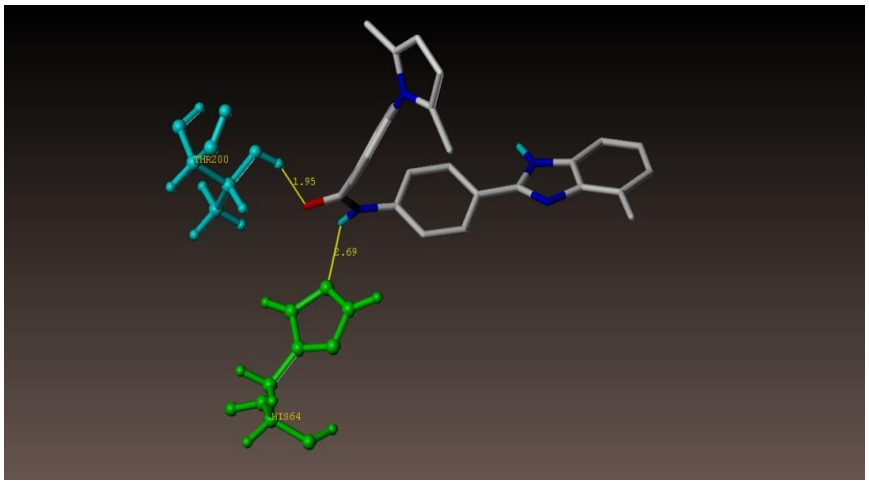
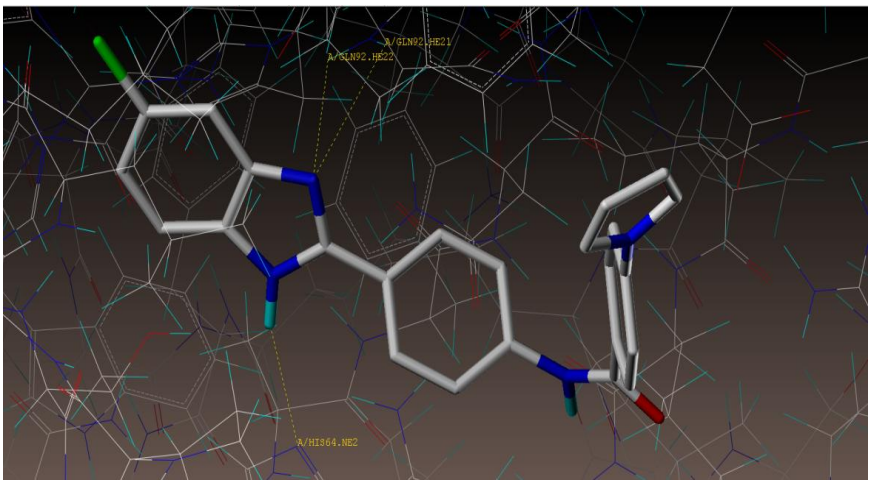
A/HIS64.NE2


THR200
1.95
2.69
HIS64


A/GLN92.HE21
A/GLN92.HE22
A/HIS64.NE2

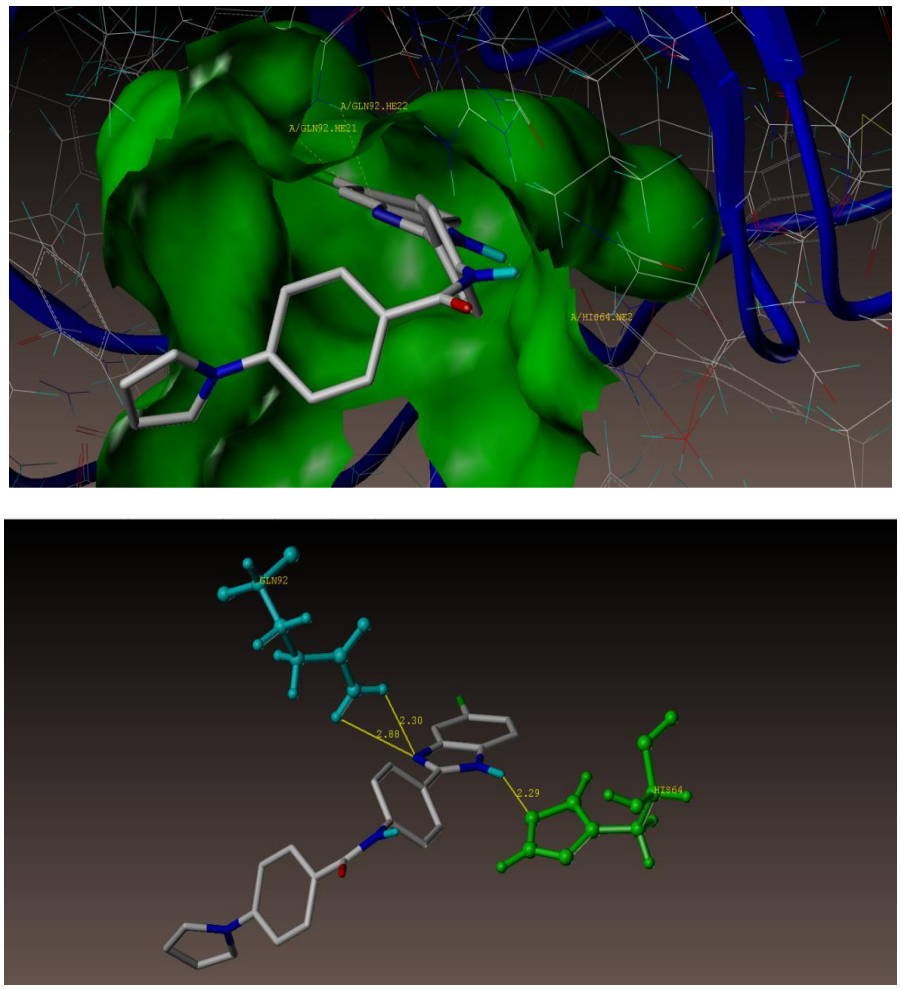
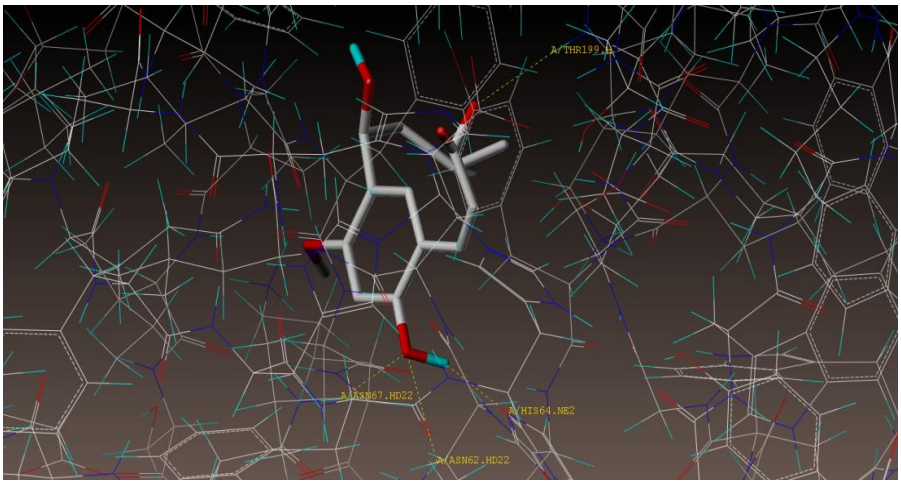


Figure 3. Docked view of compound 4 at the active site of the enzyme PDB: 3F8E.



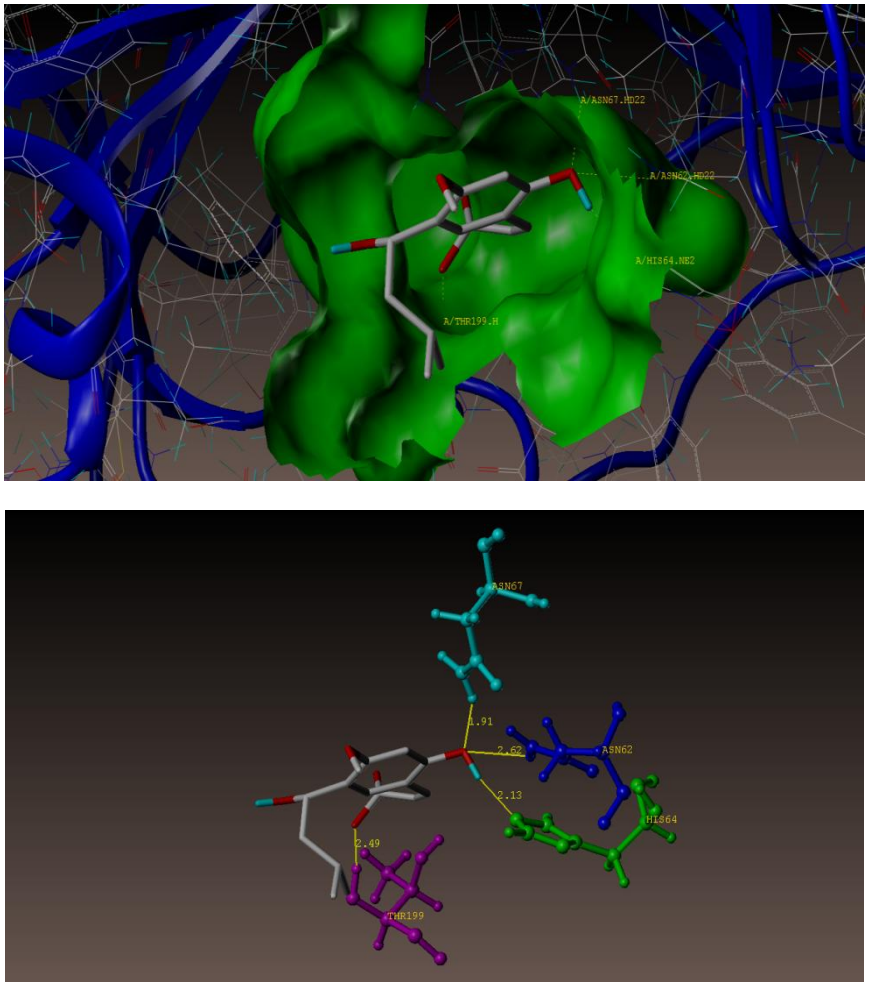
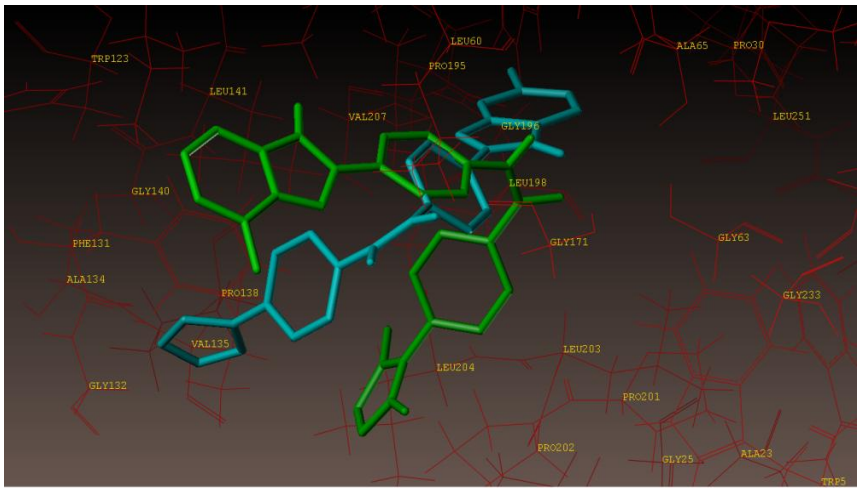


Figure 4. Docked view of Ligand at the active site of the enzyme PDB: 3F8E.



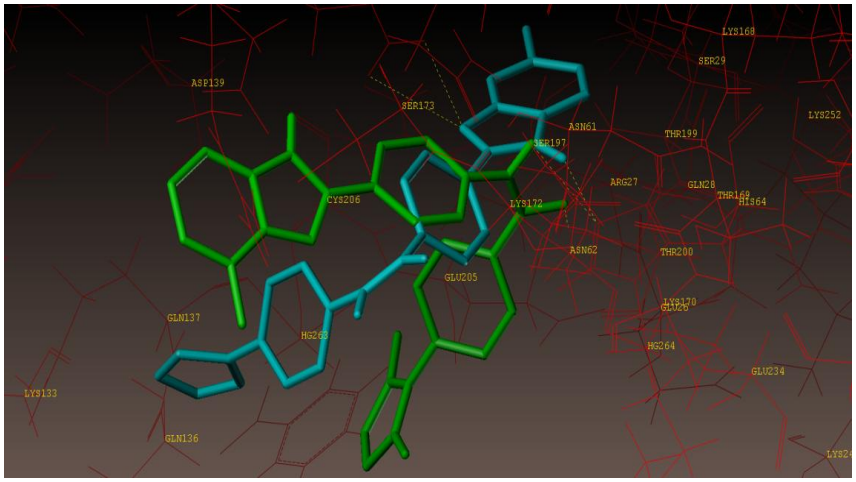


Figure 5. A) Hydrophobic amino acids surrounded to compounds 10 (green color) and 4 (cyan color). B) Hydrophilic amino acids surrounded to compounds 10 and 4.

Pharmacological Screening

Anticonvulsant activity of Pyrrolyl benzimidazole derivatives

The models used to evaluate the effectiveness of few synthesized compounds selected on basis of molecular docking studies compound 6e, 7d, 10a and 10e are (1) Maximal Electroshock Seizure and (2) Pentalene tetrazole seizure.

The MES model is generally used to evaluate the anticonvulsant drugs against generalized tonic-clonic seizure (grand mal) in rodents, which is related to intensity of current stimulus and the dose. MES produced various phases of convulsion i.e. Flexion, Extension, Clonus and Stupor. The duration of tonic extension of the hind limb was used as end point i.e. prevention or decrease in the duration of hind limb extension was considered as a protective action.

Group	Treatment (mg/kg b.w.)	Time (sec) in Various Phases of Convulsions (Mean±SEM)				
		Flexon	Extensor	Clonus	Stupor	Recovery/ Death
1.	Control (Saline 1ml/rat)	2.66±0.021	21.50±0.63	3.16±0.02	209.6±1.3	Recovery
2.	Standard Phenytoin (25)	0.026±0.012***	0.00±0.00***	0.00±0.00***	6.04±0.64***	Recovery
3.	Compound 6e (10)	1.65±0.015***	12.84±0.65***	1.16±0.03***	168.2±0.92	Recovery
4.	Compound 7d (10)	2.50±0.035**	12.49±0.31***	1.2±0.2***	156.8±0.66	Recovery
5.	Compound 10a (10)	2.32±0.031***	9.8±0.34***	1.32±0.09***	140.50±1.41	Recovery
6.	Compound 10e (10)	2.32±0.018***	11.83±0.44***	1.5±0.17***	149.33±1.0	Recovery

Table-2. Evaluation of anticonvulsant activity of different pyrrolyl benzamide derivatives against MES induced convulsions.
*p<0.05, **p<0.01, ***p<0.001 compared with the respective Control.

The synthesized compounds 6e, 7d. 10a and 10e were given orally with the help of stomach tube to rats. The results of tested compounds are compared with the result produced by control. The data resulted from anticonvulsant effect of different tested compounds showed that compounds 6e, 7d. 10a and 10e decrease the duration of hind limb extension, compound 6e(12.84±0.65sec), compound 7d (12.49±0.31sec), compound 10a (9.8±0.34sec), and compound 10e (11.83±0.44sec) which are highly significant when compared to control (21.50±0.63sec).

The synthesized compounds 6e, 7d, 10a and 10e also showed significantly decrease in durations of Flexon, Clonus and stupor phase.

Table-3. Evaluation of anticonvulsant activity of different pyrrolyl benzamide derivatives against PTZ induced convulsions.

Group	Treatment (mg/kg b.w.) (Dose)	Duration of Convulsions in Seconds (Mean±SEM)	% Of Mortality
1.	Control (Saline 1 ml/kg) + PTZ [80mg]	559.6 ± 2.99	100%
2.	Diazepam + PTZ [4 + 80]	0.00 ± 0.00***	0%
3.	Compound 6e + PTZ [10 + 80]	140 ± 2.02***	15%
4.	Compound 7d + PTZ [10 + 80]	285.6 ± 4.16***	50%
5.	Compound 10a+ PTZ [10 + 80]	236 ± 1.30***	35%
6.	Compound 10e + PTZ [10 + 80]	160 ± 2***	15%

The anti-convulsant property of the drug in this model will be assessed by its ability to delay the onset of action and protection against PTZ induced convulsions.

From the statistical data it was observed that compound 6e (140±2.02 sec), compound 7d (285.6±4.16 sec), compound 10a (236±1.30 sec) and compound 10e (160±2 sec) showed highly significant anti-convulsant activity against PTZ induced seizures as compared to the effect produced by control (559±2.99 sec).

CONCLUSIONS

The title compounds were obtained by o-phenylene diamine(1) is treated with para amino-2-chloro benzoic acid (2) in ethanol and reaction mixture made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole-2-chloro aniline(3a-e) which is further stirred with 4-pyrrole-1-yl-benzoic acid(4) and 4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(6a-e) and (7a-e). Further appropriate o-phenylene diamine(1) is treated with para amino benzoic acid (8) in ethanol and reaction mixture made alkaline by adding 10% sodium hydroxide solution to form substituted benzimidazole aniline(10a-e) which is further stirred with 4-(2, 5-dimethyl-1yl)-benzoic acid (5) by dissolving in a dry DMF in presence of HBTU and DIEA yielded the corresponding final compounds(10a-e).To investigate the mechanism of anti-convulsant activity and detailed intermolecular interactions between the synthesized compounds, molecular docking studies were performed on the hCA II isomer which was taken from the RCSB data bank (PDB file with code 3F8E) using the surflex-dock programme of sybyl-X 2.0 software. The docking study revealed that all the compounds have showed very good docking score against the enzyme. Synthesized compounds 6e, 7d, 10a and 10e screened for in-vivo anticonvulsant activity against MES and PTZ induced convulsions and these compounds showed significant anticonvulsant activity when compared with control group against both MES and PTZ induced convulsions, based on docking and screening results, it can be concluded that combination of pyrrole and benzimidazole improve anticonvulsant activity of synthesized compounds. Hence these compounds can consider as a lead molecule for future research.

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List of Abbreviations

°C	Degree centigrade
$CDCl_3$	Deuterated chloroform
Conc	Concentrated
DMSO	Dimethyl sulphoxide
DMF	Dimethyl formamide
DIEA	Di isopropyl ethyl amine
FT-IR	Fourier Transform Infrared
Gm	Gram
hr/h	Hour
M.P.	Melting Point
Min	Minutes
Mol	Mole
NMR	Nuclear Magnetic Resonance
pH	Hydrogen ion concentration
HBTU	2(1H-benzotriazole-1yl-)1,1,3,3-tetramethyl uranium hexaflurophosphate
Ppm	Parts per million
R_f	Retention factor
TLC	Thin Layer Chromatography
TMS	Tetra methyl silane
MIC	Minimum Inhibitory Concentration

Authors' agreements

Authors hereby declare that there is no conflict of interest for the publication.

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