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TARGET-BASED APPROACH FOR *IN SILICO* STUDIES, DESIGN, SYNTHESIS, AND ANTIULCEROGENIC POTENTIAL OF NOVEL 1,4 DIHYDROPYRIDINE DERIVATIVES

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ABSTRACT: *In-silico* studies play a very crucial role in medicinal chemistry and synthesis of the lead compound. As we know that 1,4-Dihydropyridine is a versatile molecule, and previous studies have shown that it possesses therapeutic activity in different diseases, such as anticancer, anticonvulsant, anticoagulant, anti-Alzheimer, antitubercular antiulcer. As described by the researchers, 1,4 Dihydropyridine with sulphanilamide substitution possess good antiulcer activity so, here, in our research work, we decided to synthesized 1,4 dihydropyridine derivative by replacement with some other free amine group-containing compound to determine the antiulcer property of 1,4 Dihydropyridine. To keep this in mind, we studied its interaction with receptor site (H^+/K^+ ATPase pump), which was obtained from protein data bank (PDB) and a series of 1,4-Dihydropyridine hybrid molecule synthesized. The binding of the molecule with receptor site investigated by molecular docking studies and drug-like illness of these compound predicted by using Schrodinger maestro suite 2018-4. Omeprazole and Lansoprazole were used as a standard to validate the docking results. Synthesized molecule characterized by spectroscopic methods and evaluated for their *in-vivo* antiulcerogenic activity using Albino rats (Weight 125g to 200g). Among all the Synthesized compounds, A5, A6, B5, and B6 show significant activity in comparison to omeprazole and, among all four compounds, A5 and B6 (30mg/kg) possess the most potent antiulcer activity. These results indicate that 1,4-Dihydropyridine, is a successful calcium channel blocker, also shows the antiulcer potential, and all synthesized compound can serve as antiulcer drug after further investigation.

INTRODUCTION: The formation of mucosal lesions in the swallowing pipe (oesophagal lining), stomach or duodenum is known as gastric ulcer or peptic ulcer. These small mucosal sores are formed due to the imbalance between defensive mucosal factors such as bicarbonate, prostaglandin, mucin, nitric oxide, *etc*. and injurious factors such as Helicobacter pylori, Non-steroidal anti-inflammatory drugs, pepsin and gastric acid [1]. The microbe *Helicobacter pylori* responsible for the formation of peptic ulcers in humans, and eradication of this microbe can reduce the complication of ulcer because, as per several studies, half of the population is affected with *H. pylori* infection.

We can prevent peptic ulcers by using a sequential regimen for *H. pylori* infection, H Receptor antagonist, and proton pump inhibitors (PPI). For very severe complications of the disease, we use a surgical approach for treatment [2, 3]. Non-steroidal

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anti-inflammatory drugs are important agents for the treatment of various diseases but these drugs also responsible for ulcer formation and increase the risk of ulcer formation when given in the presence of *Helicobacter pylori* [4, 5].

Approximately about 10-15% of the world population is affected by peptic ulcer, and as a result of peptic ulcer, about, 20,000 deaths occur annually. In the era of allopathic medicine, it is impossible to find any drug without adverse effects or side effects and as we know that various medications used for ulcer treatment, such as proton pump inhibitor (omeprazole), H_2 receptor antagonist. Clinical assessment of these medications also reveals their side effect, as well as adverse effects in the long term, so there is a need to identify the safe and effective antiulcer agent [6-11].

Nowadays discovery of the H^+/K^+-ATPase pump leads to the interest of investigators on another level. *In-silico* studies play a good role in the identification of leads compounds towards a particular receptor [12-16]. 1,4-dihydropyridine possess so many therapeutic activities such as Cardio-vascular activity [17–29], anti-tumour [30-41], antituber-cular [43-49], anti-inflammatory [50,51] anti-dyslipidemia [52], anti-microbial [53-59], anti-oxidant [60-64], anti-convulsant [65-68], anticoagulant [69], Cystic fibrosis transmembrane conductance regulator activity [70,71], anti-leishmanial [72], anti-Alzheimer [73, 74], anti-osteoporosis [75] that's why it is called as a versatile scaffold. Previous studies of 1,4 dihydropyridine reveal its antiulcer property [76-83, 100].

Remarkable Structural features and the antiulcer possibility of 1,4-Dihydropyridine derivatives encouraged us to synthesize some 1,4 dihydro-pyridine derivatives and screened them for their antiulcer potential. Docking studies were carried out against human H^+/K^+ ATPase pump, which was obtained from the protein data bank (PDB). The present study is based on the development of drugs that increase the defense mechanism of gastric mucosa and prevent ulcer formation.

The study of medicines by *in-silico* methods increases the rate of drug discovery and reduces expensive laboratory work to save time and cost. By *in-silico* methods, we produce drug candidates more effectively. With the discovery of the H+/K+-ATPase proton pump, it is easy to design and synthesize a molecule that works as a proton pump inhibitor. In 2018 Abe K *et al.,* discovered the crystal structure of the gastric proton pump in complex with Vonoprazan and SCH28080. The 3D model of H^+/K^+-ATPase (gastric proton pump PDB ID: 5YLU) was retrieved from the protein data bank. SCH28080 and vonoprazan co-crystallized thus, it is necessary to read the binding sites of these inhibitors with protein. Omeprazole is possessed a similar effect in comparison with SCH28080. We used omeprazole for the comparison with other ligand molecules in the receptor site where vonoprazan co-crystallized. In our work first, we design molecules by suitable software then select a suitable lead compound for synthesis and ulcer screening by molecular docking software. Before performing any crucial *in-silico* studies (Such as Molecular docking, ADME *etc.*), it is one of the important parts of computational studies. From most of the *in-silico* studies, molecular docking is one of the most important for the determination of suitable lead for the target site. For performing the molecular docking studies, we needed the acceptable software which performs docking studies very well, like Auto dock, Auto dock Vina, Glide, *etc*., for our study; we used GLIDE module version 4.4.12.0 Schrodinger, LLC, New York, NY, 2018 [83-88].

MATERIALS AND METHODS: Using the combination of various keywords such as 1,4-dihy-dropyridine, antihypertensive, antianginal, anti-tumor, anti-inflammatory activity, antituberculosis activity and antiulcer activity, a literature search was performed on different database sites such as PubMed, science direct. The literature search was customized by applying the required filter to get the most relevant articles to meet the objective of this research. All required chemicals and apparatus issued from the college laboratory. Melting point determined by capillary tube method for characterization of compounds, IR spectra recorded on PERKIN-ELMER FTIR Spectrophotometer. For NMR, MASS of compounds were analyzed from the chemistry department of IIT Kanpur. NMR spectra were recorded on the JEOL DELTA NMR instrument by using Tetramethyl silane as a reference and DMSO D6 (99.9%) as a solvent. MASS spectra recorded on WATERS-Q-TOF Premier-HAB213 spectrometer. For toxicity and screening of compound, Wistar rats were used and

approved by the college ethical committee and, all In-silico studies carried out in different applications of Schrodinger Maestro Software, module version 4.4.12.0 Schrodinger, LLC, New York, NY, 2018. Docking studies of synthesized compounds performed by using GLIDE module version 4.4.12.0 Schrodinger, LLC, New York, NY, 2018. Docking studies of synthesized compounds used against H^+/K^+-ATPase receptor antagonist (PDB ID: 5YLU). Software license provided by Schrodinger. We performed drug-like illness or drug-ability of the molecule by open-source tool SWISS ADME tool for drug-like illness prediction.

***In-silico* Studies:** The first step of molecular docking in maestro software was ligand preparation. All the prepared molecule which are already drawn by Chem Draw Software and saved in mol. the format used here for ligand preparation along with standard drug structure Omeprazole. For ligand preparation, we used ligprep application So that we can generate an accurate 3D molecular structure with minimized energy, maximum diversity at one time. It also generates a structure for glide software which can be used for the docking process.

The protein that we obtained from the protein data bank not prepared for the docking step so first, we needed to prepare it for docking. For the preparation of protein, we used the protein preparation wizard Which was automatically import protein structure from the local database or PDB websites, after that with appropriate instructions this application prepare protein for docking by applying some changes in protein which are as follows: add missing hydrogen bond, Correct metal ionization, Enumerate heterocyclic group bond orders, Remove Co-crystallized water molecules, Highlight missing atoms and residues, easily determined protonation state as well as energy penalties in connection with alternative protonation, optimize the protein's hydrogen bond network. It also performs restrain minimization so that hydrogen atoms freely minimize and allows sufficient heavy atom movement to relax strained bonds, angle and clashes. After preparation, protein preparation confirmed by the Ramachandran plot. Ramachandran plot used to validate protein structure. By Grid generation process software excluded co-crystallized ligand and determine the size, shape, and interaction site of the receptor with the co-crystallized ligand [83-88]. Docking is one of the most important tools which is mostly used for molecular modelling. In Molecular docking steps, we dock prepared ligand into a grid-generated protein. If protein is a receptor, then action may be agonism or antagonism, or if a protein is an enzyme, then it inhibits the enzyme activity. It is also helpful to find a lead compound between the N number of hits compound and save our time as well as money. After docking visualization of results, one of the most important stages where we analyze docking results, scores, and interaction sites of the ligand with receptor sites [83-88].

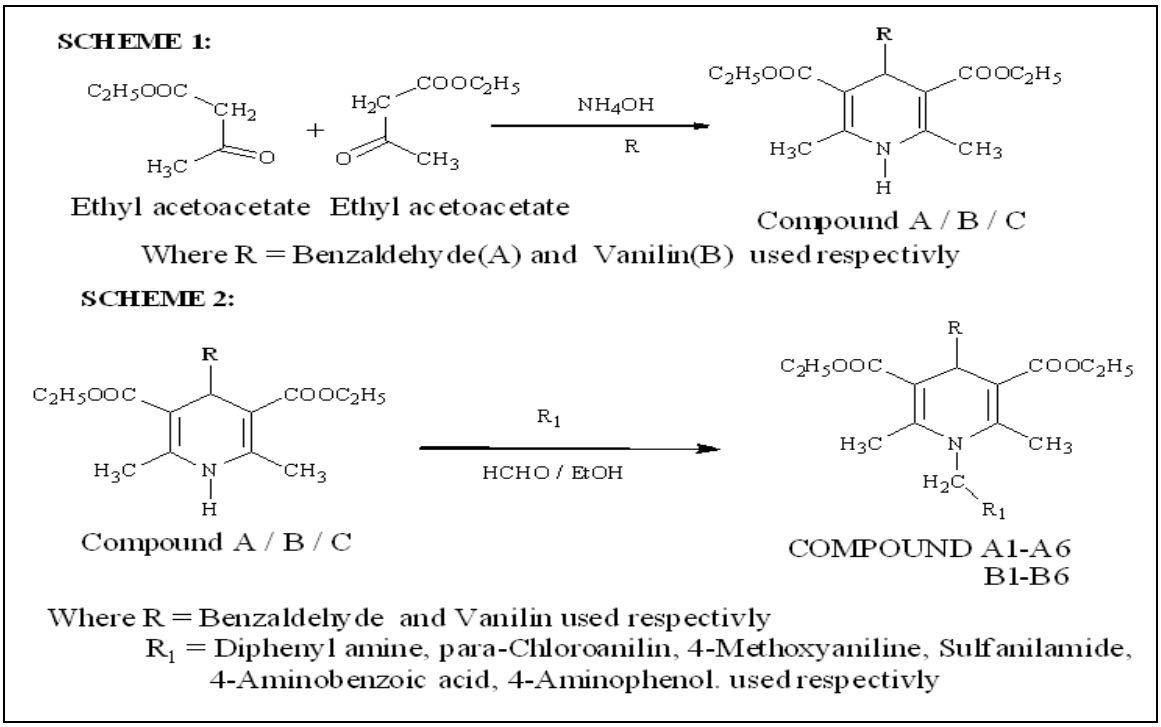
Drug-Like Illness: Drug-like illness of compounds assessed based on Lipinski rule of five which was suggested by Christopher A in 1997. According to the Rule of Five, most active oral drugs are relatively small and moderately lipophilic molecules. This rule also describes the Pharmacokinetics properties of a drug molecule in the human body, such as absorption, distribution, metabolism, and excretion (ADME). ADME properties determination is one of the most difficult tasks during the whole drug discovery process. Nowadays, most of the software's provide the facility for the determination of ADME properties. As per these rule compounds should have a molecular weight of ≤500 Da, a logP ≤ 5, hydrogen bond donor ≤5, and hydrogen bond acceptor sites (N and O atoms) ≤10 that they have strong absorption. In our work after molecular docking, we predicted drug-ability of the molecule by open-source tool SWISS ADME tool for drug-like illness prediction [6, 83-88].

Synthesis, Purification and Characterization of Compounds:

Synthesis of Step 1 Compound: A solution of aldehyde (1 mol), ethyl acetoacetate (2 mol), ammonium hydroxide (1 mol) taken in ethanol (60 ml.) was heated under reflux in a round bottom flask, for 2 h at 140°C temperature. The resulting mixture was poured into an ice bath. Separated product (A/ B) was filtered off and recrystallized with 60% Alcohol **Scheme 1** [89, 90].

Synthesis of Step 2 Compound: Equimolar quantities of amino group-containing compounds (1, 2, 3, 4, 5, 6) (1mol) in 10 mL of ethanol added into a slurry containing the mixture of compound

(A/ B) and aqueous formaldehyde solution. The reaction mixture was heated with continuous stirring at water bath, till a clear solution was not obtain then the resulting mixture poured into an ice bath. The products [A/B (1, 2, 3, 4, 5, and 6)] were separated by suction filtration and recrystallized with 60% ethanol **Scheme 2** [90, 91].



Characterization:

Diethyl 2, 6- Dimethyl-4- Phenyl-1, 4-Dihydro-pyridine-3,5-Dicarboxylate (A): $C_{19}H_{23}NO_4$, Mol. Wt: 329.16 R_f value: 0.48, Yield 51%, m.p. 115-120, IR (cm^{-1}): 3338.4 (NH), 1474.4(C=C), 1705.4 (C=O), 1196(C-O), 2983.3(C-H aliphatic), 3030(C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.26 (6H-CH_3), 4.20 (4H CH_2), 4.42 (2H CH_2), 4.82 (1H CH), 5.71 (1H NH), 7.03-7.17 (5H Ar H); C (69.28), H (7.04), N (4.25), O (19.43)% Found: C (68.87), H (6.54), N (4.28), O (17.26)%. m/z: 328.97.

Diethyl 1- ((Diphenylamino) Methyl)- 2, 6-Dimethyl- 4- Phenyl- 1, 4-Dihydropyridine-3, 5-Dicarboxylate A1: $C_{32}H_{34}N_2O_4$, Mol. Wt: 510.62, R_f value: 0.38, Yield 78%, m.p. 106-110, IR (cm^{-1}): 3338.4 (NH), 1589.9 (C=C), 1637.1 (C=O), 1196 (C-O), 2976 (C-H aliphatic), 3049.6 (C-H aromatic), NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.26 (6H-CH_3), 3.92-3.98 (4H CH_2), 3.30 (2H CH_2), 4.82 (H CH), 5.71 (1H NH), 7.02- 7.12 (5H Ar H), 7.13-7.20 (10H Ar H). C (75.27), H (6.71), N (5.49), O (12.53)% Found: C(73.17), H (7.78), N (5.29), O (12.51)%. m/z: 510.10.

Diethyl 1-((4-Chlorophenylamino) Methyl)-2, 6-Dimethyl-4-Phenyl-1, 4-Dihydropyridine-3, 5-Dicarboxylate A2: $C_{26}H_{29}ClN_2O_4$, Mol. Wt.: 468.97, R_f value: .53, Yield: 69.44%, m.p. 108-111, IR (cm^{-1}): 3343.7 (NH), 1479.6 (C=C), 1642.4 (C=O), 1206.6 (C-O), 2897.3 (C-H aliphatic), 2965.6 (C-H aromatic), 818 (-Cl) NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.21 (6H-CH_3), 3.94-3.97 (4H CH_2), 3.29 (2H CH_2), 4.78 (H CH), 6.65 (1H NH), 7.02-7.07(4H Ar H) 7.10-7.17(5H Ar H), C (66.59), H (6.23), N (5.97), O (13.65), Cl (7.56) %. Found C (67.19), H (6.13), N (4.67), O (12.95), Cl (6.96) %. m/z: 467.95.

Diethyl 1-((4-Methoxyphenylamino) Methyl)-2,6-Dimethyl-4-Phenyl-1,4-Dihydropyridine-3,5-Dicarboxylate A3: $C_{27}H_{32}N_2O_5$, Mol. Wt: 464.55, R_f value: 0.61, Yield 70.90%, m.p. 115-120, IR (cm^{-1}): 3338.4 (NH), 1458.6 (C=C), 1637.1 (C=O), 1201.3 (C-O), 1022.8 (C-O-C), 2750 (C-H aliphatic), 2965 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.22 (6H-CH_3), 3.94-3.98 (4H CH_2), 3.50 (2H CH_2), 4.82 (H CH), 6.73 (1H NH), 6.97-7.03 (4H Ar H), 7.10-7.17 (5H Ar H); C(69.81), H(6.94), N(6.03), O(17.22)% found C(67.71), H(5.90), N(7.13), O(16.62)%. m/z: 464.13.

Diethyl 2,6-Dimethyl-4-Phenyl-1-((4-Sulfamoyl-phenylamino) Methyl)-1,4-Dihydropyridine -3, 5-Dicarboxylate (A4): $C_{26}H_{31}N_3O_6S$, Mol. Wt: 464.55, R_f value: 0.65, Yield 97%, m.p. 115-118, IR (cm^{-1}): 3333.2 (NH), 1474.4 (C=C), 1642.4 (C=O), 1201.3 (C-O), 2897.3 (C-H aliphatic), 2965.6 (C-H aromatic), 1369.4 (S=O) NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.21 (6H-CH_3), 3.93-3.98 (4H CH_2), 3.29 (2H CH_2), 4.82 (H CH), 7.05 (1H NH), 7.11 (2H NH_2) 7.05-7.11 (4H Ar H), 7.12-7.17(5H Ar H) C (60.80), H (6.08), N(8.18), O (18.69), S (6.94) % found: C (59.60), H (5.78), N(7.98), O (16.79), S (6.14)%. m/z: 513.00.

4-((3, 5-Bis(Ethoxycarbonyl)-2, 6- Dimethyl- 4-Phenylpyridin-1(4H)-Yl)Methylamino) Benzoic Acid (A5): $C_{27}H_{30}N_2O_6$, Mol. Wt: 478.54, R_f value: 0.46, Yield 66.52%, m.p. 125-130, IR (cm^{-1}): 3333.2 (NH), 1474.4 (C=C), 1658.2 (C=O), 1201.3 (C-O), 2830 (C-H aliphatic), 2900 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.07 (6H-CH_3), 2.21 (6H-CH_3), 3.91-3.98 (4H CH_2), 3.30 (2H CH_2), 4.82 (H CH), 6.67 (1H NH), 6.86-7.07 (4H Ar H), 7.10-7.17 (5H Ar H); C (67.77), H (6.32), N (5.85), O (20.06) % found: C (66.97), H (5.92), N (4.95), O (18.96) %. m/z: 478.05.

Diethyl 1-((4-Hydroxyphenylamino) Methyl)-2, 6-Dimethyl-4-Phenyl-1,4-Dihydropyridine-3,5-Dicarboxylate A6: $C_{26}H_{30}N_2O_5$, Mol. Wt: 450.53, R_f value: 0.46, Yield 83.33%, m.p. 115-120, IR (cm^{-1}): 3335.02 (NH), 1488.9 (C=C), 1645.8 (C=O), 1209.79 (C-O), 2836.4 (C-H aliphatic), 2944.7 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.07 (6H-CH_3), 2.21 (6H-CH_3), 3.89-4.00 (4H CH_2), 4.82 (H CH), 6.52 (1H NH), 7.04-7.10 (4H Ar H), 7.11-7.17 (5H Ar H). C (66.31), H (6.71), N (6.22), O (17.76) % found: C (65.97), H (6.32), N (5.95), O (19.16) %. m/z: 550.12.

Diethyl4-(4-Hydroxy-3-Methoxyphenyl)-2,6-Dimethyl-1,4-Dihydropyridine-3, 5 Dicarboxylate (B): $C_{20}H_{25}NO_6$, Mol. Wt: 375.42, R_f value: 0.56, Yield 66.96%, m.p. 120-125, IR (cm^{-1}) 3313.8 (OH), 3340 (NH), 1456.4 (C=C), 1651.2 (C=O), 1207.4 (C-O), 1018(C-O-C), 2827.5 (C-H aliphatic), 2941 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.11 (6H-CH_3), 2.20(6H-CH_3), 3.92-4.00 (4H CH_2), 3.64 (2H CH_2), 3.83 (3H OCH_3), (H OH), 4.71 (H CH), 8.61 (1H NH), 6.46-6.65 (3H Ar H); C (63.99), H (6.71), N (3.73), O (25.57)% found C (62.79), H (5.91), N (3.56), O (24.17)%. m/z: 375.07.

Diethyl 1- ((Diphenylamino) Methyl)- 4- (4-Hydroxy-3-Methoxyphenyl)- 2, 6-Dimethyl-1, 4-Dihydropyridine-3,5-Dicarboxylate B1: $C_{33}H_{36}N_2O_6$, Mol. Wt: 556.65, R_f value: 0.23, Yield 59.27%, m.p. 106-115, IR (cm^{-1}): 3323.5 (OH), 3345 (NH), 1494.3 (C=C), 1651.2(C=O), 1212 (C-O), 1018 (C-O-C) 2831 (C-H aliphatic), 2944 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.06 (6H-CH_3), 2.20 (6H-CH_3), 3.91-4.01 (4H CH_2), 3.30 (2H CH_2), 3.64 (3H OCH_3), (H OH), 4.71 (H CH), 6.46-6.79 (3H Ar H), 7.16-7.20 (10H Ar H). C (71.20), H (6.52), N (5.03), O (17.25) % Found C (70.99), H (6.54), N (4.97), O (16.95) %. m/z: 557.26.

Diethyl 1-((4-Chlorophenylamino)Methyl)-4-(4-Hydroxy-3-Methoxyphenyl)-2,6-Dimethyl-1,4-Dihydropyridine-3,5-Dicarboxylate B2: $C_{27}H_{31}ClN_2O_6$, Mol. Wt: 515.00, R_f value: 0.15, Yield 84.46%, m.p. 85-90, IR(cm^{-1}): 3307.3 (OH), 3345.2 (NH), 1488.9 (C=C), 1651.2 (C=O), 1207.4 (C-O), 1018 (C-O-C), 2831 (C-H aliphatic), 2944.7 (C-H aromatic), 812.36 (-Cl) NMR (500MHz, δ ppm, DMSO D_6) 1.07 (6H-CH_3), 2.21 (6H-CH_3), 3.92-4.00 (4H CH_2), 3.30 (2H CH_2), 3.64 (3H OCH_3), (H OH), 4.98 (H CH), 6.46 (1H NH), 6.95-7.06 (3H Ar H), 7.14-7.19 (4H Ar H). C (62.97), H (6.07), N (5.44), O (18.64), Cl (6.88) % found C (62.15), H (5.99), N (6.41), O (16.67), Cl (5.98) %. m/z: 515.18.

Diethyl 4-(4-Hydroxy-3-Methoxyphenyl)-1-((4-Methoxyphenylamino) Methyl)-2, 6- Dimethyl-1,4-Dihydropyridine-3,5-Dicarboxylate B3: $C_{28}H_{34}N_2O_7$, Mol. Wt.: 510.58, R_f value: 0.53, Yield 81.37, m.p.

125-130, IR (cm^{-1}): 3312.7 (OH), 3345.2 (NH), 1510.5 (C=C), 1651.2 (C=O), 1212.8 (C-O), 1018 (C-O-C), 2831 (C-H aliphatic), 2939.3 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.11 (6H-CH_3), 2.20 (6H-CH_3), 3.92-4.00 (4H CH_2), 3.29 (2H CH_2), 3.61 (3H OCH_3), (H OH),4.62 (H CH), 6.46 (1H NH), 6.65-6.76 (3H Ar H), 6.91-6.99 (4H Ar H). C (65.87), H (6.71), N (5.49), O (21.94) % found C (65.10), H (5.97), N (6.19), O (20.84) %. m/z: 509.20.

Diethyl 4- (4- Hydroxy-3-Methoxyphenyl)-2, 6-Dimethyl-1-((4-Sulfamoylphenylamino) Methyl)-1, 4-Dihydropyridine-3,5-Dicarboxylate (B4): $C_{27}H_{33}N_3O_8S$, Mol. Wt: 559.63, R_f value: 0.30 , Yield 85.86%, m.p. 118-123, IR (cm^{-1}): 3312.7(OH), 3348.26 (NH), 1451 (C=C), 1651.2 (C=O), 1212.8 (C-O), 1022.65 (C-O-C), 2831 (C-H aliphatic), 2944.42 (C-H aromatic), 1360 (S=O) NMR (500MHz, δ ppm, DMSO D_6) 1.11 (6H-CH_3), 2.20 (6H-CH_3), 3.92-4.00 (4H CH_2), 3.30 (2H CH_2), 3.64 (3H OCH_3), (H OH), 4.71 (H CH), 6.46 (1H NH), 6.65 (2H NH_2), 6.47-6.55 (4H Ar H), 6.65-6.65 (3H Ar H). C (57.95), H (5.94), N (7.51), O (22.87), S (5.73) % found C (57.05), H (4.94), N (6.51), O (20.67), S (4.93)%. m/z: 558.90.

4-((3,5-Bis(Ethoxycarbonyl)-4-(4-Hydroxy-3-Methoxyphenyl)-2,6-Dimethylpyridin-1(4H)-Yl) Methylamino)Benzoic Acid B5: $C_{28}H_{32}N_2O_8$, Mol. Wt: 524.56, R_f value: 0.33, Yield 81.10%, m.p. 132-137, IR (cm^{-1}): 3301.9 (OH), 3345.2 (NH), 1418.5 (C=C), 1602.5 (C=O), 1212.8 (C-O), 1018 (C-O-C), 2831 (C-H aliphatic), 2944.7 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.09 (6H-CH_3), 2.20 (6H-CH_3), 3.89-4.00(4H CH_2), 3.31(2H CH_2), 3.64 (3H OCH_3), (H OH), 4.71 (H CH), 6.52 (1H NH), 7.05-7.09 (3H Ar H), 7.64-7.72(4H Ar H). C (64.11), H (6.15), N (5.34), O (24.40)% found C (63.91), H (5.95), N (4.94), O (23.56)%. m/z: 523.05.

Diethyl 4-(4-Hydroxy-3-Methoxyphenyl)-1-((4-Hydroxyphenylamino) Methyl)- 2, 6- Dimethyl-1, 4- Dihydropyridine-3, 5-Dicarboxylate (B6): $C_{27}H_{32}N_2O_7$, Mol. Wt: 496.55, R_f value: 0.15, Yield 67.33, m.p. 85-90, IR(cm^{-1}): 3356 (OH), 3330 (NH), 1494.3 (C=C), 1667.4 (C=O), 1216.3 (C-O), 1018 (C-O-C), 2836.4 (C-H aliphatic), 2944.6 (C-H aromatic) NMR (500MHz, δ ppm, DMSO D_6) 1.08 (6H-CH_3), 2.20 (6H-CH_3), 3.89-4.00 (4H CH_2), 3.59 (2H CH_2), 3.64 (3H OCH_3), (HOH), 4.71 (H CH), 6.34 (1H NH), 6.56-6,59 (3H Ar H), 6.65-6.86 (4H Ar H). C (65.31), H (6.50), N (5.64), O (22.55) % found C (65.15), H (5.96), N (6.14), O (20.65) %. m/z: 495.97.

Pharmacological Assay: Albino rats (weighing 125-200 g) housed at the animal house of the Advance Institute of Biotech and Paramedical Sciences under a controlled environment (23–25°C). Before beginning the experiment, animals were kept in plastic cages and fasted for 24 hours. Tap water ad libitum and the regular pellet diet were given to animals. All the animals were randomly divided into six rats in each group. A1 to B6 compound, administered orally or intra-peritonially.

In the case of acute toxicity studies, the test was carried out using increasing doses (250, 500 and 1500 mg/kg) of test compounds administered to rats orally in 1 ml volume. Food was allowed for the animals and animals kept under observation for 24 hours mortality. Experiments conducted comply with the regulations of the institute of Laboratory Animal Resource, National research council's and authorized by Ethical Committee of Advance Institute of Biotech and Paramedical Sciences, Dr A.P.J. Abdul Kalam Technical University. (AEC) clearance was done with reference no: 1273/PO/Re/S/09/CPCSEA [93].

Antiulcer Activity:

Gastric Lesions Induced by 99.9% Ethanol: The Control group receives only normal saline (1 ml.). Compound (A1 to B6) and reference drug omeprazole at a dose of 30 mg/kg given to animals into the treatment group. After 1 hour, 1 ml of absolute ethanol administered to each group of animals. The rats were sacrificed 2 hours later, stomachs removed, and rinsed with water. Rats stomach was cut along with greater curvature and again rinsed with distilled water. Open, stomachs pinned to a white wooden board for the observation of ulcer. Ulcer Protection Ulcer index calculated according to the given formula described by Saibu S *et.al.* and Ulcer area in mm2 determined as the total sum of gastric lesions for each animal's stomach in the group [94-96].

Ulcer Index: U.I. = [Ulcerated area/total stomach area] × 100

% Ulcer inhibition = [U.I. in control − U.I. in test] × 100/U.I. in control.

Gastric Lesions Induced by Indomethacin: Animals fasted for 24 h and, water was allowed to ad libidum. Each group-administered standard drug omeprazole at a dose of 30mg/Kg and three-dose level (10, 20 and 30 mg/Kg) of synthesized A5 and B6 compound. After 30 min of Indomethacin (30 mg/Kg body weight) and carboxymethylcellulose (CMC) (1%), suspension in water administered orally. After 6 h, all animals sacrificed, and gastric mucosal damage examined by microscope [97, 98].

Acetic Acid Induced Gastric Ulcer: Animals divided into four groups and each group containing six animals. Animals fasted for 24 h deprived of food but, excess water is allowed. The Control group receives only normal saline. Under xylazine/ ketamine (7.5 mg/kg and 60 mg/kg) anaesthesia were administered to animals by the intraperitoneal route and, after that, the abdomen was open and stomach exposed. Anterior and posterior walls of the stomach, clamped with a forceps having round ring (internal diameter 6 mm.) after that of 1 ml 50% acetic acid solution is injected into clamped portion through fore-stomach by a gauge needle for 1 min. One minute later acid solution removed, the area washed with saline and the abdomen was closed with sutures.

On the second day after the ulcer induction, control group animals treated with vehicle, and other animal groups were treated with Omeprazole (30mg/Kg), A5 and B6 compounds (30mg/kg) respectively twice a day for two weeks by gavage. Two weeks after, proper feeding and monitoring, animals sacrificed and, stomach removed. Gastric acid content discard and stomach placed in 15 ml of 2% formalin solution for 20 min. After, that stomach removed from the formalin solution and the Open stomach pinned to a white wooden board for the observation of the ulcer. The surface area of each lesion was measures and calculate with their ulcer index [99].

RESULT:

***In-silico* Studies:** A library of 23 molecules along with omeprazole and Lansoprazole were prepared by ChemDraw software and saved in mol Format. And molecular docking was performed by GLIDE software module version 4.4.12.0 Schrodinger, LLC, New York, NY, 2018. All designed and standard Molecules used for ligand preparation from a molecule library. By use of ligprep application, we generated an accurate 3D molecular structure of all molecules with minimized energy, maximum diversity at one time. It also generates a Structure for glide software which further used for the docking process. Protein preparation for docking process done by using Protein preparation wizard. In our study, we needed an H+/K+-ATPase pump for docking study which obtained from PDB by using PDB ID-5YLU. Obtained protein prepared by protein preparation wizard and protein preparation confirmed by Ramachandran plot. Ramachandran plot used to validate protein structure based on φ (phi), ψ (psi) and ω (omega) angles.

A Receptor grid was generated for the prepared protein and exclude the co-crystallized ligand (Vanoprazan) without any changes in the prepared protein. Grid box range X, Y, Z 23.155, grid box range for the ligand at different angle X, Y, Z are 10×10×10 and, exhaustiveness for molecules set at 100.

After all the preparation of protein preparation, ligand preparation, and grid generated protein, molecular docking performed into grid generate protein. All docking results analyzed. As shown in **Fig. 1**, a receptor protein is obtained from a Protein data bank and, it indicates the binding of co-crystallized ligand vonoprazan. Obtained protein prepared by the protein preparation wizard and confirmed by Ramachandran plot **Fig. 2**. Docking scores of best docked possess are given in **Table 1**. On the evaluation of docking scores, we predict that all the synthesized molecule will show the difference in inactivity. Compound A5 shows the highest activity while compound A4 shows the minimum activity but possess maximum activity in comparison to the omeprazole which, is considered as standard in our study.

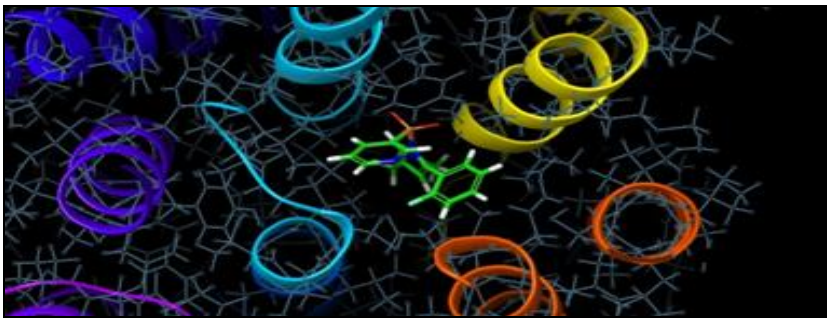


FIG. 1: POCKET OF PROTEIN WHERE VONOPRAZAN, A CO-CRYSTALLIZED LIGAND, BIND AND INTERACT WITH BINDING SITES OF PROTEIN

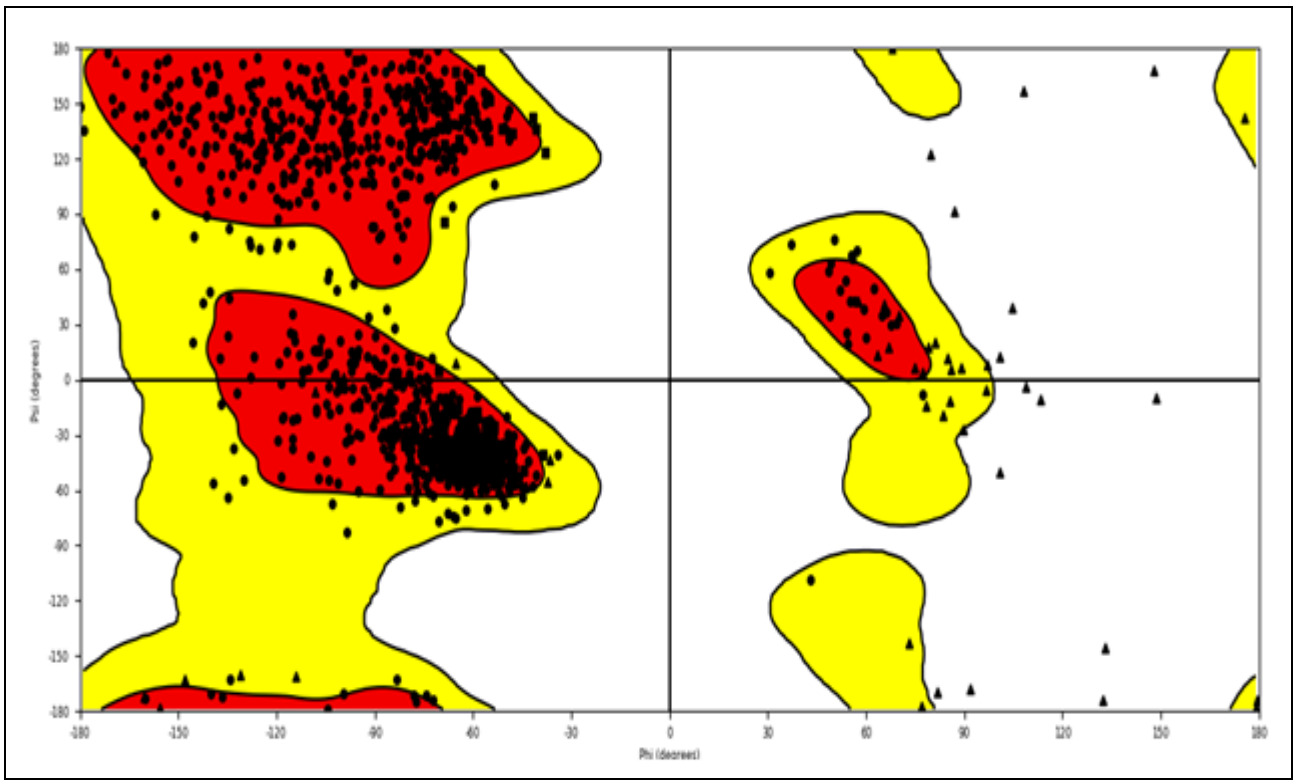
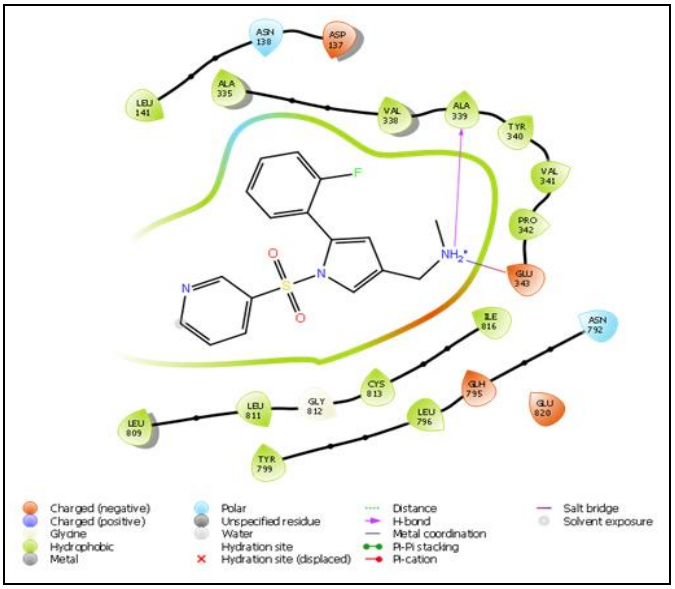


FIG. 2: RAMACHANDRAN PLOT OF PREPARED 5YLU PROTEIN. RETRIEVED FROM PROTEIN DATA BANK AND PREPARED IN PROTEIN PREPARATION WIZARD APPLICATION OF SCHRODINGER MAESTRO SUITS

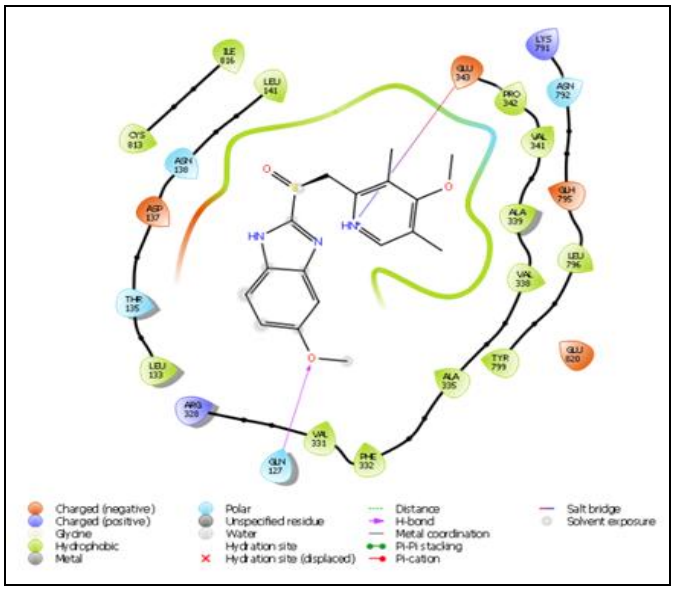
TABLE 1: DOCKING SCORE OF COMPOUNDS WHICH POSSESS HIGHER INTERACTION THAN STANDARD DRUG

Title	docking score	XP G Score	glide gscore	glide energy	Energy
A5	-10.946	-10.946	-10.946	-48.745	34.464
B	-9.595	-9.595	-9.595	-51.844	13.696
B6	-9.387	-9.387	-9.387	-66.875	34.223
B4	-9.255	-9.255	-9.255	-75.78	32.406
A4	-7	-7	-7	-62.901	39.103
Omeprazole 1	-6.999	-7.092	-7.092	-44.083	23.359
B3	-6.868	-6.869	-6.869	-61.397	29.565
A6	-6.552	-6.552	-6.552	-55.404	31.144
A2	-6.262	-6.262	-6.262	-58.692	32.527
A3	-6.195	-6.195	-6.195	-59.119	36.913
A1	-5.66	-5.66	-5.66	-45.033	41.804
B2	-5.285	-5.285	-5.285	-16.06	26.928
B1	-5.124	-5.124	-5.124	-61.753	37.73
Lansoprazole 1	-5.011	-5.031	-5.031	-45.29	15.988
A	-4.975	-4.975	-4.975	-38.327	19.419
Omeprazole 2	-3.295	-5.064	-5.064	-47.212	17.08
Omeprazole 3	-3.129	-4.524	-4.524	-44.777	23.589
Lansoprazole 2	-2.821	-4.855	-4.855	-43.673	9.451
B5	-2.155	-2.155	-2.155	-55.194	36.725

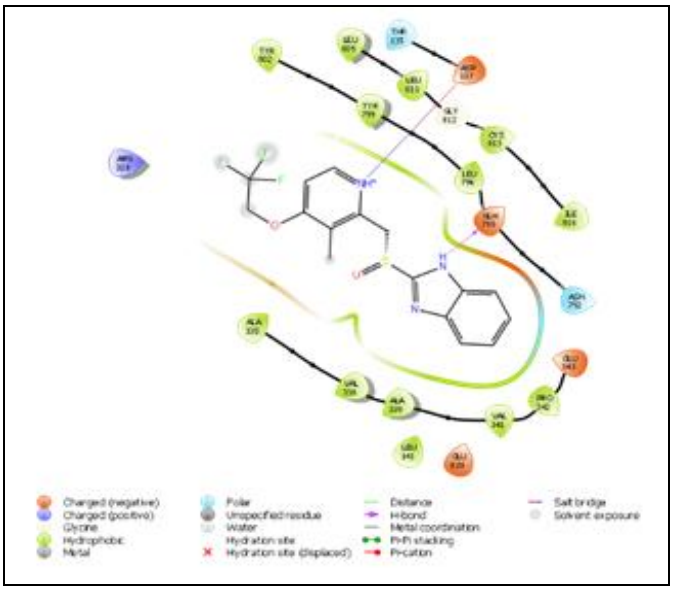
In Docking analysis, we observed that standard omeprazole shows interaction with TYR 799, GLU 343, GLN 127 and all compounds show good interaction with receptor site which binds almost as same pose but, the difference is between molecule interaction sites. All synthesized compounds show binding with TYR 799 and, all compounds also show some other interaction site with protein which is clearly shown, in **Fig. 3** except compound B6. B6 shows interaction GLN 127, ARG 328, ASN 138, which is approximately similar to omeprazole. All compounds are showing more interaction with the amino acid residues which are surrounding the active site in comparison with standard molecules. It observes that co-crystallized ligand vonoprazan **Fig. 3** has less interaction with active site as compared to synthesized compounds and Standard molecule.



VONOPRAZAN

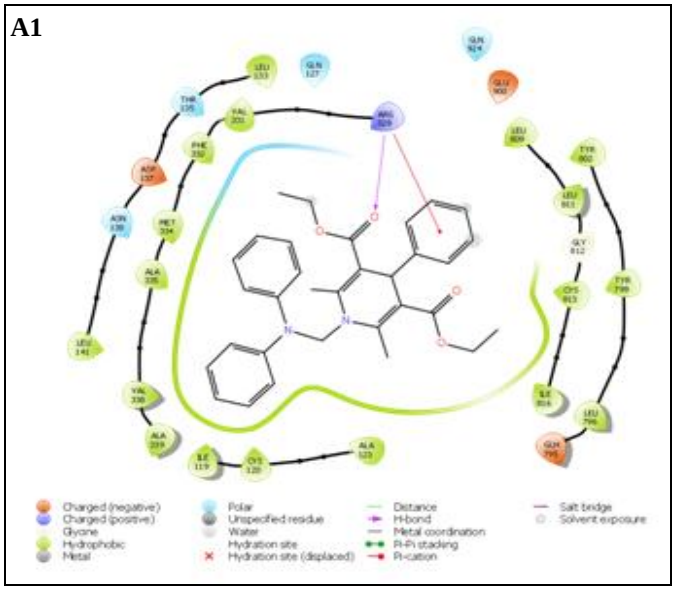


OMEPRAZOLE

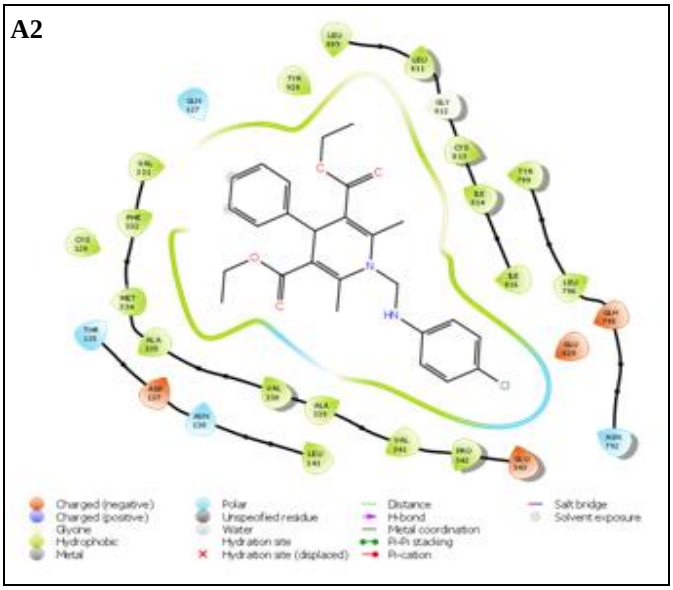


LANSOPRAZOLE

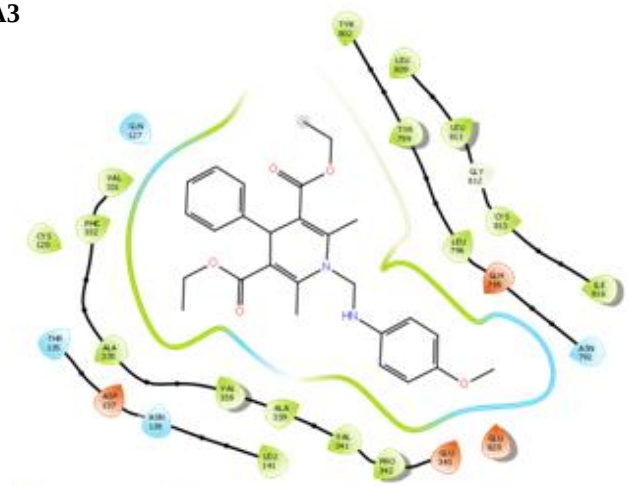
A1



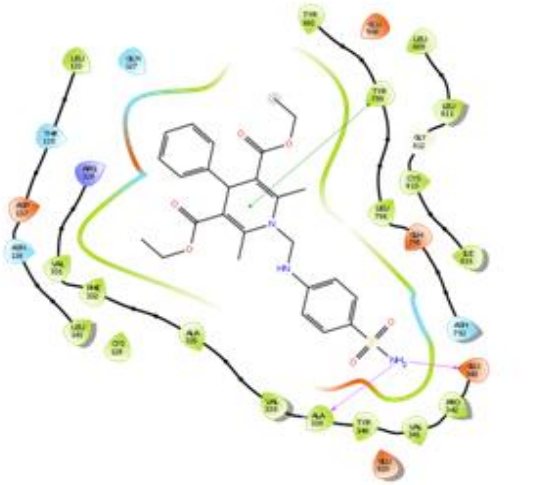
A2



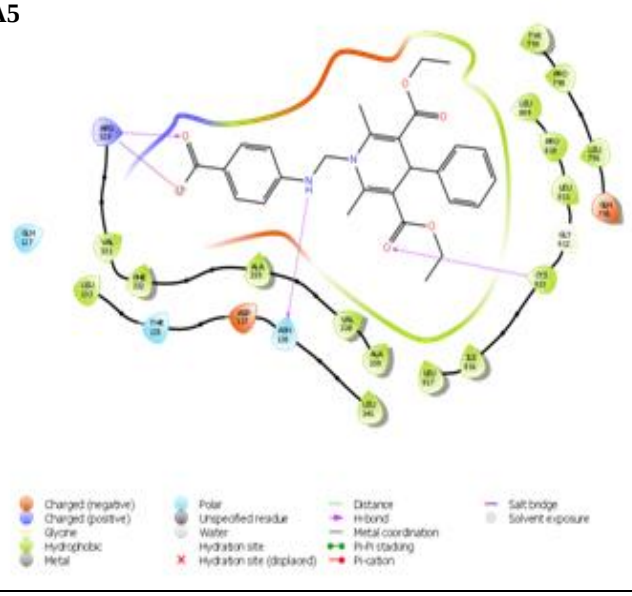
A3



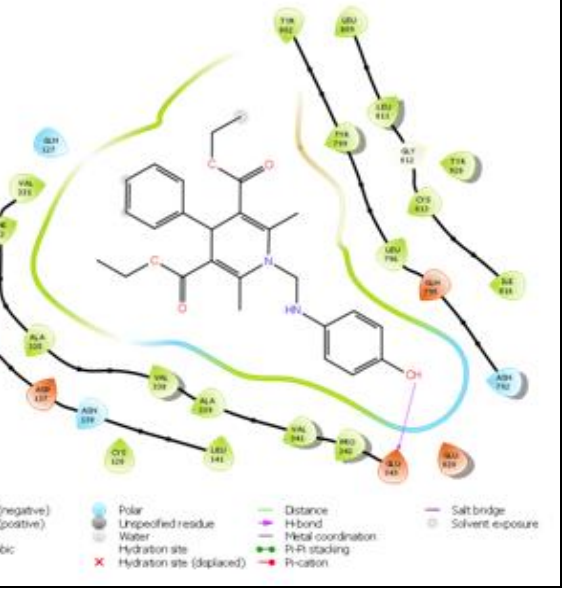
A4



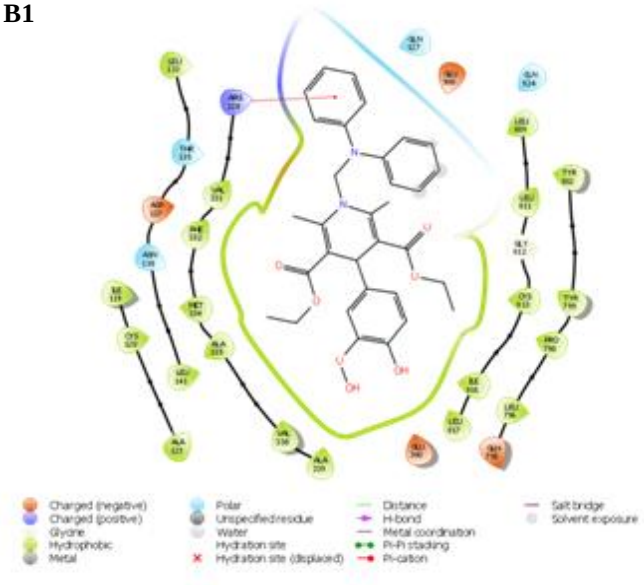
A5



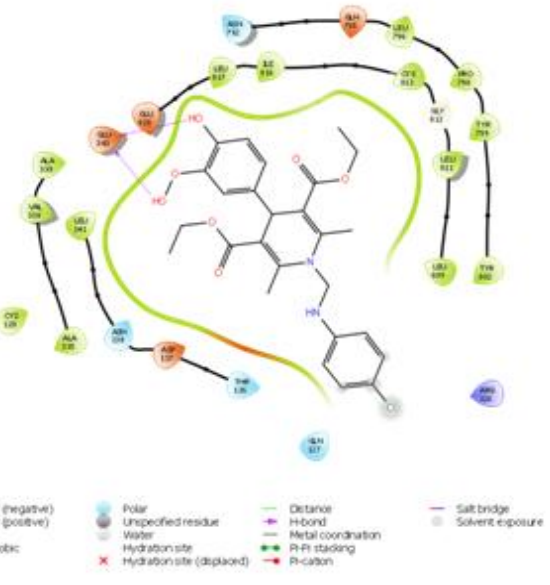
A6



B1



B2



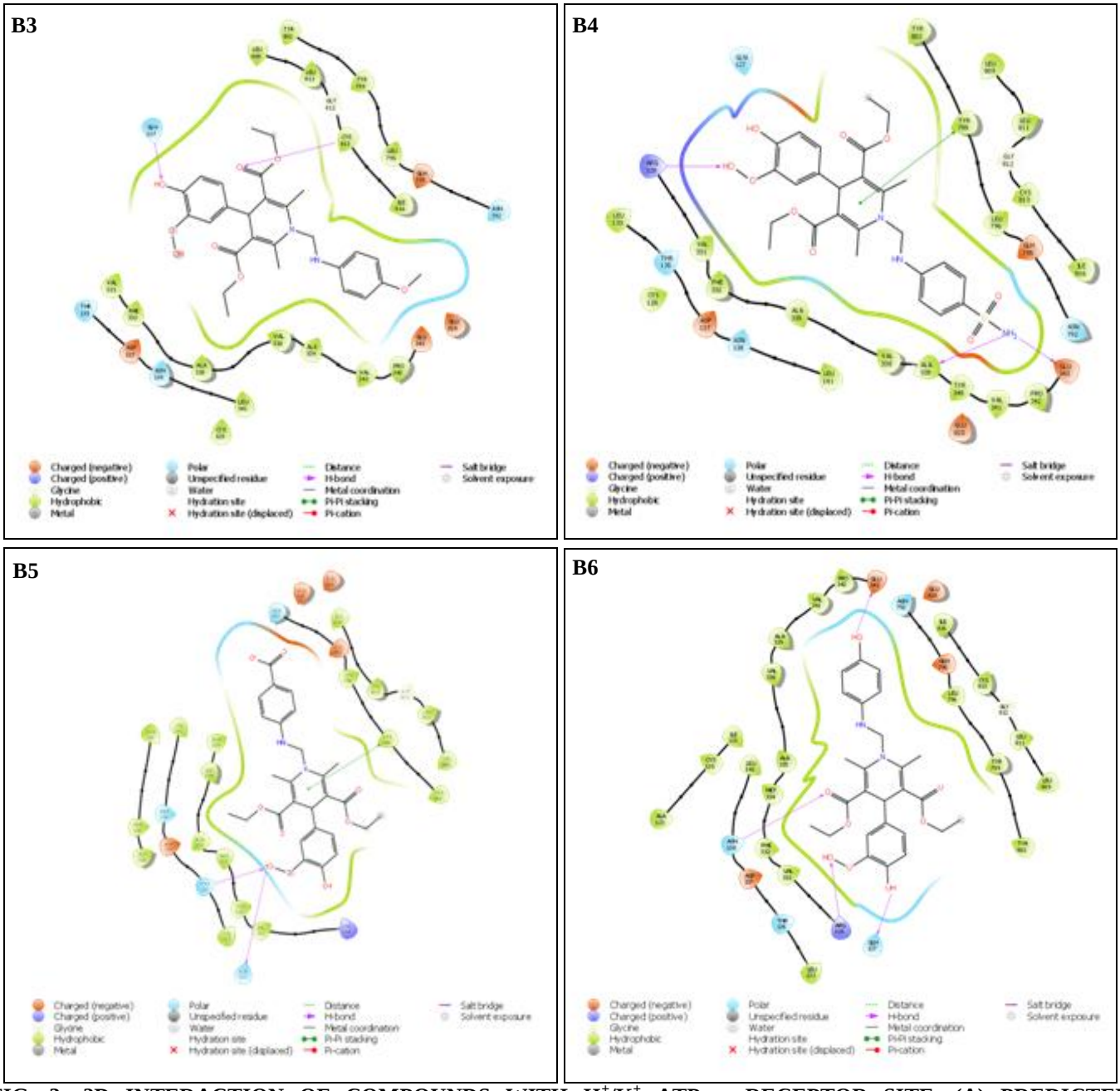


FIG. 3: 2D INTERACTION OF COMPOUNDS WITH H^+/K^+ ATPase RECEPTOR SITE. (A) PREDICTED INTERACTION OF CO-CRYSTALLIZED LIGAND VONOPRAZAN, OMEPRAZOLE, LANSOPRAZOLE, AND SYNTHESIZED MOLECULE WITH ACTIVE SITE

***In-silico* Drug-like Illness Assessment:** Drug-ability of our compounds indicates that all the compounds fulfill the criteria of rule of five except A4, B4, and the predicted values of ml logP for all compounds are around 5 **Table 2**. Compounds A, B, possess 100% oral absorption, and compound B4 shows lower 44.60% human oral absorption. Based on these predictions, we can say that all compounds have identical activity except compounds A4, and B4 because these compounds higher in molecular weight and a higher number of bond acceptors which are equivalent to 10. After the rule of five predictions, among all the Compounds, compound A5 and B6 have a maximum number of hydrogen bond acceptor and hydrogen bond donor properties. The polar surface area is calculated for all Compounds, Which fulfill the rule of five criteria and results obtained within range (it should be≤140). Compound A5 has the highest polar surface area of 120.45. Drug-like illness of these compounds suggested that all these Compounds (A, A5, B, and B6), can be used as a drug.

TABLE 2: DRUG LIKE ILLNESSS ASSESSMENT OF COMPOUNDS THAT POSSESS HIGHER INTERACTION

Code	Mol. Wt.	ml Log P	H bond Donar	H bond Acceptor	No. of rotat. bond	Volume	Human Oral Abs. (%)	PSA
A	329.395	3.03	1	4	7	1109.428	100	70.898
A1	510.632	5.51	0	4	11	1556.027	100	60.235
A2	468.979	4.78	1	4	10	1468.479	100	70.909
A3	464.56	4.25	1	5	11	1515.157	100	78.985
A4	513.607	3.06	2	7	11	1556.71	68.217	136.024
A5	478.544	3.61	2	6	11	1512.233	74.454	120.45
A6	450.533	3.86	2	5	10	1456.515	93.937	93.471
B	375.421	2.62	2	6	8	1209.013	100	100.821
B1	556.657	5.14	1	6	12	1635.141	92.999	90.293
B2	515.005	4.39	2	6	11	1546.592	83.84	101.427
B3	510.586	3.90	2	7	12	1558.858	80.089	109.357
B4	559.633	2.74	3	9	12	1679.225	44.604	166.497
B5	524.569	3.24	3	8	12	1599.032	62.657	150.913
B6	496.559	3.38	3	7	11	1542.316	94.858	123.836

Chemistry:

Synthesis: As shown in the reaction scheme, the 1,4 Dihydropyridine hybrids synthesized by a two-step reaction starting from ethyl-acetoacetate. Treatment of ethyl-acetoacetate with different aldehyde respectively benzaldehyde, or vanillin in the presence of ammonium hydroxide at 140 °C gives compound A (yield 51%), B (yield 66.96%), respectively kept for drying. After drying, in the presence of ethanol and formaldehyde, compound A, and B again reacted with different amine group-containing compounds, respectively. All the compound, purified by recrystallization with the help of a suitable solvent (60% ethanol). Completion of synthesis confirmed by TLC. TLC of compounds indicates the formation of compounds during the reaction. The melting point of the compounds is determined in one end fused capillary tube method. All compounds show a melting point above 105 °C. The solubility of the compounds analyzed in the different solvents and reported. All compounds were rapidly soluble in DMSO, DCM. Sparingly soluble in Acetone, Ethyl Acetate, Toluene, Chloroform. With the increase in temperature, compounds soluble in ethanol and methanol. All compounds were insoluble in Water, Di Ethyl Ether, and Pet-Ether Hexane. Compounds A5, A6, B5, and B6 are insoluble in chloroform also. Structure of the compounds elucidated by Perkin Elimer FTIR spectrophotometer. The IR value measured in cm^{-1}. IR spectra were recorded by PerkinElmer FTIR (Spectrum software) and obtain spectra were shown the presence of a functional group at their respective regions. NMR spectra were recorded on a JEOL DELTA NMR instrument using TMS as a reference and DMSO D6 (99.9%) as a solvent. The NMR Spectra were predicted and confirmed that compounds having a similar number of hydrogen later which confirmed, by the *ChemDraw* software. All hydrogens of the structures shown in NMR Spectra except hydroxy group's hydrogen it is possible that hydrogen of hydroxyl group replaced by deuterated DMSO solvent. MASS Spectra of compounds analysed, from the Chemistry department of IIT Kanpur. MASS spectra recorded on WATERS-Q-TOF Premier-HAB213 spectrometer. The mass spectro-scopic values measured in m/e ratio and, the molecular ion peak corresponds to the molecular weight of the compound. Results of mass spectral analysis also clearly indicate the molecular weight of the compounds. Based on physical and spectral analysis, we came to the conclusion that the entire designed compound was developed and structurally corrected.

Acute Toxicity Studies: Acute toxicity studies performed according to OECD guidelines under favorable conditions. On 14 days of Experiment, we observe that there was no single sign of abnormalities present. Individual mortality data and necropsy inspected. Acute toxicity studies revealed that synthetic derivatives are non-toxic in nature after the administration. Both group rats were observed immediately for 4 h, for autonomic and the central nervous system, motor activity, and behavior pattern for any changes or lethality for the next 14 days. Absence of lethality or toxic reactions (tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma) were found at the dose of 1500 mg/kg till the last part of the study period. During acute toxicity study, all the animals

were safe and, no abnormalities were detected which means all compounds were safe for oral use.

Antiulcer Activity: In our first phase study, we screened all the synthesized compounds (A1 to B6) at graded doses (10, 20, and 30mg/kg) in a 99.9% ethanol-induced gastric ulcer model with Omeprazole (30 mg/kg) as standard drug. The maximum amount of ulcer index 93.20±0.37 was recorded **Fig. 4.** The screening results are summarised in **Table 3**. As we know, NSAIDs are also responsible for ulcer formation in animals as well as humans because they suppress PGE2 bio-synthesis and cause mucous depletion. Indomethacin (30mg/Kg) induced gastric ulcer in animals and compound A5, A6, B5, and B6 shows the significant result with ulcer index of 18.70 ± 0.17, 17.89 ± 0.05, 22.64 ± 0.12 and 21.68 ± 0.20 respectively these results provide proof about the cytoprotective nature of these compound. The administration of Indomethacin (30 mg/kg) orally induced gastric damage in animals. Compound A6 was found the most active antiulcer agent in this method **Table 4**. Ulcer formation in acetic acid-induced gastric ulcer was significantly inhibited by compounds at the dose of 30 mg/kg. In control animals, the ulcer index was 87.51±0.11 for acetic acid. All compounds A5, A6, B5, and B6, shows the significant result with ulcer index of 40.67 ± 0.14, 42.67 ± 0.12, 44.33 ± 0.09, and 41.42 ± 0.11, respectively, and compound A5 shows the most potent activity **Table 5**.

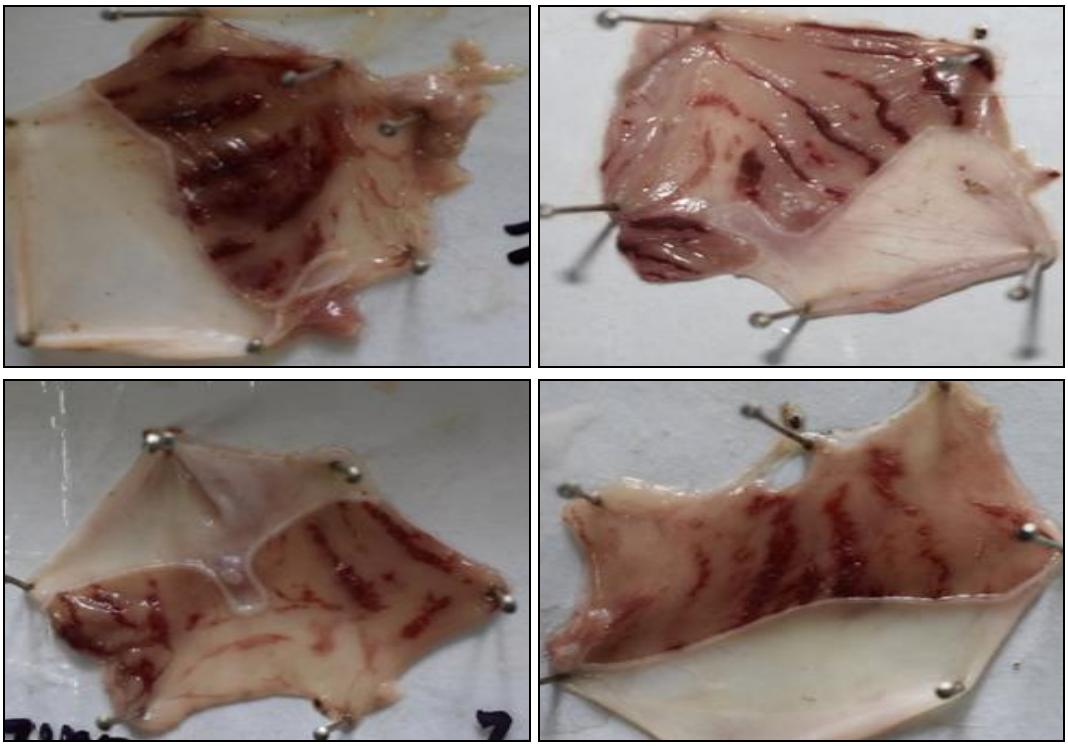


FIG. 4: GASTERIC LESIONS OCCURS IN ANIMAL DUE TO ETHANOL (A), AND PROTECTIVE EFFECT OF STANDARD DRUG OMEPRAZOLE (B), DERIVATIVE A5 (C), AND DERIVATIVE

TABLE 3: THE EFFECT OF COMPOUNDS ON GASTRIC LESIONS INDUCED BY 99.9% ETHANOL (MEAN ± SE)

	Control (99.95 EtOH)	Omeprazole 30mg/Kg	Compound					
			10 mg/Kg		20 mg/Kg		30 mg/Kg	
	Mean ± SE	Mean ± SE	% Change	Mean ± SE	% Change	Mean ± SE	% Change	Mean ± SE
A1	92.31±0.43	22.34±0.39	75.79	83.56±0.44	9.47	74.24±0.21	19.57	70.74±0.45
A2	91.93±0.36	21.33±0.34	76.79	82.50±0.44	10.25	74.71±0.4	18.73	71.71±0.35
A3	92.59±0.27	21.66±0.45	76.60	84.80±0.34	17.26	74.72±0.35	19.30	70.62±0.48
A4	92.02±0.28	22.21±0.26	75.86	83.03±0.47	9.76	73.27±0.22	20.37	72.60±0.49
A5	90.39±0.28	22.45±0.38	75.16	46.26±0.44	48.82	38.60±0.42	57.29	31.61±0.44
A6	92.57±0.37	22.22±0.28	75.99	54.80±0.38	40.80	40.89±0.41	55.82	34.56±0.10
B1	93.20±0.37	21.68±0.46	76.73	84.30±0.21	9.54	76.06±0.19	18.39	73.52±0.12
B2	91.48±0.29	22.99±0.35	74.86	84.94±0.16	7.14	78.82±0.39	13.83	71.75±0.39
B3	91.64±0.44	21.66±0.22	76.36	82.48±0.48	9.99	74.42±0.48	18.79	69.42±0.15

B4	92.11±0.37	21.66±0.28	76.48	83.61±0.37	9.22	74.84±0.17	18.74	70.41±0.49
B5	92.68±0.34	21.57±0.38	76.72	58.30±0.36	37.09	48.42±0.49	47.75	36.59±0.42
B6	90.78±0.47	21.72±0.45	76.07	51.66±0.41	43.09	42.94±0.17	52.69	32.72±0.43
A1	92.31±0.43	22.34±0.39	75.79	83.56±0.44	9.47	74.24±0.21	19.57	70.74±0.45

TABLE 4: THE EFFECT OF COMPOUNDS ON INDO-METHACIN-INDUCED GASTRIC MUCOSAL LESIONS (MEAN ± SE)

Treatment	Dose (mg/Kg)	Ulcer index
Control		46.06±0.19
Omeprazole	30	16.82±0.29
A5	10	31.62±0.39
A5	20	24.72±0.25
A5	30	18.70±0.17
A6	10	30.68±0.12
A6	20	23.79±0.06
A6	30	17.89±0.05
B5	10	34.32±0.10
B5	20	28.28±0.12
B5	30	22.64±0.12
B6	10	33.12±0.31
B6	20	27.18±0.23
B6	30	21.68±0.20

TABLE 5: THE EFFECT OF COMPOUNDS ON GASTRIC LESIONS INDUCED BY ACETIC ACID (MEAN ± SE)

Treatment	Dose (mg/Kg)	Ulcer index
Control		87.51±0.11
Omeprazole	30	36.69±0.06
A5	10	66.54±0.16
A5	20	50.12±0.19
A5	30	40.67±0.14
A6	10	67.45±0.12
A6	20	51.69±0.10
A6	30	42.67±0.12
B5	10	69.62±0.10
B5	20	54.42±0.17
B5	30	44.33±0.09
B6	10	68.44±0.07
B6	20	52.88±0.19
B6	30	41.42±0.11

DISCUSSION AND CONCLUSION: As previously it is proved that 1.4-DHP possess the antiulcer activity and it blocks the H^+/K^+ ATPase pump. When Abe et.al. discover the H^+/K^+ ATPase pump they reported that two P-CABs vonoprazan, and SCH28080 inhibit K^+ ion entry by blocking at cation binding site in H^+/K^+ ATPase pump and concluded that in both cases of drugs, the interaction between drugs and binding sites are hydrophobic which responsible for the increase in water entropy thus drugs effectively bind to the binding site (H^+/K^+ ATPase pump) in acidic medium and most of the carboxylic groups become protonated. They also indicate that TYR-799 is a very important amino acid for the interaction of the drugs with binding sites. In our docking studies, it is indicated that all the designed compounds show hydrophobic interactions with different amino towards the binding site. All Compound shows interaction with TYR-799. Compound A5, B, B6 shows higher docking score among all the designed compound along with standard drug Omeprazole and Lansoprazole. On the study of drug-like illness of compounds, it was found that all the compounds fulfil the criteria for the oral absorption as well as the rule of five of the drug molecule except A4 and B4. Based on *in-silico* studies, a series of newly synthesized 1,4dihydropyridine scaffold hybrids were synthesized and characterized by various spectral data. These synthesized molecules also screened for antiulcer activity in different *in* vivo ulcer models. The newly synthesized molecules show a significant gastroprotective effect by reducing the formation of gastric ulcers induced by 99.9% ethanol. Among all synthesized compounds only four compounds A5, A6, B5, and B6 were found to the most potent compound of the series. These four compounds were further evaluated with different *in-vivo* antiulcer models, and compound A5 was found to be a highly potent compound of the series.

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