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DESIGN, SYNTHESIS & PHARMACOLOGICAL EVALUATION OF NEW SUBSTITUTED BENZIMIDAZOLE DERIVATIVES AS ANTIULCER, ANTISECRETORY & ANTICONVULSANT AGENT

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ABSTRACT

The present research study was designed to investigate the effect of 2-(pyrimidinylsulfinyl)benzimidazole derivative experimentally tested as Antiulcer & Antisecretory Agents. Aspirin-induced gastric ulcer model was used for Antiulcer Activity by using ulcer inducing agents, i.e acetylsalicylic acid and indomethacin screening model in Wistar rats and compound were also assayed on gastric acid secretion of animals, acute models of gastric mucosal lesions for gastric H+/K+- ATPase inhibition. The second series derivatives of 2-Amino benzimidazole experimentally tested as Anticonvulsant Activities. The pharmacological screening protocol for the anticonvulsant activity of the synthesized compound was checked by electroshock method. various degrees of inhibitions by 2-(pyrimidinylsulfinyl) benzimidazole & 2-Amino benzimidazole derivative (50-200 mg/kg/p.o) were statistically significant ($p<0.001$). The effect of several benzimidazole synthesized compound were compared to that of the standard drugs used.

KEYWORDS: 2-Pyrimidinylsulfinyl Benzimidazole, 2-Amino Benzimidazole derivative, Antiulcer, Antisecretory, Anticonvulsant activities.

INTRODUCTION

Benzimidazole derivatives are of wide interest of research because of their diverse biological activity and clinical applications[1-8] dependent on the different substitution on the benzimidazole nucleus. Introduction of a substitution on 2nd and 5th position of benzimidazole shows anthelmintic activity whiles bulky substitution on 2nd positions showed antihistaminic activity and proton pump inhibitory. Hence, benzimidazole moiety was therapeutically important moiety.[9] In the treatment of gastric and duodenal ulcer disease inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle.[10]

Proton pump inhibitors (PPIs) category of therapeutic agents for most acid-related diseases, including, gastroesophageal reflux diseases, peptic ulcer diseases, and acute gastrointestinal bleeding.[11] Benzimidazole type agents contribute significantly to these agents like omeprazole and pantoprazole.[12-15] An epileptic seizure is a transient occurrence of signs and symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[16] Epilepsy is a one of the most common neurological condition occurring in about 1% of the world population. It is second most common disorder after stroke. The etiology of seizure includes genetic and heredity, inflection, metabolic disorder, and brain lesion.[17] The development of novel agents, particularly compounds effective against complex seizures, remains a major focus of anticonvulsant drug research.[18]

In our research program to develop antiulcer, antisecretory and anticonvulsive agents from benzimidazole derivatives. Benzimidazoles structures are categories under several classes of drugs.[19-20] Benzimidazoles are have high melting compounds. The parent compound melts at 170ºC.[21] The benzimidazoles are commonly soluble in polar solvents and sparingly soluble in nonpolar solvents and sparingly soluble in nonpolar solvents. Introduction of nonpolar substituents on different position of benzimidazoles ring increases their solubility in nonpolar solvents e.g. 2 methyl benzimidazoles is soluble in ether. Similarly, introduction of polar groups in ring increases solubility in polar solvents e.g. 2 amino benzimidazoles is soluble in water.[22] Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in treatment of various inflammatory diseases such as arthritis, rheumatisms to relieve the aches and pain of everyday life NSAIDs also exhibit their action by restricting the biosynthesis of prostaglandin, by inhibiting the cyclooxygenase (COX) enzyme involved in the inflammatory cascade.[23-24]

EXPERIMENTAL

MATERIALS AND METHODS

The chemicals used in the present research project work were purchased from Loba, Merck and Fisher scientific chemicals. The melting point of the synthesized compounds were determined in open capillary using LABHOSP melting point apparatus. Thin layer chromatography (TLC) was performed on silica gel plates using Butanol: Ethanol: Water (9:1:1) solvent system. Visualization was done in UV light chamber at 254 nm, iodine chamber. The infrared spectra for the synthesized compounds were recorded using SHIMADZU-FTIR 8400 spectrophotometer using potassium bromide pellet technique and sodium chloride cells for liquid samples. H^1NMR spectra of the synthesized compounds were taken using Bruker ACF-300 MHz spectrometer using tetramethyl silane (TMS) as an internal standard. H^1NMR spectra were recorded with pyridine/chloroform as a solvent and the chemical shift data were expressed as δ values relative to TMS.

SYNTHESIS OF COMPOUNDS

The synthesis of compounds is illustrated in Scheme 1, 2, 3 and 4. Details are described as follows.

SCHEME 1

1. PREPARATION OF BENZIMIDAZOLE 2-THIOLATE

A mixture of 32.4 g(0.1 mol) of Ortho phenyldiamine (OPD) & 19.5g (0.1 mol) of Potassium hydroxide (KOH) and 26 g (0.1 mol) of carbon disulphide (CS2) with 300 ml of 95% ethanol and 45 ml of water in round bottom flask was reflux for 3 hour . Norit was then added cautiously & after mixture has been heated for 10 minutes. Norit was removed by filtration. A yellowish filtrate of Benzimidazole 2- thiolate was collected in conical flask.

2. PREPARATION OF BENZIMIDAZOLE 2-THIOL

Filtrate of benzimidazole 2-thiolate was heated at 60-70^{0}C later mix 300ml of water followed by 25 ml of glacial acetic acid with efficient stirring. The product Benzimidazole 2- thiol was separated as glisten white crystal. Then it was placed in refrigerator for 3 hours to complete crystallization.

SCHEME 2

2.1. PREPARATION OF SUBSTITUTED PYRIMIDINE

1. Preparation of Ethanimide

Acetonitrile, hydrochloric acid and methanol was taken in double necked conical flask in ratio 1:3:1 followed by the ammonia solution, the pressure was maintained less than 26.6kPa by using null vacuum, cooling was maintained up to 30 ° C with the help of water which flowed continually, the reaction has been carried out for 3 hours, ethanimide crystals were collected on upper surface of solution. The yield of 85% Nature: a white long-prism-like crystal. 177-178 ° C melting point. Soluble in water, soluble in acetone, ethyl ether. Extreme moisture absorption.

1. Preparation of 2-Methyl, 6-Alkylpyrimidine-4-ol

In 250 ml round bottom flask 5.8 g(0.1 mol) of ethanimide and 10.80 ml (0.1 mol) alkyl acetoacetate were placed then sodium ethoxide was added and refluxed for 2-3 hours Reaction mixture filtered and 2-Methyl 6-pyrimidine-4-ol was collected the solid.

2. Preparation of 4-Chloro 2 Methyl, 6-Alkylpyrimidine- 4- ol

In 250 ml round bottom flask 2.5gm (0.1 mol) of 2,6 alkylprimidine-4-ol and 10 ml (0.1 mol) thionyl Chloride was placed followed by few pieces of porcelain and refluxed for 2-3 hours, the reaction mixture was filtered and solid product of 4-Chloro 2 methyl,6 Alkyl pyrimidine- 4-ol was collected.

SCHEME 3

1. PREPARATION OF 2-(PYRIMIDINYLSULFINYL) BENZIMIDAZOL DERIVATIVES

1.1 Preparation of 2-[(2, 6- Alkylpyrimidin-4-Yl) Sulfanyl] 5- Alkyl-1*H*- Benzimidazole

Sodium hydroxide 0.13 g (3.3mol) was slowly added over 5 minutes to a stirred solution of 2-mercaptobenzimidazole 0.29 g (1.4 mol) in ethanol 20 ml. 4-chloro 2 methyl, 6 alkylpyrimidine- 4-ol was slowly added to the 2- mercaptobenzimdazole solution at 0 ^{0}C, and stirred for 12 hours at room temperature. After the solvent was removed under reduced pressure, the residue was poured into 10% NaHCO3 solution and extracted with ethyl acetate. The organic layer was dried over MgSO4, and concentrated. The desired coupling product 0.35 g, (74%) was obtained as a semi-solid.

1.2 Preparation of 2-[(2,6- Alkylpyrimidin-4-Yl) Sulfinyl] 5- Alkyl-1*H* Benzimidazole

A solution of *m*-chloroperbenzoic acid 0.30 g (1.75 mol) was added drop wise to solution of 2-[(2 methyl,6-alkylpyrimidin-4-yl) sulfinyl]-5-alkyl- 1*H*-benzimidazole in 35 ml of CH2Cl2 at 0 ^{0}C. The reaction mixture was stirred at the same temperature for an hour. The solution was washed with 10% Na2CO3 solution and dried over MgSO4. After removal of the solvent, the residue was purified by column chromatography.2-[(2 alkyl,6-alkylpyrimidin-4-yl) sulfinyl]-5-alkyl-1*H*benzimidazole was obtained in 89% yield. The structure of final compounds was characterized by, IR, NMR techniques.

SCHEME 4

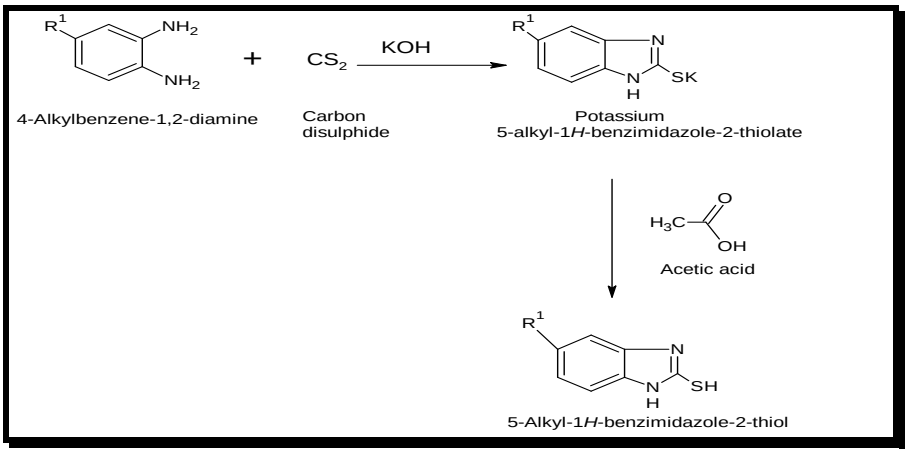
1. Preparation of 2-amino 1*H*- benzimidazole derivative

A mixture of 1*H*-benzimidazole-2-thiol derivative (0.1mol) was refluxed for 2 hrs along with hydrochloric acid and substituted aniline (0.1mol) to yield the crude product of 2-amino 1*H*-benzimidazole derivative. The crude products were recrystallized from ethanol to obtain

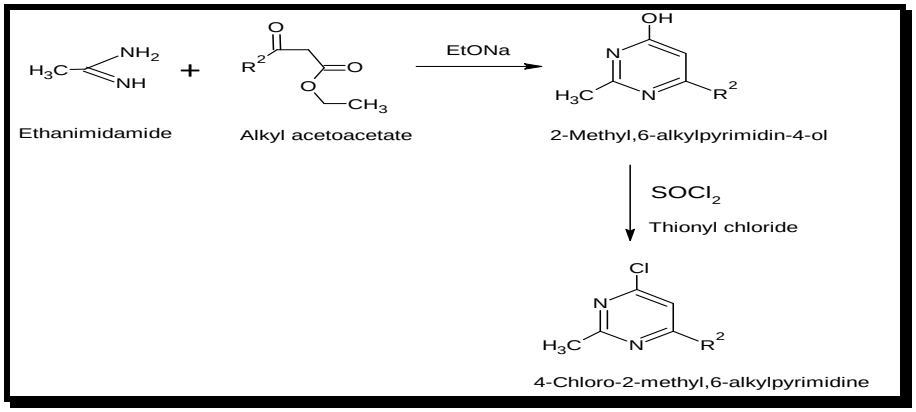
pure product. Using same procedure twelve derivatives were synthesized by using aniline derivatives.

1.2 Preparation of 1-alkyl-2-amino benzimidazole derivative

To a mixture of 2-amino benzimidazole derivative (2mmol) in dimethyl formamide (10 mL) and sodium hydride (60%, 2.4 mmol) was added at 0 °C. After completion of addition the temperature of the reaction mixture was slowly raised to room temperature and stirred at this temperature for 1h. The reaction mixture was again cooled to 0 °C and the respective ethyl iodide (2.4 mmol) was added. The temperature of the reaction mixture was then allowed to warm to room temperature and stirred for 2h and water (50 mL) was slowly added to reaction mixture and extracted with ethyl acetate (2×25 mL). The organic layer was washed with water (2×25 mL), brine and dried over anhydrous magnesium sulfate and concentrated under vacuum to yield the corresponding N-substituted derivative. The crude compounds were recrystallized from ethanol to obtain pure products. Using same procedure twelve derivatives were synthesized by using ethyl iodide.



SCHEME 1



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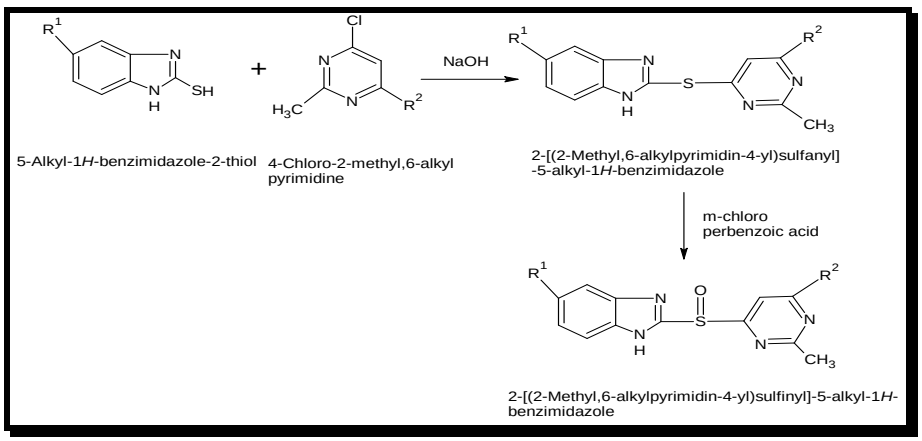
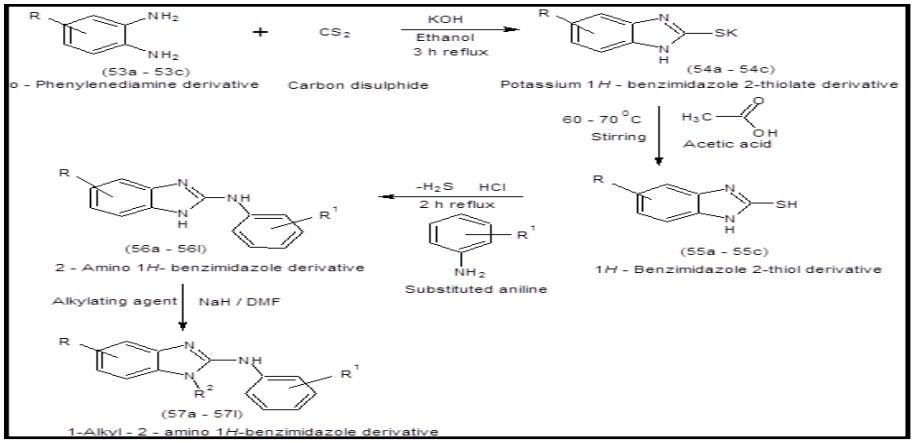


SCHEME 3



SCHEME 4

Table No.1: Spectral data of synthesized compound (2-Pyrimidinylsulfinyl Benzimidazole).

Code	Compound. Name	IR (KBr)cm^{-1}/1H NMR (CDCl3, δ)
54a	2-[(2,6-dimethylpyrimidin-4-yl)sulfinyl]-1*H*-benzimidazole	IR (KBr, v, cm-1):3450 (O-H), 3050 (C-H), 1600 (N-H), 1483 (C-H), 825 (C-H); H-NMR(200 MHz, CDCl3):δ 3.65 (d, J=15.46, 1H, CH2-Fu), 3.81 (d, J=15.28, 1H, HA), 3.85 (dd, J=1.86 & 15.28, 1H, HB), 4.91 (d, J=15.47, 1H, CH2-Fu), 6.09 (d, J=3.08, 1H, H3-Fu), 6.26 (t, 1H, H4-Fu), 6.54 (d, J=2.08, 1H, H-2), 7.10-7.39 (m, 4H, H3, H4, & H5-Ph and H5-Fu).
54b	2-[(6-ethyl-2-methylpyrimidin-4-yl)sulfinyl]-1*H*-benzimidazole	IR (KBr, v, cm-1): Vmax C=O 1683 cm-1; H-NMR(200 MHz, CDCl3):δ 3.65 (d, J=15.29, 1H, CH2-Fu), 6.09 (d, J=3.11, 1H, H3- Fu), 6.23 (m, 1H, H4-Fu), 6.99 (m, 1H, H4-Ph), 7.19 (d, J=1.17, 1H, H-2), 7.23-7.29 (m, 3H, H3, & H5-Ph and H5-Fu)
54c	2-[(2-methyl-6-propylpyrimidin-4-yl)sulfinyl]-1*H*-benzimidazole	IR (KBr, v,cm-1): Vmax C=O 1688cm-1; 1H-NMR (200 MHz, CDCl3):δ 3.65 (d, J=15.15, 1H, HA), 3.82(d, J=15.48, 1H, CH2-Fu), 3.90 (d, J=15.15, 1H, HB), 4.87 (d, J=15.47, 1H, CH2-Fu), 6.00 (s, 1H, H-2), 6.15 (d, J=3.04, 1H, H3-Fu), 6.25 (t, 1H,H4-Fu), 6.85 (t, 2H, H3, & H5-Ph), 7.22-7.37 (m, 2H, H4-Ph and H5-Fu).
54d	2-[(2,6-dimethylpyrimidin-4-yl)sulfinyl]-5-methyl-1*H*-benzimidazole	IR (KBr, v, cm-1):3410 (O-H), 3020 (C-H), 1500 (N-H), 1465 (C-H), 780 (C-H); H-NMR(200 MHz, CDCl3):δ 3.77 (d, J=15.80, 1H, CH2-Fu), 3.91 (d, J=15.42, 1H, HA), 3.92 (dd, J=1.88 & 15.44, 1H, HB), 5.10 (d, J=15.65, 1H, CH2-Fu), 6.22 (d, J=3.18, 1H, H3-Fu), 6.36 (t, 1H, H4-Fu), 6.55 (d, J=2.28, 1H, H-2), 7.20-7.35 (m, 4H, H3, H4, & H5-Ph and H5-Fu).
54e	2-[(6-ethyl-2-methylpyrimidin-4-yl)sulfinyl]-5-methyl-1*H*-benzimidazole	IR (KBr, v, cm-1): Vmax C=O 1710 cm-1; H-NMR(200 MHz, CDCl3):δ 3.87 (d, J=15.32, 1H, CH2-Fu), 6.18 (d, J=3.21, 1H, H3- Fu), 6.38 (m, 1H, H4-Fu), 7.11 (m, 1H, H4-Ph), 7.29 (d, J=1.19, 1H, H-2), 7.28-7.34 (m, 3H, H3, & H5-Ph and H5-Fu)
54f	5-methyl-2-[(2-methyl-6-propylpyrimidin-4-yl)sulfinyl]-1*H*-benzimidazole	IR (KBr, v,cm-1): Vmax C=O 1695cm-1; 1H-NMR (200 MHz, CDCl3):δ 3.82 (d, J=15.28, 1H, HA), 3.92(d, J=15.48, 1H, CH2-Fu), 3.90 (d, J=15.25, 1H, HB), 4.94 (d, J=15.49, 1H, CH2-Fu), 6.12 (s, 1H, H-2), 6.18 (d, J=3.14, 1H, H3-Fu), 6.28 (t, 1H,H4-Fu),6.87 (t, 2H, H3, & H5-Ph),7.28-7.39(m, 2H, H4-Ph and H5-Fu).
54g	2-[(2,6-dimethylpyrimidin-4-yl)sulfinyl]-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1) Vmax C=O 1677cm-1; 1H-NMR (200 MHz, CDCl3):δ d 1.58 (d, J=7.0, 3H, CH3), 3.78 (d, J=15.57, 1H, CH2-Fu), 4.01 (q, J=7.00, 1H, CHCH3), 4.85 (d, J=15.48, 1H, CH2-Fu), 5.92 (s, 1H,CH), 6.14 (d, J=15.48 1H,CH2-Fu), 5.92 (s, 1H, CH), 6.14(d, J=3.09, 1H, H3-Fu), 6.23 (t, 1H, H4-Fu), 7.23- 7.31 (m, 2H, H4-Ph and H5-Fu).
54h	2-[(6-ethyl-2-methylpyrimidin-4-yl)sulfinyl]-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1): Vmax C=O 1688cm-1; 1H-NMR (200 MHz, CDCl3):δ 2.65 (s, 3H, CH3), 3.88(d, J=15.48, 1H, HA), 4.11 (dd, J=2.05 & 15.84, 1H, HB), 7.03-7.18 (m, 2H, H3 & H5-Ph), 7.25 (m, 1H, H4-Ph), 7.31 (d, 1H, J=1.61 H2), 7.71 (d, J=8.74, 1H,H3-Py), 7.93 (d, J=8.73,1H,H4-Py),
54i	2-[(2-methyl-6-propylpyrimidin-4-yl)sulfinyl]-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1) Vmax C=O 1672cm-1; 1H-NMR (200 MHz, CDCl3):δ 1.61-2.35 (m, 10H), 3.66 (d, J=14.48, 1H,HA), 3.91 (d, J=14.94, 1H,HB), 6.66 (s, 1H,H-2), 7.16-7.36 (m, 3H, H3, H4 & H5-Ph).

Table No. 2: Spectral data of synthesized compound (2 Amino Benzimidazole).

Code	Compound. Name	IR (KBr)cm^{-1}/1H NMR (CDCl3, δ)
57a	*2*(4-chlorophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm-1):1590 (NH),1438(C-C),1213(CN), 1600(CN),750 (CCl), H-NMR (500 MHz, CDCl3):δ 9.15 - 9.10 (m, 1H), H4-Fu),8.46 (ddd, J=24.1,1.72,1.8 Hz, 1H, HB), 8.25-8.21 (m, 2H,), 4.91 (dq, J=23.4, 6.1 Hz, 1H), (d, J=12.3 Hz, 1H)
57b	*2*(2-chlorophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm-1):1622 (NH),1504(C-C),1670(CN), 1261(CN),738 (CCl),3010(CH) H-NMR (500 MHz, CDCl3):δ 9.15 - 9.10 (m, 1H), H4-Fu),8.46 (ddd, J=24.1,1.72,1.8 Hz, 1H, HB), 8.25-8.21 (m, 2H,), 4.91 (dq, J=23.4, 6.1 Hz, 1H), (d, J=12.3 Hz, 1H)
57c	2(4-nitrophenyl) amino 1-ethyl 1*H*-benzimidazole	IR (KBr, v, cm-1): 3030 cm-1(CH); 1519 (NH), 1635(C-C),1635(CN), 12653(CN),3030(CH) H-NMR (500 MHz, CDCl3):δ 9.20 - 9.14 (m, 1H), H4-Fu),8.59 (ddd, J=25.1,1.74,1.7 Hz, 1H, HB), 8.35-8.22 (m, 2H,), 5.41 (dq, J=23.8, 6.3 Hz, 1H), (d, J=12.5 Hz, 1H)
57d	*2*(4-bromophenyl) amino 1-ethyl-1*H*-benzimidazole	IR (KBr, v, cm-1): 3050 (CH); 1623 (NH), 1500(C-C),1676(CN), 1253(CN),740(CBr) H-NMR (500 MHz, CDCl3):δ 9.34 - 9.44 (m, 1H), H4-Fu),8.44 (ddd, J=24.8,1.763,1.8 Hz, 1H, HB), 8.30-8.22 (m, 2H,), 5.43 (dq, J=24.1, 6.4 Hz, 1H), (d, J=12.8 Hz, 1H)
57e	*2*(4-chlorophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1): 3020 (CH); 1635 (NH), 1488(C-C),1656(CN), 1242(CN),820(CCl) H-NMR (500 MHz, CDCl3):δ 9.22 - 9.18 (m, 1H), H4-Fu),7.85 (ddd, J=23.9,1.76,1.5 Hz, 1H, HB), 7.40-7.52 (m, 2H,), 5.23 (dq, J=25.1, 6.8 Hz, 1H), (d, J=12.9Hz, 1H)
57f	*2*(2-chlorophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1): 3055 (CH); 1678 (NH), 1480(C-C),1670(CN), 1268(CN),933(CCl) H-NMR (500 MHz, CDCl3):δ 9.21 - 9.17(m, 1H), H4-Fu),7.80 (ddd, J=24.3,1.88,1.8 Hz, 1H, HB), 7.65-7.72 (m, 2H,), 5.42 (dq, J=25.5, 6.9 Hz, 1H), (d, J=13.1Hz, 1H)
57g	2(4-nitrophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1): 1590 (NH), 1500(C-C),1600(CN), 1260(CN),1480(CNO2) H-NMR (500 MHz, CDCl3):δ 9.38 - 9.42 (m, 1H), H4-Fu),8.42 (ddd, J=24.6,1.73,1.9 Hz, 1H, HB), 8.32-8.28 (m, 2H,), 5.48 (dq, J=24.2, 6.7 Hz, 1H), (d, J=12.5 Hz, 1H)
57h	*2*(4-bromophenyl) amino 1-ethyl-5-nitro-1*H*-benzimidazole	IR (KBr, v, cm-1): 3040 (CH); 1642 (NH), 1550(C-C),1688(CN), 1265(CN),1490(CNO2) H-NMR (500 MHz, CDCl3):δ 9.34 - 9.44 (m, 1H), H4-Fu),9.14 (ddd, J=24.3,1.63,1.6 Hz, 1H, HB), 8.20-8.24 (m, 2H,), 5.48 (dq, J=24.2, 6.5 Hz, 1H), (d, J=12.7 Hz, 1H)
57i	2(4-chlorophenyl) amino 1-ethyl-5-chloro-1*H*-benzimidazole	IR (KBr, v, cm-1): 1660 (CN); 1570 (NH), 1514(C-C),1688(CN), 1365(CN),740(CCl) H-NMR (500 MHz, CDCl3):δ 9.02 - 9.08 (m, 1H), H4-Fu),7.95(ddd, J=24.7,1.80,1.85 Hz, 1H, HB), 7.90-7.95 (m, 2H,), 5.92 (dq, J=25.7, 6.6 Hz, 1H), (d, J=12.9Hz, 1H)
57j	2(2-chlorophenyl)amino 1-ethyl-5-chloro-1*H*-benzimidazole	IR (KBr, v, cm-1): 1690 (CN); 1590 (NH), 1490(C-C),1656(CN), 1330(CN),650(CCl) H-NMR (500 MHz, CDCl3):δ 8.92 - 8.88 (m, 1H), H4-Fu),7.75(ddd, J=24.6,1.90,1.9 Hz, 1H, HB), 7.80-7.95 (m, 2H,), 5.85 (dq, J=25.8, 6.5 Hz, 1H), (d, J=12.8Hz, 1H)
57k	2(4-nitrophenyl) amino 1-ethyl-5-chloro-1*H*-benzimidazol	IR (KBr, v, cm-1): 1620 (NH), 1512(C-C),1615(CN), 1275(CN),1490(CNO2) H-NMR (500 MHz, CDCl3):δ 9.58 - 9.62 (m, 1H), H4-Fu),9.22 (ddd, J=24.3,1.65,2.1 Hz, 1H, HB), 8.42-8.38 (m, 2H,), 5.38 (dq, J=24.4, 6.8 Hz, 1H), (d, J=12.8 Hz, 1H)
57l	*2*(4-bromophenyl) amino 1-ethyl-5-chloro-1*H*-benzimidazole	IR (KBr, v, cm-1): 1660 (CN); 1537 (NH), 1490(C-C),1656(CN), 1330(CN),730(CCl),613(CBr) H-NMR (500 MHz, CDCl3):δ 8.80 - 8.75(m, 1H), H4-Fu),7.85(ddd, J=25.6,1.90,1.9 Hz, 1H, HB), 7.80-7.95 (m, 2H,), 5.65 (dq, J=24.8, 6.5 Hz, 1H), (d, J=11.8Hz, 1H)

PHARMACOLOGICAL EVALUATION

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of College, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), Government of India.

Preliminary pharmacological screening was performed, which includes approximate toxicity testing (LD50) and antiulcer activity. The LD50 of the test compounds performed on the rats as per the OECD guidelines for selecting the dose. The LD50 of all the derivatives was found >200mg/kg.

1. Antiulcer activity

Antiulcer activity was carried out by Aspirin-induced gastric ulcer model, where ulceration induced by Acetylsalicylic acid (ASA) drug.

Procedure

Albino rats of either sex weighing between (160-200 g) were divided into 11 groups each groups contain six animal (n=6) and drugs/vehicle was administered as, Group I was served as normal control given with vehicle (2 ml/kg tween 80) only. Group II (pantoprazole 25 mg/kg body weight) with standard drug, and groups III, IV, V,VI, VII,VIII,IX, X and XI were treated with doses of (2 pyrimidinylsulfinyl Benzimidazole derivatives) with dose 200mg/kg body weight respectively, per orally. The animals were then fasted (with free access to water) for a period of 24 h so as to ensure complete gastric emptying and a steady state gastric acid secretion. The 24 h fasted animals were again administered with the drugs/vehicle on the morning of the experiment. Sixty minutes after administration of the drugs/vehicle, Acetylsalicylic acid (ASA) was administered in a dose of 300 mg/kg body weight orally to all the animals. Food was withheld for a duration of 5 more hours. Animals were then sacrificed by an overdose of anesthetic ether.

The abdomen was opened and a ligature is placed around the esophagus close to the diaphragm. The stomach is removed, and the contents are drained in a centrifuge tube. Along the greater curvature the stomach is opened and pinned on a cork plate. The mucosa is examined for ulcers microscopically with the help of hand lens (10x). Gastric juice collected into centrifuge tubes and centrifuged at 1000 rpm for 10min and volume was noted. The pH of the gastric juice was recorded by pH meter. In the rat, the upper two fifths of the stomach form the rumen with squamous epithelium and possess little protective mechanisms against the corrosive action of gastric juice. Below a limiting ridge, in the glandular portion of the stomach, the protective mechanisms are better in the mucosa of the medium two fifths of the stomach than in the lowest part, forming the antrum. Therefore, lesions occur mainly in the rumen and in the antrum. The mucosal surface was then gently scraped with a blunt surface to collect the adherent mucus.

An ulcer index UI is calculated:

$$UI = UN + US + UP \times 10^{-1}$$

- UN= average of number of ulcers per animal.
- US = average of severity score.
- UP = percentage of animals with ulcers.

2. Antisecretory activity

Antisecretory activity was performed in fasting Wistar strain rats of either sex weighing between (160-200 g) were divided into 11 groups of 6 rats in each. Group I was served as normal control given with vehicle only. Group II with standard drug, and groups III, IV, V, VI, VII, VIII and IX were treated with doses of BD (2 pyrimidinylsulfinyl Benzimidazole derivatives) Respectively. After 30 min ASA was administered at a dose of 300 mg/kg, and after 6 h rats were sacrificed by using anesthetic ether and their stomachs were dissected out for determination of gastric lesions, washed in warm water and examined for ulcers microscopically with the help of hand lens (10x).

Gastric juice collected into centrifuge tubes and centrifuged at 1000 rpm for 10min and volume was noted. The pH of the gastric juice was recorded by pH meter and the gastric content is subjected for analysis of free and total acidity. Total acidity of the gastric juice was titrated with 0.1N NaOH, using 2% phenolphthalein as indicator.

Acidity was calculated by using the formula

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality of NaOH}}{\text{meq /lt/ 100g}} \times \frac{100}{0.01}$$

5. Anticonvulsant Activity

The electroshock assay in rat is used primarily as in indication for compounds which are effective in grand mal epilepsy. Tonic hind limb extension is evoked by electric stimuli which are suppressed by anti-epileptics but also by other centrally acting drugs.

Procedure

The rats (190-210g, body weight) of either sex were employed. They were fasted over night but had free access of water. The animals were first tested by giving maximum current of 150mA for 0.2 sec duration through electroconvulsometer (Techno, India) using corneal electrodes. Only those animals showing characteristics hind limb were selected.

The selected animals were divided into no. of groups of 6 animals each. These animals were treated with control 0.3mL 1% w/v solution of tween 80, standard (phenytoin sodium, dose: 20mg/kg) and test groups (Comp. 57a-57l, dose: 20mg/kg) were given by oral route. After 1h all animals received shock (150mA for 0.2 sec) and the convulsions were induced. The duration of extensor tonus was noted. The complete abolition of hind leg tonic extensor or reduction time was also noted. The onset of action and duration of action were recorded.

RESULT AND DISCUSSION

The 2-(pyrimidinylsulfinyl) & 2-Amino Benzimidazole compound was successfully prepared by developed process and further purified using different solvents the compound was recrystallized by using ethanol and checked the purity by thin layer chromatographic techniques.

DISCUSSION

The antiulcer of test compounds was performed in the Albino rats of Wister strain. Ulcer induced by acetylsalicylic acid as control dose. The test compound 54c (36.25 ± 1.10**), 54f (72.87**), 54g(70.57**) & 54i (75.15***) showed significant antiulcer activity compared with the standard drug pantoprazole (76.16).

with Standard drug. While the Compound 54c (36.25 ± 1.10**), 54d (35.21 ± 1.21***), 54f (37.35 ± 1.10**) and 54g (38.20 ± 1.07*) possess good Antisecretory activity. The electroshock assay in rat shows test compound 57b(81.07±3.02), 57c(74.15±2.65), 57e(75.31±2.84), 57f(73.87±3.07), 57i(76.51±2.85), 57k(87.39±1.15) and 57l(86.78±1.17) significant anticonvulsant activity when compared with standard drug phenytoin sodium. (88.99±0.96).

Table No.3: Anti-ulcer effect of 2-(pyrimidinylsulfinyl) benzimidazole derivatives

Group No.	Group specification	Number of Ulcer	Ulcer Score	Total ulcer index	% inhibition of Ulcer
I	Control (ASA)	4.83 ± 0.54	2.5±0.22	17.33	-
II	Standard (PTZ)	0.33 ± 0.21	0.5±0.12	4.13	76.16
III	54 a	3.33± 0.35	2.16±0.15	9.50	45.20
IV	54 b	2.16± 0.52	1.83±0.10	8.32	51.99
V	54 c	0.66± 0.20	0.58±0.08	4.50	74.03**
VI	54 d	3.01± 0.77	2.02±0.23	10.08	41.83
VII	54 e	1.80 ± 0.24	1.75±0.21	8.20	52.68
VIII	54 f	0.55± 0.22	0.75±0.11	4.70	72.87**
X	54 g	0.62 ± 0.21	0.84±0.04	5.10	70.57**
XX	54 h	1.16± 0.40	1.41±0.51	11.02	37.10
XXI	54 i	0.55 ± 0.35	0.58±0.33	4.40	75.15***

Results are means ± SE of the numbers of animals in parenthesis.
Different from control group (ANOVA, and Dunnett's test $p < 0.05$; $p < 0.01$).

Table No. 4: Anti-Secretory activity of 2-(pyrimidinylsulfinyl) benzimidazole derivatives.

Treatment	Volume (ml)	pH	Total acidity
CTL Drug (ASA)	4.76 ± 0.12	2.23±0.14	93.23± 1.89
STD Drug (PNTZ)	3.19 ± 0.07	5.12 ± 0.03	32.73 ± 1.07
Test Compound (n = 9)			
54a	2.89 ± 0.05	3.63 ± 0.15	47.70 ± 1.12
54b	3.12 ± 0.05	3.98 ± 0.09	54.13 ± 1.23
54c	4.02 ± 0.20	4.13 ± 0.03	36.25 ± 1.10**
54d	4.82 ± 0.04	4.25 ± 0.17	35.21 ± 1.21***
54e	5.02 ± 0.06	3.01 ± 0.05	68.15 ± 1.45
54f	4.08 ± 0.10	4.45 ± 0.03	37.35 ± 1.10**
54g	3.37± 0.11	4.65 ± 0.08	38.20 ± 1.07*
54h	5.17±0.07	3.42 ± 0.03	82.21 ±1.68
54i	5.32±0.12	3.21 ± 0.02	75.15 ± 0.15

Results are means ± SE of the numbers of animals in parenthesis.
Different from control group (ANOVA, and Dunnett's test $p < 0.05$; $p < 0.01$).

Table No. 5: Anticonvulsant activity of 2-Amino benzimidazole derivatives.

Test Comp	Extensor in sec Mean	% inhibition
Ctrl	14.83±0.59	00
STD	1.63±0.16	88.99±0.96***
7a	12.5±0.70	15.52±4.70
57b	2.70±0.35	81.07±3.02**
57c	3.80±0.29	74.15±2.65**
57d	7.03±0.49	52.08±5.01
57e	3.63±0.38	75.31±2.84**
57f	3.83±0.33	73.87±3.07**
57g	7.13±0.36	51.42±4.36
57h	5.93±0.87	60.10±5.49
57i	3.43±0.28	76.51±2.85**
57j	5.66±0.68	61.45±5.05
57k	1.86±0.17	87.39±1.15***
57l	1.96±0.22	86.78±1.17**

Dose of STD and test group 20mg/kg body weight, No. of animal in group (n) = 6
Values are the mean ± SEM, table follows one way ANOVA

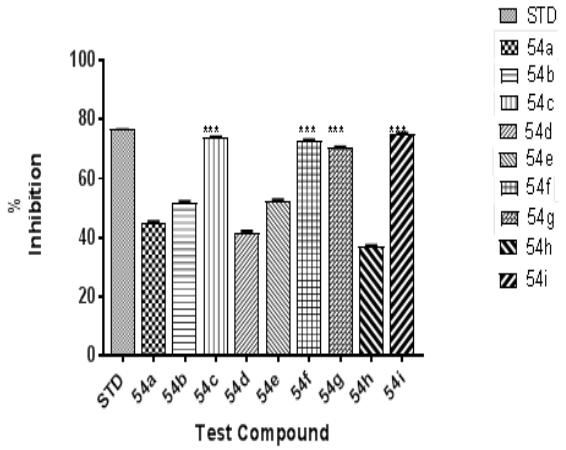


Figure No: 1 Antiulcer activity of 2-(pyrimidinylsulfinyl) benzimidazole.

Note: Antiulcer activity of the test compounds were compared w.r.t control. Data are expressed as % inhibition ± S.E.M. and analysed by one way ANOVA followed by Dunnett's test was applied to determine the significances of the difference between the standard group and rats treated with the test compounds. The differences in results were considered significant when. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$ Vs STD. All statistical calculations were carried out using Graph Pad® Prism 7.0 (USA) statistical software.

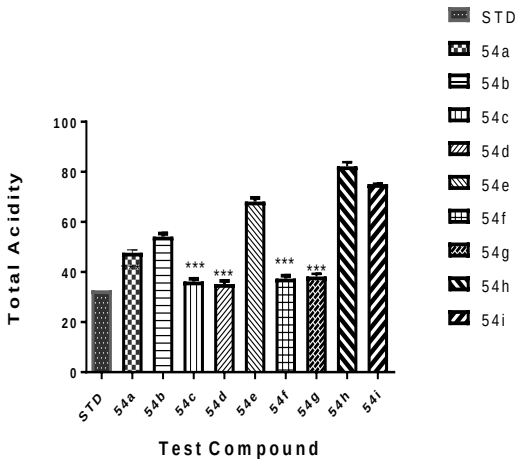


Figure No: 2 Antisecretory activity of 2-(pyrimidinylsulfinyl) benzimidazole.

Note: Antiulcer activity of the test compounds were compared w.r.t control. Data are expressed as % inhibition ± S.E.M. and analysed by one way ANOVA followed by Dunnett's test was applied to determine the significances of the difference between the standard group and rats treated with the test compounds. The differences in results were considered significant when. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$ Vs STD. All statistical calculations were carried out using Graph Pad® Prism 7.0 (USA) statistical software.

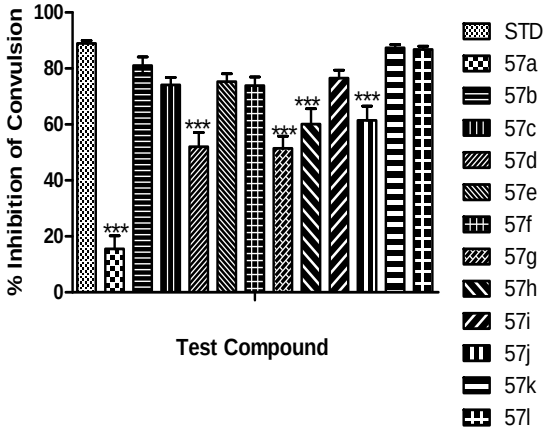


Figure No: 5 Anticonvulsant activity of synthesized compounds.

Note: Anticonvulsant activity of the test compounds were compared w.r.t control. Data are expressed as % inhibition ± S.E.M. and analysed by one way ANOVA followed by Dunnett's test was applied to determine the significances of the difference between the standard group and rats treated with the test compounds. The differences in results were considered significant when. $^{*}p< 0.05$, $^{**}p< 0.01$, $^{***}p< 0.001$ Vs STD. All statistical calculations were carried out using Graph Pad® Prism 3.0 (USA) statistical software.

CONCULSION

All the synthesized 2-(pyrimidinylsulfinyl) benzimidazole derivatives were screen their pharmacological activities of test compounds were performed in the Albino rats of Wister strain. The Antiulcer activity of compounds was done by Aspirin induces gastric Ulcer method induction of ulcer by acetylsalicylic acid as control dose. The test compounds showed significant antiulcer activity compared with the standard drug pantoprazole. The Compound 54c, 54f, 54g and 54i possess significant antiulcer activity when compared with Standard drug. While the Compound 54c, 54d, 54f and 54g possess good Antisecretory activity. Similarly, the 2 Amino benzimidazole derivatives compounds were screen their pharmacological and anticonvulsant activity by electro shock method respectively. It was observed that compounds 57b, c, e, f, i, k, and l showed good anticonvulsant activity where as other compounds possess significant activity with compared to standard drug phenytoin sodium.

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REFERENCES

1. M. Kidwai A. Jahan et all "Polyethylene glycol: A recyclable solvent system for the synthesis of benzimidazole derivatives using CAN as catalyst" J. Chem. Sci., 2010; 122(4): 607-612.
2. MR Mohammadizadeh, SZ Taghavi "Trifluoroacetic acid as an efficient catalyst for the room temperature synthesis of 2-Aryl-1-arylmethyl-1H-1,3-benzimidazole derivatives in Aqueous Media" E.J. of chemistry, 2011; 8(1): 101-1-6.
3. VD Patil, G.Medha et all "A mild and efficient synthesis of Benzimidazole by using lead peroxide under solvent free conditions" Der Chemica Sinica, 2010; 1(2): 125-129.
4. R. Somani, S. Pawar et all "Microwave Assisted synthesis and antimicrobial activity of some Schiffs bases" I. J. of chemitech Research, 2010; 2(2): 860-864.
5. M.A. Pasha, A. Nizam "Amberlite IR-120 catalyzed microwave-assisted rapid synthesis of 2-aryl-benzimidazoles" Journal of Saudi chemical society, 2012; 16: 237-240.
6. H. Goker, C. Kus, D. Boykin W, S. Yildiz and Altanlar, Bioorg. Med. Chem., 2002; 10: 2589- 2595.
7. H. Goker, S. Ozden, S. Yildiz and D.W. Boykin Eur. J. Med. Chem., 2005; 40: 1062-1074.
8. K.G. Desai and K.R. Desai Bioorg. Med. Chem., 2006; 14: 8271-8295.
9. Khokra SL and Deepika Choudhary. Benzimidazole an Important Scaffold in Drug Discovery, Asian Journal of Biochemical and Pharmaceutical Research, 2011; 3(1): 476-486.
10. Prous, J. R. Drug News Perspect, 1988; 1: 38.
11. Mössner, J.; Caca, K. Eur. J. Clin. Invest, 2005; 35: 469, Devault, K. R. Expert Rev. Gastroenterol. Hepatol, 2007; 1: 197.
12. Sjöström, J.-E.; Fryklund, J.; Kühler, T.; Larrson, H. Antimicrob. Agents Chemother, 1996; 40: 621.
13. Nagata, K.; Satoh, H.; Iwahi, T.; Shimoyama, T.; Tamura, T. Antimicrob. Agents Chemother, 1993; 37.
14. Sato, M.; Souda, S. EP 585722, Chem. Abstr, 1994; 120: 253362.
15. Kurt, K.; Uwe, K.; Ernst, S.; Joerg, S.-B. PCT Int WO 1992004898, Chem. Abstr, 1992; 117: 163853.
16. N. Siddiqui, M. S. Alam, Anticonvulsant and toxicity evaluation of newer 1-{(1-(2-substitutedbenzyl)-1H-benzo[d]imidazol-2-yl)metyl}-3-arylthioueras,Scholars Research Library, 2010; 2(2): 163-171.
17. E. A. Swinyard, J. K. Woodbury, C.E. Penry, Antiepileptic Drugs, Pippenger, Reven Press, New York, 2nd ed., 1982; 5-20.
18. W. Loscher, D. Schmidt, Drug Resistance in Epilepsy, putative Nurobiogenic and clinical mechanism, Epilepsia Res., 1994; 95.
19. Phillips m, A. J. Chem. Soc., 1931; 1143.
20. Oddo B, and Ingraffia F, Gazz. Chim. Et.al, 1952; 62: 1092. /Chem. Abst, 27, 286.
21. Hoebrecker F, Chem. Rev., 1872; 5: 920.
22. Velik J, Baliharova V, Fink-Gremmels J, etal., Res. Ve t . Sci., 2004; 76: 95.
23. E. Limbird, P. B. Molinoff, R. W. Ruddon, Basic of Pharmacology, McGrawHill, New York, Med Res. Rev, 17th ed., 1997; 537.
24. J. H. Wolff, J. M. Baele, Wilson and Gisvild, Textbook of organic Medicinal and Pharmaceutical Chemistry, 8th ed., 1982; 340.