Amitha Sony et al /J. Pharm. Sci. & Res. Vol. 14(9), 2022, 887-893

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis of Novel 1,5-Benzodiazepine Derivatives and their *In Vivo* Antiulcer Activity

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Abstract

Peptic ulcer is an ulcerative disorder of the upper GIT . Stomach ulcer is an ailment that leaves millions across the globe suffering. Even though many anti ulcer medications are available, all of them suffer from various side effects .The chemistry y of 1,5-Benzodiazepines is a very dynamic and challenging area in the field of medicinal chemistry and 1,5-Benzodiazepines possess diverse biological activities. As part of our effort to develop novel 1,5-Benzodiazepine derivatives as antiulcer agents, synthesis, docking and antiulcer screening of ten novel 1,5-Benzodiazepines were carried out. The prepared derivatives were characterized using Infrared,Nuclear magenetic resonance ,mass spectral and CHNS analysis . *In vivo* antiulcer activity was carried out by pyloric ligation method using ranitidine as a positive control. Two of the derivatives exhibited comparable antiulcer activity with that of the standard. It can be concluded that 1,5-Benzodiazepines offer high potential in the search for safe and effective antiulcer agents.

Key Words: Stomach Ulcer, Benzodiazepines, Acute toxicity, Pyloric ligation,

INTRODUCTION

Peptic ulcer disease (PUD) refers to a group of ulcerative disorders of the upper gastric ointestinal tract that require acid and pepsin for their formation[1]. Ulcers differ from gastric itis and erosions in that they extend deeper into the muscularis mucosa. Stomach ulcer is the ailment that leaves millions of patients across the globe suffering. [2.]It is widely accepted that the pathogenesis of the peptic ulcers is still not fully understood. Increased acid secretion and pepsin activity, reduced mucus, bicarbonate secretion, enhanced contractility of the gastric wall and reduced gastric mucosa blood flow represent some of the established pathogenic factors of gastric ulceration.[3] There are several different kinds of ulcers, and their names usually describe their locations in the digestive tract. A duodenal ulcer or peptic ulcer can be found in the small intestines, just past the stomach while a gastric ulcer is located inside the stomach itself. The peptic and duodenal ulcers are usually benign, but gastric stomach ulcers can be cancerous.[4] Stomach ulcer can sometimes become so raw that it will start to bleed.[5]

The three common forms of peptic ulcers include *Helicobacter pylori* associated ulcers, nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, and stress-related mucosal damage (also called stress ulcers).[6]

Various medications including proton pump inhibitors and H2 receptor antagonists are available for the treatment of gastric ulcers,however clinical assessment of these medications have demonstrating side effects,incidences of relapses and drug interactions.[7]

Benzodiazepine derivatives are known to exhibit wide range of pharmacological activities like anti-psychotic,[8,9,10] sedative-hypnotic,[11,12] , anxiolytic,[13] anti-convulsant,[14,15]anti-cancer[16,17] anti-microbial,[18,19]anti-inflammatory,[20,21]anti-viral,[22]analgesic,[23] anti-oxidant,[24,25] anti HIV[26] antiulcer [27,28,29] to name a few.The pioneering work of pharmaceutical scientists across the globe has resulted in the development of novel 1,5-Benzodiazepine analogues as potential drug candidates.

Therefore the studies involving the synthesis and biological evaluation of benzodiazepine analogues is considered to be one of the most rewarding in the field of drug development embracing a wide spectrum of advances in both theoretical and practical relevance.

An efficient synthetic methodology and evaluation of activity against ulcer, of a series of benzodiazepine derivatives had offered a potent tool towards new drug development in the field of GIT disorders. The need for newer antiulcer agents in therapy and the diverse biological activities of 1,5-benzodiazepine derivative s prompted us to synthesize novel analogues of 1,5-benzodiazepines and screen them for their antiulcer activity.

MATERIALS AND METHODS

All the chemicals used in the study were of analytical grade and were procured from spectrum, S.D fine chem and Alfa aesar. The melting points of the synthesized compounds were obtained using open capillary tubesand required no corrections. . The infrared spectrum of the synthesized compounds was recorded using Avatar 370 and the nuclear magentic resonance spectrum was recorded using Bruker Avancell. TMS was used as the internal standard. The mass spectra was recorded using Q-Tof mass spectrometer. Glass plates coated with Silica gel G was used for thin layer chromatographic studies. Ethyl acetate: n-hexane in the ratio 8:2 was used as the mobile phase.

EXPERIMENTAL

STEP I -SYNTHESIS OF 2,4-BIS(SUBSTITUTED PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE (BZ1-BZ10). [30,31]

A mixture of O-Phenylene diamine (0.504g,5mmol,finely ground) and magnesia(MgO,1.5g)was prepared in a mortar and pestle by grinding them together until a fine homogeneous mixture was obtained(5-

10min).Phosphorus oxychloride (0.8ml) was added to this mixture. After 10 min of vigorous stirring, the ketone (10 mmol)was added to this mixture, which was stirred for 0.5hr.The reaction mixture was washed with n-hexane (200ml),dried and solvent evaporated to give crude product. Reaction completeness was checked by using TLC by taking ethyl acetate: ethanol (7:3) as solvent system. Pure product was obtained by recrystallization from ethanol. The physical properties of the synthesized compounds are listed in table in no 1.

The spectral and elemental analysis of the synthesized derivatives are listed below.

2,2,4-TRIMETHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ1)

IR: 3321(N H stretching etching) 2869(Alkyl CH Stretching) ,1450(Aryl C-C stretching) 1200(C-N Stretching)

^{1} HNMR : 9.35 (s,NH) 8.32 (m 9 H)7.123(d, Ar C-H) 7.317(d,CH3) ,

^{13}CNMR: 158.64((C=N),139.91(C,Ar),130.98(CH Ar),39.79(CH_2)

MASS: 188.13(M+)

CHNS analysis Calculated: C(76.55%) H(8.57%) N(14.88%)

Found : C(75.85%) H(8.27%) N(14.54%)

2-METHYL-2,4-DIPHENYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ2)

IR: 3229,(NH stretching), 3001(Aryl C H stretching), 2920(Alkyl CH Stretching) ,1499(Aryl C-C stretching) 1129(C-N Stretching),

^{1} HNMR :7.001(d, Ar CH) 7.097(d,CH3) 7.574(d,CH3)

^{13}CNMR: 154.45((C=N),128.29(C,Ar),132.88(CH Ar),45.79(CH_2)

MASS: 312.18(M+)

Elemental Analysis Calculated: C(76.55%) H(8.57%) N(14.88%)

Found : C(75.58%) H(8.52%) N(14.37%)

2,4-BIS(4-FLUOROPHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ3)

3312 ,(NH stretching), 3010(Aryl CH stretching) 2824(Alkyl CH Stretching) ,1520(Aryl C-C stretching) 1150(C-N Stretching),1299(C-F Stretching)

^{1} HNMR :7.084(d, Ar CH) 7.985(d,CH3) 7.476(d,CH)

^{13}CNMR: 155.36((C=N),128.56(C,Ar),128.48(CH, Ar),33.79(CH_2)

MASS: 352.25 (M+2)

CHNS analysis Calculated: C(75.85%) H(5.21%) F(10.91%) N(8.04%)

Found : C(75.65%) H(5,32%) F(11.41%) N(8.22%)

2,4-BIS(4-CHLORO PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ4)

IR: 3289,(NH stretching)3001(Aryl CH stretching) 2953(Alkyl CH Stretching) ,1502(Aryl C-C stretching) 1099(C-N Stretching) 798(C-Cl Stretching)

^{1} HNMR :7.831(d, Ar CH) 7.901,(d, Ar CH) 7.078(d, Ar CH)

^{13}CNMR: 158.64((C=N),143.55(C,Ar),125.68(CH Ar),29.79(CH_2)

MASS: 381.12(M+1)

CHNS analysis Calculated: C(69.30%) H(4.76%) Cl(18.60%) N(7.35%)

Found : C(69.45%) H(4.63%) Cl(18.52%) N(7.27%)

2,4-BIS(4-METHYL PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ5)

IR: 3229,(NH stretching) 3100(Aryl CH stretching) 2819(Alkyl CH Stretching) 1479(Aryl C-C stretching) 1140(C-N Stretching)

^{1} HNMR :7.507(d, Ar CH) 7.499(d,CH3) 7.216(d, Ar C--H)

^{13}CNMR: 158.64((C=N),139.91(C-C,Ar),130.98(C-H Ar),53.49(CH_2)

MASS: 340.19(M+)

Elemental Analysis Calculated :C(84.67%) H(7.11%) N(8.23%)

Found : C(83.77%) H(7.42%) N(8.41%)

2,4-BIS(2-METHOXY PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ6)

IR : 3329,(NH stretching)3032 (Aryl CH stretching) 2925 (Alkyl CH Stretching),1506(Aryl C-C stretching) 1143((C-N Stretching),

^{1} HNMR :7.939 (d, 3 Ar CH) 7.484 (d,CH3) 6.497 (t,OCH3),

^{13}CNMR: 148.34((C=N),139.91(C,Ar),140.98(CH Ar),53.79(CH_2)

MASS: 372.18(M+),

CHNS analysis calcd: C(77.39%) H(6.49%) N(7.52%) O(8.59%)

Found : C(78.19%) H(6.27%) N(8.13%) O(8.32%)

2,4-BIS(2-CHLORO PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ7)

IR: 3310 (NH stretching)3053(Aryl CH stretching) 2862(Alkyl CH Stretching) ,1525(Aryl C-C stretching) 1079(C-N Stretching)658(C-Cl stretching)

^{1} H NMR :7.871(d, Ar CH) 7.797(d,Ar CH) 7.081(d, CH3)

^{13}CNMR: 158.64((C=N),139.91(C,Ar),130.98(CH Ar),38.45(CH_2)

MASS: 381.16(M+1)

Elemental Analysis Calculated: C(69.30%) H(4.76%) Cl(18.60%) N(7.35%)

Found : C(70.19%) H(4.57%) Cl(18.38%) N(7.25%)

2,4-BIS(4-METHOXY PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE(BZ8)

IR: 3229,(NH stretching)3020(Aryl CH stretching) 2781(Alkyl CH Stretching) 1499(Aryl C-C stretching) 1064(C-N Stretching),702(C-Cl stretching)

^{1} HNMR :7.971(d, Ar CH) 6.879(d, Ar CH) 6.999(d,CH3)

^{13}CNMR: 148.65((C=N),135.29(C -C,Ar),130.98(CH Ar),39.79(CH_2)

MASS: 372.17 (M+)

Elemental Analysis Calculated: C(77.39%) H (6.49%) N(7.52%) O(8.59%)

Found : C(79.03%) H (6.20%) N(7.86%) O(8.34%)

2,4-BIS(4-METHYL PHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE (BZ9)

IR: 3305,(NH stretching)3029(Aryl CH stretching) 2900(Alkyl CH Stretching) 1570(Aryl C-C stretching) 1198(C-N Stretching)

^{1} HNMR :7.906(d, Ar CH) 7.460(d,CH3) 6.400(d,CH3)

^{13}CNMR: 145.64((C=N),139.91(C-C,Ar),147.98(C-H Ar),

MASS: 340.23(M+),

Elemental Analysis Calculated: C(84.67%) H(7.11%) N(8.23%)

Found : C(85.33%) H(7.18%) N(8.33%)

2,4-BIS(2-FLUOROPHENYL)-2-METHYL-2,3-DIHYDRO-1*H*-1,5-BENZODIAZEPINE (BZ10)

IR: 3250(NH stretching) ,3070(Aryl CH stretching), 2915(Alkyl CH Stretching) ,1499(Aryl C-C stretching) ,1098(C-N Stretching)

[1] HNMR :7.737(d, Ar CH) 7.075(d,CH3) 6.208(t,OCH3)

[13]CNMR: 167.64((C=N),128.91(C,Ar),134.98(C-H Ar), 41.26(CH_2)

MASS: 352.19 (M+2)

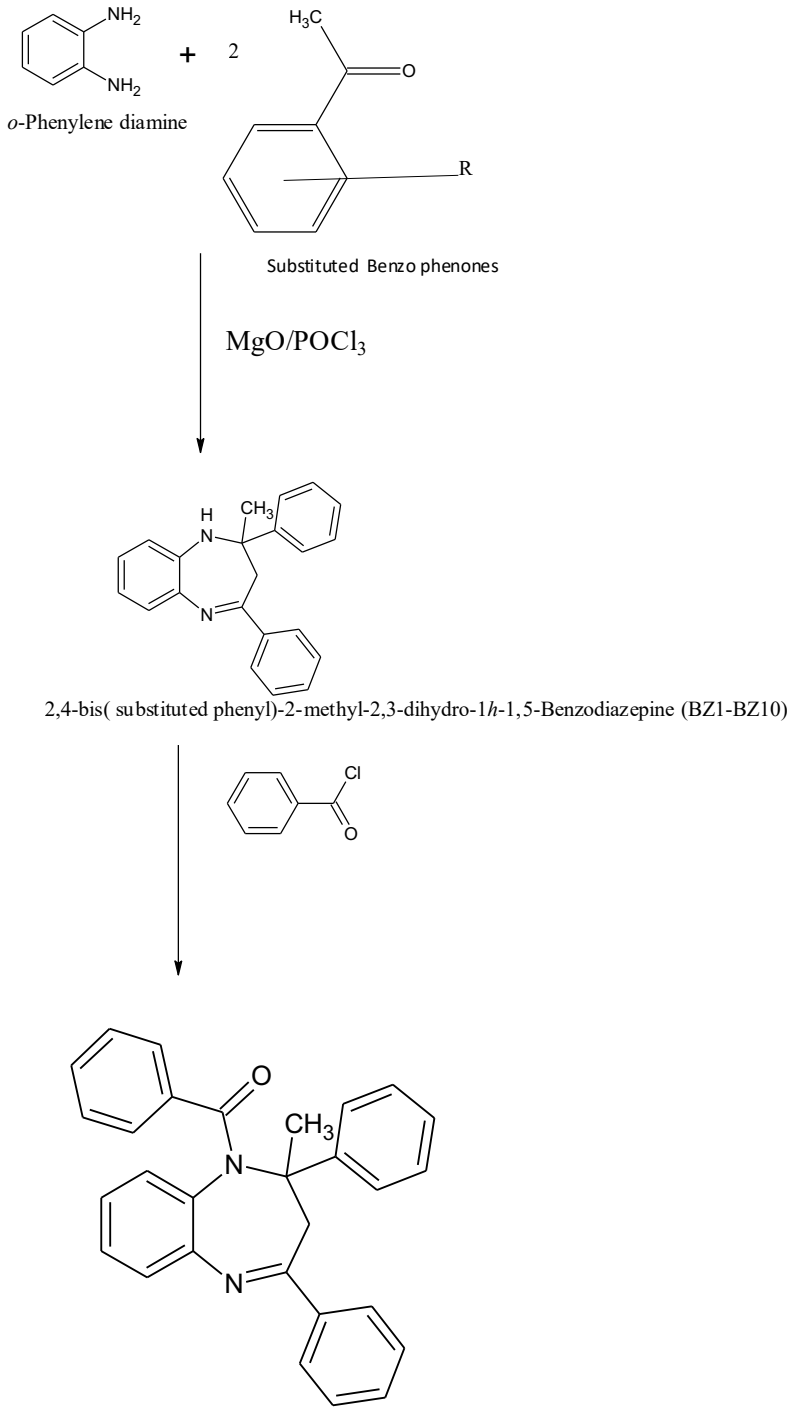
CHNS analysis Calculated: C(75.85%) H(5.21%) F(10.91%) N(8.04%)

Found : C(74.16%) H(5.13%) F(11.13 %) N(7.84%)

STEP II-SYNTHESIS OF 1-BENZOYL-2, 4- (SUBSTITUTED PHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ1-BBZ10)

To the above 1, 5 benzodiazepine intermediate 4 mmol of benzoyl chloride (C6H5COCl) was added. Reaction completedness was checked by using TLC by taking n-hexane: ethanol (7:3) as solvent system. Filtered product was dried and recrystallized from ethanol.The physical properties of the synthesized compounds are listed in table no:2.The detailed scheme of synthesis is also presented below.

SCHEME OF SYNTHESIS



1-Benzoyl-2, 4- (substituted phenyl)- 2 methyl 3 dihydro-1h, 1, 5- Benzodiazepine (BBZ1-BBZ10)

The spectral data of the synthesized compounds are listed below.

1-BENZOYL-2,2, 4- (TRIMETHYL)- 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ1)
IR: 3071(Aryl CH stretching) 2679(Alkyl CH Stretching) 1760(C=O stretching) 1550(Aryl C-C stretching) 1200(C-N Stretching)1021(C-O Stretching)
[1] HNMR :7.123(d, Ar CH) 7.317(d,CH3) 7.007(d,CH3)
[13]CNMR: 167.80(C=O), 158.64((C=N),139.91(C,Ar),130.98(CH Ar),39.79(CH_2)
MASS: 298.31(M+)
CHNS analysis Calculated: C(83.63%) H(5.81%) N(6.73%) O(3.84%)
Found : C(82.45 %) H(5.46%) N(6.58%) O(3.92%)

1-BENZOYL-2, 4- (DI PHENYL)- 2 METHYL- 3- DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ2)
IR: 3001(Aryl CH stretching) 2920(Alkyl CH Stretching) 1711(C=O stretching) 1499(Aryl C-C stretching) 1129(C-N Stretching)1010(C-O Stretching)
[13]CNMR: 177.20(C=O), 168.64((C=N),142.11(C-C,Ar),133.98(CH Ar),42.45 (CH_2)

[1] HNMR : 7.001(d, Ar CH) 7.097(d,CH3) 7.574(d,CH3)
MASS: 416.18(M+)
CHNS analysis Calculated: C(83.63%) H(5.81%) N(6.73%) O(3.84%)
Found : C(84.26%) H(5.47%) N(6.28%) O(3.37%)

1-BENZOYL-2, 4- (4-FLUROPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ3)
IR: 3010(Aryl CH stretching) 2824(Alkyl CH Stretching) 1717(C=O stretching) 1520(Aryl C-C stretching) 1150(C-N Stretching)1019(C-O Stretching) 1319 (C-F Stretching)
[1] HNMR :7.084(d, Ar CH) 7.985(d,CH3) 7.476(d,CH)
[13]CNMR: 165.54 (C=O), 161.74((C=N),137.25 (C,Ar),123.35(CH Ar),46.42(CH_2)
MASS: 452.17(M+2)
CHNS analysis Calculated: C(76.98%) H(4.90%) N(6.19%) O(3.54%) F(8.40%)
Found : C (76.78%), H(4.73%), N(6.17%), O(3.54%), F(8.45%)

1-BENZOYL-2, 4- (4-CHLOROPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ4)
IR: 3001(Aryl CH stretching) 2953(Alkyl CH Stretching) 1751(C=O stretching) 1502(Aryl C-C stretching) 1099(C-N Stretching)1071(C-O Stretching)798(C-Cl Stretching)
[1] HNMR :7.831(d, Ar CH) 7.901(d, Ar CH) 7.078(d, Ar CH)
[13]CNMR: 177.58(C=O), 136.24((C=N),128.91(C,Ar),145.98(CH Ar),53.79(CH_2)
MASS: 485.11(M+1)
CHNS analysis Calculated::C(71.76%) H(4.57%) Cl(14.61%) N(5.77%) O(3.30%)
Found : C(71.63%) H(4.52%) Cl(14.08%) N(5.53%) O(3.43%)

1-BENZOYL-2, 4- (4-METHYLPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ5)
IR: 3100(Aryl CH stretching) 2819(Alkyl CH Stretching) 1799(C=O stretching) 1479(Aryl C-C stretching) 1140(C-N Stretching)1001(C-O Stretching)
[1] HNMR : 7.507(d, Ar CH) 7.499(d,CH3) 7.216(d, Ar CH)
[13]CNMR: 156.80(C=O), 163.64((C=N),139.91(C-CAr),135.98(CH Ar),41.67(CH_2)
MASS: 444.21(M+)
CHNS analysis Calculated: C(83.75%) H(6.35%) N(6.30%) O(3.60%)
Found : C(82.68%) H(6.12 %) N(5.73%) O(3.74%)

1-BENZOYL-2, 4- (2-METHOXYPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ6)
IR : 3032 (Aryl CH stretching) 2925 (Alkyl CH Stretching) 1715(C=O STRETCHING ETCHING) ,1506(Aryl C-C stretching) 1143((C-N Stretching),1006 (C-O Stretching)
[1] HNMR :7.939 (d, 3 Ar CH) 7.484 (d,CH3) 6.497 (t,OCH3),
[13]CNMR: 149.80(C=O), 158.64((C=N),139.91(C,Ar),128.98(CH Ar),45.79(CH_2)
MASS: 476.97(M+),
CHNS analysis calcd C(74.60%) H(6.51%) N(6.96%) O(11.93%)F**found** C(75.34 %) H(6.88 %) N(7.14%) O(11.46%)

1-BENZOYL-2, 4- (2-CHLOROPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ7)
IR: 3053(Aryl CH stretching) 2862(Alkyl CH Stretching) 1781(C=O stretching) 1525(Aryl C-C stretching) 1079(C-N Stretching)1001(C-O Stretching)658(C-Cl stretching)
[1] HNMR :7.871(d, Ar CH) 7.797(d,Ar CH) 7.081(d, CH3)
[13]CNMR: 157.80(C=O), 168.64((C=N),139.91(C-C,Ar),148.98(CH Ar),41.79(CH_2)
MASS: 485.35 (M+1)
CHNS analysis Calculated: C(71.86%) H(4.66%) Cl(14.85%) N(5.57%) O(3.55%)
Found : C(71.76%) H(4.57%) Cl(14.61%) N(5.77%) O(3.32%)

1-BENZOYL-2, 4- (4-METHOXYPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ8)
IR: 3020(Aryl CH stretching) 2781(Alkyl CH Stretching) 1755(C=O stretching) 1499(Aryl C-C stretching) 1064(C-N Stretching)1020(C-O Stretching)702(C-Cl stretching)
[1] HNMR :7.971(d, Ar CH) 6.879(d, Ar CH) 6.999(d,CH3)
[13]CNMR: 166.480(C=O), 158.64((C=N),143.44 (-CC,Ar),136.89(CH Ar),45.43 (CH_2)
MASS: 476.86 (M+)
CHNS ANALYSIS Calculated: C(74.60%) H(6.51%) N(6.96%) O(11.93%)
Found : C (74.97%), H(6.49%), N(6.98%), O(11.63%)

1-BENZOYL-2, 4- (2-METHYLPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ9)
IR: 3029(Aryl CH stretching) 2900(Alkyl CH Stretching) 1700(C=O stretching) 1570(Aryl C-C stretching) 1198(C-N Stretching)1050(C-O Stretching)
[1] HNMR :7.906(d, Ar CH) 7.460(d,CH3) 6.400(d,CH3)
[13]CNMR: 167.80(C=O), 158.64((C=N),139.91(C,Ar),130.98(CH Ar),46.54 (CH_2)
MASS: 446.5(M+),
CHNS analysis Calculated: C(83.75%) H(6.35%) N(6.30%) O(3.60%)
Found : C(82.87%) H(6.38%) N(6.48%) O(3.32%)

1-BENZOYL-2, 4- (2-FLUROPHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BBZ10)
IR: 3070(Aryl CH stretching) 2915(Alkyl CH Stretching) 1719(C=O stretching) 1499(Aryl C-C stretching) 1098(C-N Stretching)1036(C-O Stretching)
[1] HNMR :7.737(d, Ar CH) 7.075(d,CH3) 6.208(t,OCH3)
[13]CNMR: 167.80(C=O), 158.64((C=N),139.91(C,Ar),130.98(CH Ar),39.79(CH_2)
MASS: 452.31(M+2)
CHNS analysis Calculated: C(71.76%) H(4.57%) Cl(14.61%) N(5.77%) O(3.30%)
Found : C(72.26%) H(5.18%) Cl(14.54%) N(5.17%) O(3.44%)

ACUTE TOXICITY STUDIES – OECD 423 GUIDELINES

Approval from the Institutional Animal Ethics Committee was obtained for conducting studies on animals and the IAEC approval number is SJCP/IAEC/2018-7/38.

Food was denied to the rats overnight, prior to dosing. The 4 dose levels of drugs are administered by the help of oral feeding needle over the period of 24 hours. After the drugs has been administered, food may be withheld for a further 3-4 hours in rats. The purpose of sighting study is to allow selection of appropriate starting dose.

The sample drug is administered to one rat in a continous manner following from the fixed dose levels of 5, 50, 300& 2000 mg/Kg. The interval between dosing of each level is determined by the mortality, onset, duration and severity of toxic signs over the period of 24 hours, special attention given during the first 4hours. Four hours after the drug administration, food and water were provided to the rats for 14 days. It was followed by periodic observation of some parameters such as food intake, mortality, onset, duration and severity of toxic signs. The weight of the rat was monitored once in a week, Based on the mortality result of sighting study starting dose in main study is decided and carried out with 5 animal per dose level (5, 50, 300& 2000).Based on the result on 14th day of observation, the doses for *in vivo* study were selected.

***IN-VIVO* ANTIULCER STUDY - PYLORIC LIGATION METHOD [32]**

Albino wistar rats were be divided into 4 groups of 6 animals each. They were fasted for 18 hours taking care to avoid caprophagy. Synthesized derivatives (30 & 60 mg/kg), standard drug Ranitidine (20 mg/kg) and vehicle were administered orally, 1 hour before pyloric ligation. Pylorus will be ligated under ether anaesthesia without affecting blood supply. Animals were sacrificed 6 hours later and gastric contents were removed. Stomachs were immersed in formalin solution. After 10 min, each stomach were opened along the greater curvature and examined under a dissecting microscope to find out the ulcer index score. The photographs of ulcer index score of the synthesized derivative with codeBBZ6b, standard drug ranitidine and vehicle is presented in figure 1,2 and 3. The volume of gastric contents will be measured. The gastric contents were analyzed for various biochemical parameters. All the results of antiulcer screening are presented in table no. 3

STATISTICAL ANALYSIS

Values were expressed as mean± Standard Error Mean(SEM). The results was considered statistically significant $p \leq 0.001$**, $p \geq 0.001$*** when compared to control group.

RESULTS AND DISCUSSION

Ten different novel derivatives of 1-benzoyl-2, 4- (substituted phenyl)- 2 methyl 3 dihydro-1h, 1, 5 benzodiazepine were synthesized by treating *o*-phenylene diamine with ten different ketones. The characterization of the synthesized 1,5-Benzodiazepine derivatives was carried out by infrared , proton nuclear magnetic resonance, ^{13}C nuclear magnetic resonance, mass spectra and CHNS analysis . All the ten novel derivatives synthesized were screened for their antiulcer activity by pyloric ligation method. In the antiulcer screening, compound BBZ6 was found to be the most active which was followed by compound BBZ8, which was in accordance to the docking results. The rest of the compounds were having negligible activity when compared to the standard. From the results it is clear that the Benzoyl 1,5-Benzodiazepines with methoxy substituted phenyl rings attached to the 2nd and 3rd positions of the Benzodiazepine nucleus have comparable antiulcer acivity with the standard drug ranitidine. It is clear that when the methoxy substitution is at the second position of the phenyl ring, the compound exhibited better activity.It can also be noticed that halogen substituted phenyl rings attached to 1,5-Benzodiazepines did not produce active compounds and un substituted phenyl groups attached to 1,5-Benzodizepine produced compounds with lesser activity.

Fig 1: Ulcer Index Score of BBZ6a

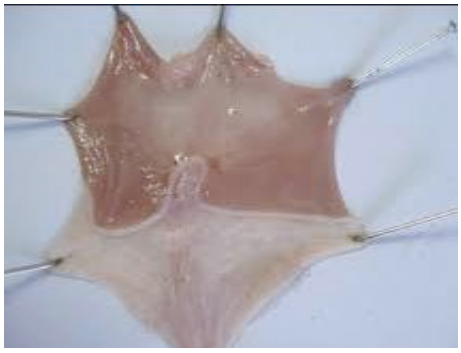


Fig 2 Ulcer Index score of standard (Ranitidine 20 mg/kg)

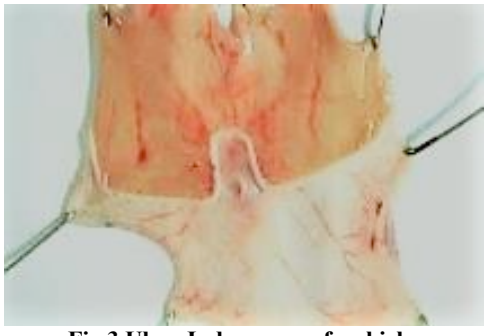


Fig 3 Ulcer Index score of vehicle.

TABLE NO : 1

PHYSICAL PROPERTIES OF 1-BENZOYL-2, 4- (SUBSTITUTED PHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BZ1-BZ10)

Sl No	Compound Code	Molecular Formula	Molecular Weight(D)	Melting Point (^{0}C)	Rf Value	Yield (%)
1	BZ1	$C_{12}H_{16}N_2$	188.26	259	0.67	70
2	BZ2	$C_{22}H_{20}N_2$	312.40	284	0.59	64
3	BZ3	$C_{22}H_{18}N_2F_2$	348.48	263	0.79	62
4	BZ4	$C_{22}H_{18}N_2Cl_2$	381.29	280	0.64	63
5	BZ5	$C_{24}H_{24}N_2$	340.46	265	0.72	59
6	BZ6	$C_{24}H_{24}N_2O_2$	372.45	246	0.67	68
7	BZ7	$C_{22}H_{18}N_2Cl_2$	381.29	301	0.65	61
8	BZ8	$C_{24}H_{24}N_2O_2$	372.45	256	0.69	68
9	BZ9	$C_{24}H_{24}N_2$	340.46	278	0.71	64
10	BZ10	$C_{22}H_{18}N_2F_2$	348.48	282	0.66	65

TABLE NO: 2

PHYSICAL PROPERTIES OF 1-BENZOYL-2, 4- (SUBSTITUTED PHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BZ1-BZ10)

Sl No	Compound Code	Molecular Formula	Molecular Weight (D)	Melting Point (^{0}C)	Rf Value	Yield (%)
	BZ1	$C_{12}H_{16}N_2$	188.26	259	0.67	70
2	BZ2	$C_{22}H_{20}N_2$	312.40	284	0.59	64
3	BZ3	$C_{22}H_{18}N_2F_2$	348.48	263	0.79	62
4	BZ4	$C_{22}H_{18}N_2Cl_2$	381.29	280	0.64	63
5	BZ5	$C_{24}H_{24}N_2$	340.46	265	0.72	59
6	BZ6	$C_{24}H_{24}N_2O_2$	372.45	246	0.67	68
7	BZ7	$C_{22}H_{18}N_2Cl_2$	381.29	301	0.65	61
8	BZ8	$C_{24}H_{24}N_2O_2$	372.45	256	0.69	68
9	BZ9	$C_{24}H_{24}N_2$	340.46	278	0.71	64
10	BZ10	$C_{22}H_{18}N_2F_2$	348.48	282	0.66	65

TABLE NO:3

ANTI ULCER ACTIVITY OF 1-BENZOYL-2, 4- (SUBSTITUTED PHENYL)- 2 METHYL 3 DIHYDRO-1H, 1, 5 BENZODIAZEPINE (BZ1-BZ10)

Compounds	**Volume of gastric juice (ml)**	**pH of gastric juice**	**Total acidity(mEq/dL)**	
Control	3.56±0.9	1.5±0.05	0.28±0.09	5.37±0.06
Ranitidine	1.15±0.02***	5.4±0.01***	0.06±0.04***	1.08±0.02***
BBZ 1a	3.50±0.9	1.57±0.09	0.28±0.01	5..33±0.01
BBZ 1b	3.46±0.8	1.61±0.07	0.27±0.07	5.24±0.07
BBZ 2a	3.44±0.7	1.64±0.06	0.27±0.03	5.14±0.03
BBZ 2b	3.41±0.5	1.69±0.05	0.26±0.06	5.09±0.03
BZ 3a	3.41±0.2	1.69.±0.09	0.26±0.09	5.07±0.02
BZ 3b	3.40±0.9	1.71±0.08	0.25±0.01	5.01±0.06
BBZ 4a	3.30±0.1	1.74.±0.09	0.24±0.07	4.27±0.01
BBZ 4b	3.29±0.7	1.91±0.05	0.23±0.02	4.10±0.07
BBZ 5a	3.16±0.03**	2.26±0.01**	0.22±0.03**	3.89±0.03**
BBZ 5b	2.66±0.04**	3.20±0.01**	0.14±0.08**	3. 04±0.07**
BBZ 6a	3.11±0.03**	2.4±0.01**	0.21±0.03**	3.86±0.05**
BBZ 6b	2.60±0.05**	3.3±0.02**	0.14±0.04**	2. 93±0.01**
BBZ 7a	3.28±0.2	2.18.±0.04	0.23±0.01	4.22±0.09
BBZ 7b	3.73±0.5	2.99±0.08	0.18±0.05	4.02±0.07
BBZ 8a	3.14±0.04**	2.30±0.04**	0.21±0.01**	3.88±0.04**
BBZ 8b	2.64±0.02**	3.27±0.03**	0.14±0.09**	2. 99±0.04**
BBZ 9a	3.27±0.01*	2.20±0.05*	0.22±0.04*	3.94±0.08*
BBZ 9b	2.72±0.04*	3.12±0.05*	0.17±0.01*	3. 09±0.07*
BBZ 10a	3.37±0.2	1.72.±0.09	0.25±0.09	5.00±0.01
BBZ 10b	3.33±0.9	1.73±0.08	0.25±0.01	4.70±0.03

CONCLUSION

Based on *in vivo* antiulcer activity screening results, it can be concluded that few of the synthesized 1,5-Benzodiazepine derivatives exhibited antiulcer activity. Conclusion may be drawn that the substituted phenyl group at the second and third position of 1,5-Benzodiazepines are a pre requisite for antiulcer activity.Methoxy substitution at the ortho position of the phenyl ring has produced the most active compound among the series followed by methoxyl group substitution at the para position. As methoxy group is a weak activating and electron releasing group, it can be concluded that the presence of such groups at the ortho position is expected to give rise to compounds with good antiulcer activity. The work should be extended so as to get better ideas about the molecular level interactions of the synthesized compounds with the target receptor.

ACKNOWLEDGEMENT

The authors acknowledge the support provided by management and principal, St.Joseph's college of pharmacy,Cherthala,Kerala for the support and SAIF STIC CUSAT for the spectral analysis.

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