WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Synthesis, Analysis and Anti-Bacterial Activity Evaluation of DI Substituted Benzodiazepinederivatives

Thriveni[1], M. Sunithareddy[2]

Center for Pharmaceutical Sciences JNTUH University College of Engineering Science and Technology
DOI: https://doi.org/10.55248/gengpi.5.0224.0419

INTRODUCTION:

Heterocyclic chemistry has gained immense prominence over the years. 'The presences of one or more heteroatoms within the carbocyclic analogues are responsible for better biological activities in the heterocycles as compared to their carbocyclic analogues. It has been estimated that more than 65% of all published chemical studies deal in one way or another with heterocyclic systems. In the biological world, heterocyclic compounds are everywhere. More than half of the natural compounds are heterocyclic in nature. Heterocycles form the site of reaction in many enzymes and coenzymes. Heredity comes down, ultimately to the particular sequence of attachment of a half dozen heterocyclic rings to the long chains of nucleic acids. A large number of natural heterocyclic compounds have attracted the attention of chemists in order to synthesize novel heterocycles having multifarious biological and pharmacological activities. Thus, heterocycles have become inseparable and an important member of medicinal chemistry. The shelves of a typical modern pharmacy contain almost thousands of preparations, most of which contain a single active ingredient, usually a heterocyclic compound. The goal of the medicinal chemist is to find compound that have potent effects on particular diseases with minimum side effects. Thus, compounds that interact with a biological molecule, triggering a physiological effect is termed as a drug. Humen used drugs for thousands of years to alleviate pain and illness. It must be such that they react selectively with its target and have a minimal side effect on the host cell. An attempt has been made by giving brief survey of literature leading to the interest and thereby the search for novel heterocycles with β-diketones as the precursors for their synthesis. A number of versatile biologically active heterocyclic compound viz. diazepines, benzodiazepine, benzothiazepines, benzothiazines, pyrazoles, isoxazoles, coumarins, benzofurans and pyrazolopyrimidines have been synthesized using different β- diketones.

A diazepine is a seven membered ring with two nitrogen atoms. These two nitrogen atoms in the ring may occupy various positions and ring involves maximum degree of unsaturation (i.e, three double bonds). The diazepines are thus classified as 1,2; 1,3; 1,4-diazepines. Diazepines and its benzo analogues i.e. benzodiazepines are the most widely used of psychotropic drugs. Heterocyclic compounds are those which have a cyclic structure with two or more, different or same kinds of atom in the ring. Organic heterocyclic compounds are those in which at least one of the ring atom is carbon, the other being considered the heteroatoms; carbon is still by far the most common ring atom in heterocyclic compounds. Heterocyclic compounds are normally classified according to the size of the ring, nature and number of the heteroatoms. Heterocyclic compounds account for about half of some twenty million chemical entities known. It has all the reactions, properties, type of structures and synthetic challenges of aliphatic and carbocyclic chemistry together with many of its own fascinations, complexities and diverse possibilities.1 Heterocyclic chemistry is of the utmost importance from both the fundamental and applied point of view.

1,5-BENZODIAZEPINES

1,5-Benzodiazepines are conveniently prepared by the condensation of o-phenylenediamine with 1,3-diketones or β-ketoeters, the reaction is pH dependent and generally catalyzed an acid. In place of the diketones, hydroxymethylene ketones, β-chlorovinyl-aldehyde, diketothioacetal, benzaldehyde and Schiff 's base have been used as the other condensing agents (38-42). Condensation with α, βunsaturated carbonyl compoundsor β- bromocarbonyl compounds form the dihydroderivatives and also undergo ring contraction to quinoxaline and benzimidazoles. Condensation of o-phenylenediamine with β-ketoesters under neutral or basic condition also give benzodiazepine derivatives, but condensation in acidic medium gives an open chain compound which is cyclized by sodium ethylate in boiling ethanol. A series of 1,5-benzodiazepine derivatives have been identified to have peripheral cholecystokinin (CCK) receptor agonist activity and some of these compounds are equipotent to CCK as anorectic agents in rats. Based on the structure-activity relationship, the pharmacological screening of some of the compounds indicated, that the introduction of a second dialkylamino substituent to the 1,5-benzodiazepine molecule showed CNS excitant properties, while the initial monodialkylaniino derivatives containing sulphur showed a CNS depressant activity It also found that only compounds from triazolobenzodiazepine series showed antipsychotic potentiality. The lack of activity in the imidazolo- and pyridobenzodiazepines series indicated that the basicity of the heteroarene moiety might be determinant factor for the evaluation of activity.andimmuneresponses.

AIM AND PLAN OF WORK

AIM:

The aim of this project is to design molecules with potential antimicrobial activity that is **7- chloro-2,4-bis(4-fluorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine.** The designed compounds will be synthesized, characterized, and evaluated for biological activity.

OBJECTIVE: The increasing clinical importance of drug resistance bacterial and fungal pathogens has lent additional urgency to anti-microbiological research and development of new anti-microbial compound. Hence we planned in the present objectives of the study will be as below:

- Development of synthetic method for the synthesis of some Benzimidazole derivatives.
- Chemical characterization of newly synthesized compound by I.R., NMR and Mass spectral data.
- Biological screening of Benzimidazole derivatives for antimicrobial activity by agar well diffusion method and antioxidant activity by DPPH (α,α-diphenyl, β-picryl hydrazyl) method.

PLAN OF WORK:

- From literature, their was observed that the different Benzodiazepinederivatives have been evaluated as antimicrobial agent.
- In this regard we planned to synthesize the new Benzodiazepinederivatives by incorporating substitutions.
- Treatment of microbial infections including bacterial, fungal is becoming difficult because of everlasting problem of microbial resistance towards antibiotics. Hence the need for new generations of antimicrobial agents, and in particular new antimicrobial agents is essential for effective against resistance bacteria for microbial infections. so we have planned to design new compounds that can overcome microbial resistance problems.

EXPERIMENTAL METHODOLOGY

4.1 Chemicals and Reagents

Chemicals and reagents used in the research work were of AR and LR grade and procured from Astron Chemicals, Ahmedabad Lobachemie Private Limited, Mumbai Krishna chemical Industry, Vadodara Merck specialities Private Limited, Mumbai

The chemicals were used as obtained.

4.2 Analytical Techniques

4.2.1 **Thin Layer Chromatography (TLC):** Compounds purity were checked by using Silica gel G coated aluminium plates/Merck Silica gel as stationary phase and various combinations of ethyl acetate, n-hexane, methanol, toluene, benzene as mobile phase. The spots on TLC plates were visualized under ultraviolet lamp and/or by using iodine chamber.

4.2.2 **Physical data:** Open capillary method was used to determine the melting point of synthesized compounds and were uncorrected.

4.3 Instruments Characterization of synthesized compounds were carried out by IR spectra, Mass spectra, NMR spectra.

4.3.1 Infra-Red spectra: FTIR DRS 8400, Shimadzu were used to record IR spectra of synthesized compounds as KBr pellets in the range of 4000 – 500 cm-1 .

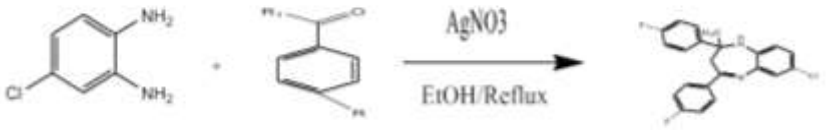
4.3.2 1H Nuclear Magnetic Resonance Spectra: 1H NMR spectra were recorded on Varian 400 MHz spectrometer in DMSO solvent.

4.3.3 Mass Spectra: Mass spectra were obtained using 2010EV LCMS Shimadzu instrument. Mass spectra were recorded on Agilent MS ion trap system

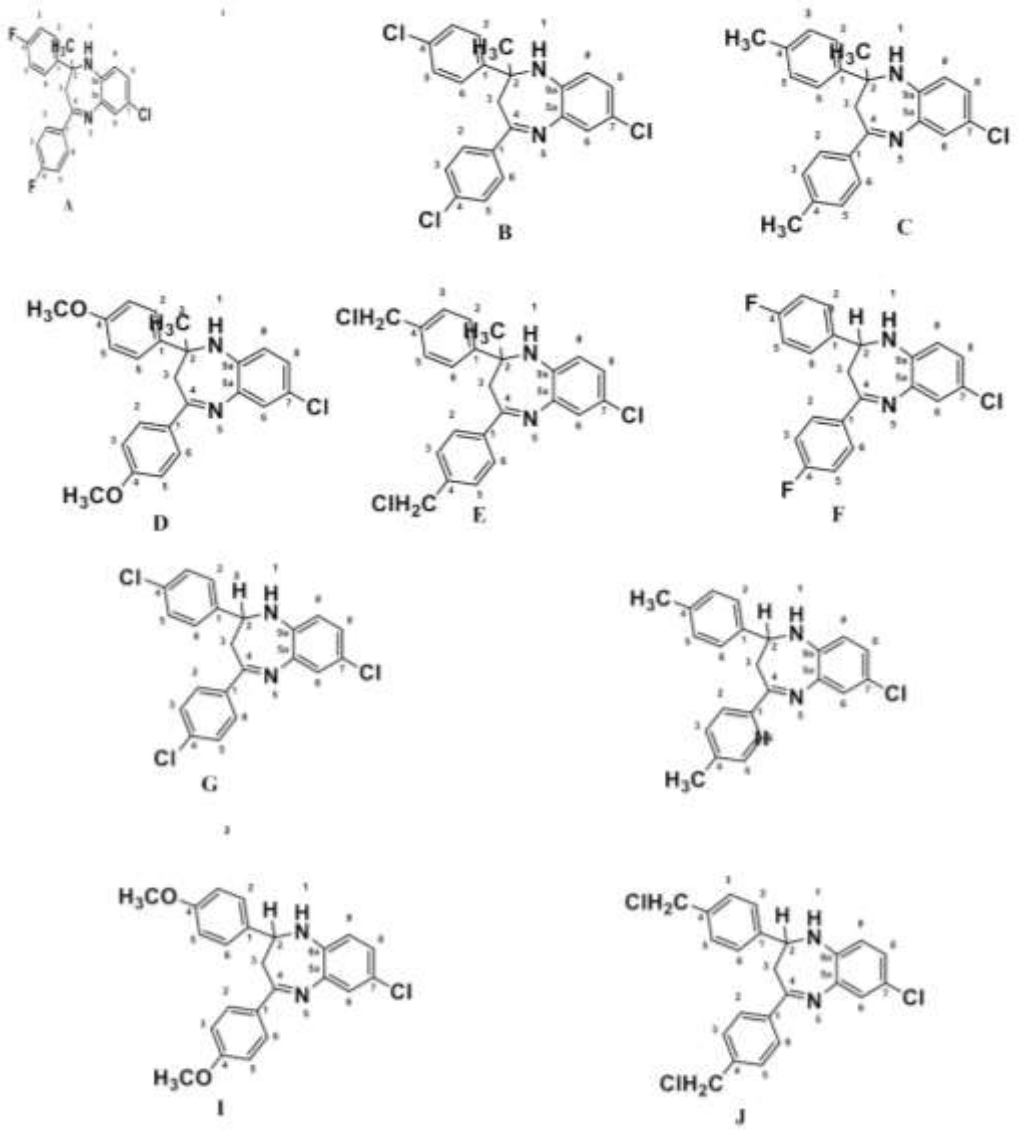
Scheme Step 1

Synthesis of 7-chloro-2,4-bis(4-fluorophenyl)-2,3-dihydro-1H-benzo[b][1,4]diazepine:

A mixture of Chloride derivative of OPDA (1 mmol), ketone (2.5 mmol), and AgNO3 was stirred in acetonitrile (4 mL) at room temperature until thin layer chromatography indicated the reaction was completed. Ethyl acetate (10%) in hexane was used as the mobile phase and both the reactant and the final product were spotted on the TLC plate. The product retention factor (Rf) was observed at 0.4. The disappearance of the reactant spot on the TLC place indicates the completion of the reaction. After completion of the reaction, ethyl acetate (20 mL) was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was concentrated and the crude product was purified by silica gel column chromatography using ethyl acetate: n-hexane (1 : 9) as eluent to afford the desired product.



SYNTHESIS OF COMPOUNDS



The obtained solid was filtered, washed with water, dried and purified by recrystallization from acetic acid.

Physial data and spectral data:

METHODS OF IDENTIFICATION:

1. Melting point
2. TLC
3. Infra red Spectroscopy
4. Nuclear Magnetic Resonance

5. Mass Spectroscopy.

The synthesized compounds were identified by using following method

Melting point:

The melting point of the compounds is determined by the capillary tube method. The synthesized compounds were start losing their crystallinity at a particular temperature.

Thin layer chromatography

Pre-coated TLC plates with silica gel GF 250 are used. Samples of reactants and products are prepared with suitable solvents.

The characterization was carried out using sophisticated methods like Infra-red spectroscopy, Nuclear magnetic resonance spectroscopy and Mass spectroscopy.

Infrared spectroscopy:

The infrared spectroscopy is one of the most powerful analytical techniques, this offers the possibility of chemical identification. The most important advantages of infrared spectroscopy over the other usual methods of structural analysis are that it provides useful information about the functional groups present in the molecule quickly. The technique is based upon the simple fact that a chemical substance shows marked selectable absorption in the infrared region. After absorbing IR radiations the molecules of a chemical compound exhibit small vibrations, giving rise to closely packed absorption bands called as IR absorption spectrum which may extend over a wide wavelength range. Various bands will be present in IR spectrum which corresponds to the characteristic functional groups and bonds present in a chemical substance. Thus an IR spectrum of a chemical compound is a fingerprint for its identification. The infrared spectrum of the prepared derivatives were taken by using FT-IR spectrometer using potassium bromide pellet technique.

Nuclear magnetic resonance spectroscopy:

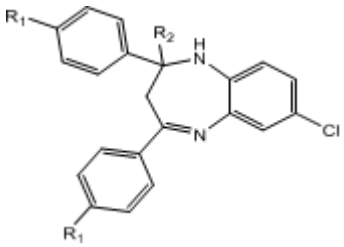
It is the branch of spectroscopy in which radiofrequency waves induces transitions between magnetic energy levels of nuclei of a molecule. The magnetic energy levels are created by keeping nuclei in a magnetic field. Without the magnetic field the spin states of nuclei are degenerated i. e., possess the same energy and the energy level transition is not possible. The energy level transition is possible with the application of external magnetic field which requires different Rf radiation to put them into resonance. This is a measurable phenomenon. It is a powerful tool for the investigation of nuclei structure. ^{1}HNMR Spectra of the prepared derivatives were done by using 400-MHz and 500-MHzBruker spectrometer using internal standard as tetra methyl silane. 1H NMR Spectra was taken with dimethyl sulphoxide (DMSO) as a solvent and the data of chemical shift were shown as delta values related to trimethylsilane (TM) in ppm.

Mass spectroscopy:

Mass spectrometer performs three essential functions. First, it subjects molecules to bombardment by a stream of more amounts of energy electrons, converting some of the molecules to ions, which are then accelerated in a field of electric. Second, the ions which are accelerated are divided according to their ratios of mass to charge in an electric or magnetic field. Finally the ions that have particular mass-to-charge ratio are detected by a device which can count the number of ions striking it. The detector's output is amplified and fed to a recorder.

The trace from the recorder is a mass spectrum a graph of particles detected as a function of mass-tocharge ratio. The Mass of the synthesized compound was taken using MSD spectrometer instrument.

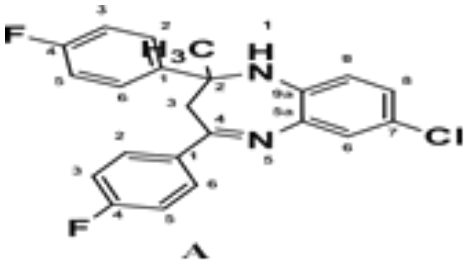
Physical data from compounds:



S.no	R	R2	Mol. Weight	Melting point	% Yield
1	F	CH3	382.10	112 ºC	70%
2	Cl,	CH3	414.05	115ºC	68.7%
3	CH3	CH3	374.15	95ºC	62.5%
4	OCH3,	CH3	406.14	102ºC	57.9%

5	CH2Cl	CH3	442.08	122ºC	54.5%
6	F	H	368.09	118ºC	49.8%
7	Cl,	H	400.03	102ºC	67.8%
8	CH3	H	360.14	122ºC	51.8%
9	**OCH3,**	H	**392.13**	108oC	**51.7%**
10	**CH2Cl**	H	**428.06**	115oC	**57.8%**

Spectral data of 7-chloro-2,4-bis(4-fluorophenyl)-2-methyl-2,3-dihydro-1H- benzo[b][1,4]diazepine:



A

Mass Spectrum (EI-MS): M+1 peak observed at 382

IR (KBr) cm^{-1}: 3422.59(-NH2), 3220.81(NH), 2984(Aromatic C-H), 1599 and 1492(C=C), 1039(C-N), 1634(C=N), 772.63(C-Cl).

^{1}H-NMR (300 MHZ,DMSO)δ ppm:

1H NMR(500.130 MHz, Chloroform-d)			^{1}H NMR(500.130 MHz, Chloroform-d)				
Atom	Shift (ppm)	J (Hz)	Atom	Shift (ppm)		J (Hz)	
1 CH	6.94	J(1-4)	0.10	J(19-15)	1.50		
		J(1-6)	7.14	19 CH	7.31	J(19-16)	0.10
4 CH	7.18	J(4-1)	0.10	J(19-18)	7.72		
		J(4-6)	2.00	J(19-26)	3.26		
6 CH	7.26	J(6-1)	7.14	J(20-21)	8.10		
		J(6-4)	2.00	J(20-23)	0.10		
7 NH	5.15		20 CH	7.81	J(20-24)	1.50	
9' CH2	3.50	J(9'-9")	17.04	J(20-27)	3.82		
9" CH2	3.75	J(9"-9')	17.04	J(21-20)	8.10		
12 CH3	1.84	J(12)	8.88	21 CH	7.16	J(21-23)	1.50
		J(15-16)	7.72	J(21-24)	0.10		
15 CH	7.31	J(15-18)	0.10	J(21-27)	10.16		
		J(15-19)	1.50	J(23-20)	0.10		
		J(15-26)	3.26	23 CH	7.16	J(23-21)	1.50
		J(16-15)	7.72	J(23-24)	8.10		
16 CH	7.03	J(16-18)	1.50	J(23-27)	10.16		
		J(16-19)	0.10	J(24-20)	1.50		
		J(16-26)	10.16	24 CH	7.81	J(24-21)	0.10

18 CH	7.03	J(18-15)	0.10	J(24-23)	8.10
		J(18-16)	1.50	J(24-27)	3.82
J(18-19)		7.72			
J(18-26)		10.16			

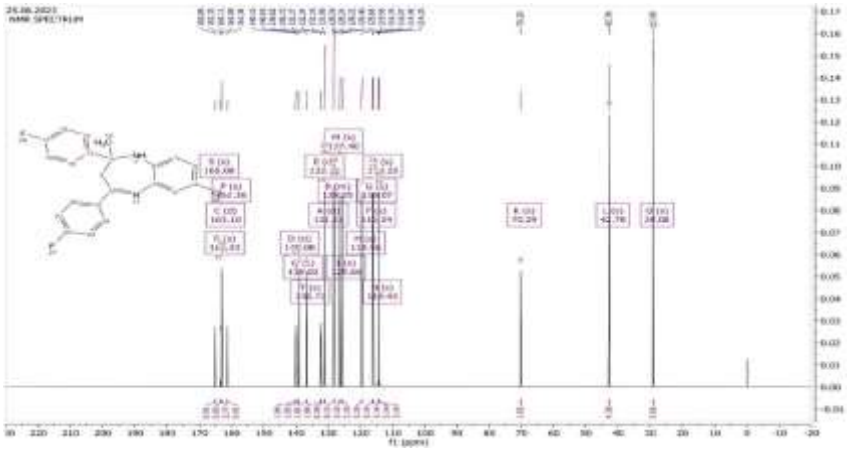
13C NMR

13C NMR(125.032 MHz, Common NMR Solvents) Atom Shift J (Hz) (ppm) J(1-1) 162.4 1 CH 119.6 J(1-4) 0.9 J(1-6) 2.3 J(2-1) 1.5 J(2-4) 6.2 2 C 136.7 J(2-6) 7.0 J(2-9) 0.4 J(2- 0.3 12) J(3-1) 7.6 3 C 139.0 J(3-4) 2.5 J(3-6) 1.0 J(3-9) 0.5 J(4-1) 0.9 4 CH 125.6 J(4-4) 167.5 J(4-6) 6.7 J(5-1) 8.6	13C NMR(125.032 MHz, Common NMR Solvents) Atom Shift J (Hz) (ppm) J(9-9) 128.8 J(9-12) 3.9 9 CH2 42.8 J(9-15) 0.5 J(9-19) 0.5 J(9-20) 0.5 J(9-24) 0.5 J(10-4) 0.4 J(10-9) 4.5 J(10-12) 0.4 J(10-20) 4.9 10 C 163.1 J(10-21) 0.4 J(10-23) 0.4 J(10-24) 4.9 J(12-9) 3.9 J(12-12) 127.4 12 CH3 29.1 J(12-15) 0.3 J(12-19) 0.3 J(13-9) 3.2 J(13-12) 3.9	13C NMR(125.032 MHz, Common NMR Solvents) Atom Shift J (Hz) (ppm) J(15-9) 0.5 J(15-12) 0.3 J(15-15) 158.7 15 CH 128.2 J(15-16) 2.3 J(15-18) 1.0 J(15-26) 8.8 J(16-15) 2.3 J(16-16) 160.4 16 CH 114.3 J(16-19) 1.0 J(16-26) 22.5 J(17-15) 7.7 J(17-16) 2.6 17 C 162.3 J(17-18) 2.6 J(17- 7.7	13C NMR(125.032 MHz, Common NMR Solvents) Atom Shift J (Hz) (ppm) J(21-20) 2.3 J(21-21) 161.8 21 CH 116.1 J(21-24) 1.0 J(21-27) 22.5 J(22-20) 7.7 J(22-21) 2.6 22 C 164.1 J(22-23) 2.6 J(22-24) 7.7 J(22- 246.4

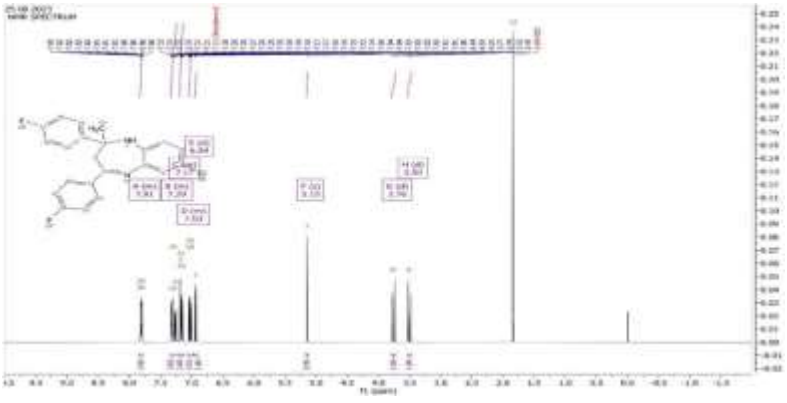
5 C 128.2 J(5-4) 2.9 J(5-6) 2.8 J(6-1) 2.3 6 CH 126.4 J(6-4) 6.7 J(6-6) 164.9 J(8-1) 0.6 J(8-9) 2.6 J(8- 2.2 12) J(8- 3.0 8 C 70.3 15) J(8- 0.6 16) J(8- 0.6 18) J(8- 3.0 19)	J(13- 15) 1.6 J(13- 13 C 140.1 16) 7.1 J(13- 18) 7.1 J(13- 19) 1.6 J(13- 26) 5.9 J(14-9) 3.2 J(14- 1.5 20) J(14- 7.0 21) 14 C 132.2 J(14- 7.0 23) J(14- 1.5 24) J(14- 3.2 27)	19) J(17- 246.4 26) J(18- 1.0 15) J(18- 160.4 18 CH 114.3 18) J(18- 2.3 19) J(18- 22.5 26) J(19-9) 0.5 J(19- 0.3 12) J(19- 16) 1.0 19 CH 128.2 J(19- 18) 2.3 J(19- 19) 158.7 J(19- 26) 8.8 J(20-9) 0.5 20 CH 131.1 J(20- 20) 161.4	27) J(23- 1.0 20) J(23- 161.8 23 CH 116.1 23) J(23- 2.3 24) J(23- 22.5 27) J(24-9) 0.5 J(24- 1.0 21) J(24- 2.3 24 CH 131.1 23) J(24- 24) 161.4 J(24- 27) 9.1

		J(20- 21) 2.3 J(20- 23) 1.0 J(20- 27) 9.1	

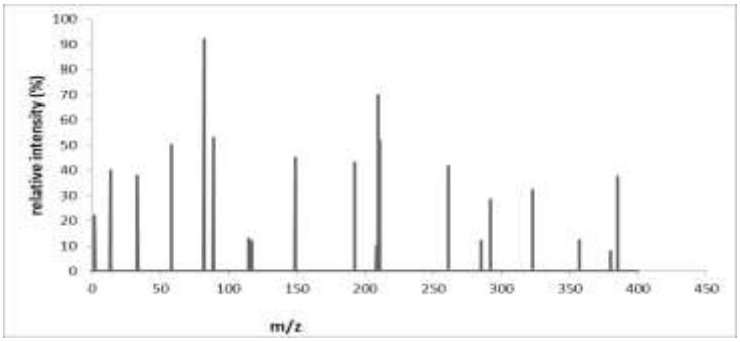
1H NMR:



13C NMR



Mass Spectrum:



IV. PHARMACOLOGICAL EVALUATIONS

ANTIBACTERIAL ACTIVITY OF SYNTHESISED COMPOUNDS:

Antibacterial activity by Agar Well Diffusion method by measuring the zone of inhibition in mm.

Materials:

- Nutrient Broth Media
- Nutrient Agar media

- Dimethyl sulfoxide
- Ciprofloxacin
- Distilled water

Test Organisms:

Gram positive Gram negative

Staphylococcus aureus Escherichia coli

Micrococcus luteus Klebsiella pneumoniae

Nutrient media Composition:

Beef extract : 3 grams

Peptone : 5 grams

Sodium chloride : 5 grams

Agar agar : 15 grams

Distilled Water : 1000 liters

pH : 7.4±0.2

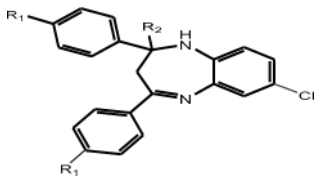
Preparation of bacterial cultures for assay:

The test organisms were sub cultured using nutrient broth medium. The tubes containing sterilized media were inoculated with respective bacterial strains. After incubation at 37±1ºC for 24 hours, they were stored in refrigerator. The stock cultures were maintained. Bacterial inoculums were prepared by transferring a loop full of culture to nutrient broth in conical flasks. The flasks were incubated at 37±1ºC for 48 hours before the experiment.

Test sample preparation:

The test compounds were prepared for assay by dissolving them in dimethyl sulfoxide in required concentrations making 50µg/ml, 100µg/ml, 500µg/ml, and 1000µg/ml respectively for evaluation. A reference standard for both Gram-positive and Gram-negative bacteria Ciprofloxacin was made in same concentrations as test compounds where dimethyl sulfoxide as control.

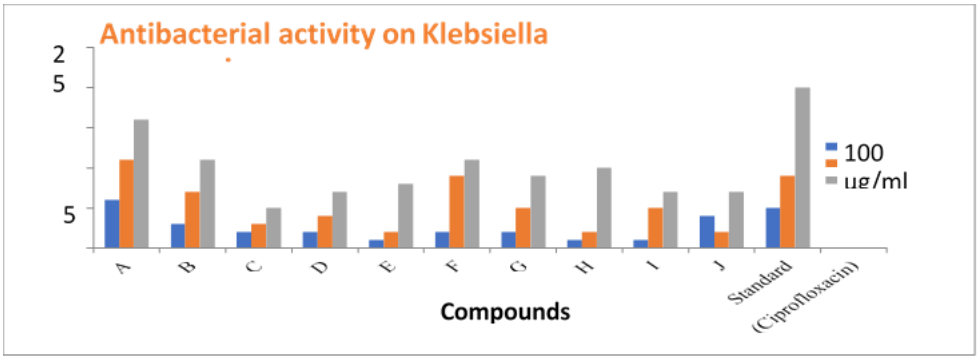
Assay by Agar well diffusion method:



Antibacterial activity on Klebsiella pneumoniae:

COMPOUNDS	100µg/ml	500µg/ml	1000µg/ml
A	**6mm**	**11mm**	**16mm**
B	**3mm**	**7mm**	**11mm**
C	**2mm**	**3mm**	**5mm**
D	**2mm**	**4mm**	**7mm**
E	**1mm**	**2mm**	**8mm**
F	**2mm**	**9mm**	**11mm**
G	**2mm**	**5mm**	**9mm**
H	**1mm**	**2mm**	**10mm**
I	**1mm**	**5mm**	**7mm**

J	**4mm**	**2mm**	**7mm**
Standard (Ciprofloxacin)	**5mm**	**9mm**	**20 mm**



RESULTS AND DISCUSSION:

- The preliminary studies on antimicrobial activity of the new Benzodiazepine derivatives have generated some interesting data. An attempt has been made to infer the ultimate outcome of the present studies basing on this data.
- The compounds were confirmed by TLC, melting point and spectral studies such as FT-IR, MS, and 1H NMR.
- All the synthesized new Benzodiazepinederivatives were evaluated for antibacterial activity by using standard ciprofloxacin, antifungal activity by using standard fluconazole and antioxidant activity by using ascorbic acid.

ANTIMICROBIAL ACTIVITY:

All the new Benzodiazepinederivatives employed in the antimicrobial activity. All the test compounds were prepared for assay by dissolving them in DMSO in required quantity in concentrations making 100µg/ml, 500 µg/ml and 1000µg/ml respectively for evaluation of antibacterial activity against gram positive and gram negative bacteria. Ciprofloxacin used as standard.

Bacteria:

Gram positive Gram negative

Staphylococcus aureus Escherichia coli

Micrococcus luteus Klebsiella pneumonia

- Among all the synthesized compounds the following shown high activity for antibacterial activity when comparing with standard ciprofloxacin chlorineand methyl derivatives are found to have promising antibacterial activity.

Conclusion: Broadly the following conclusion could be drawn from the results of these investigations.

- Synthetic work of the studies could go positively as per the planning and as such in all the reactions carried out. The expected compounds alone could be obtained.
- Newly synthesized compounds were characterized by TLC, IR, ¹H-NMR and Mass spectral analysis.
- New Benzodiazepinederivatives showed promising antimicrobial activity. Compounds chlorine and methyl derivatives were found to be the more potent antibacterial activity respectively towards gram positive (Micrococcus luteus).
- New Benzodiazepinederivatives showed promising antioxidant activity. Compounds A(R1=CH3, R2=H)& B (R1=Cl, R2= CH3) were found to be more potent antioxidant compounds among the all test compounds

REFERENCES:

1. Barker HA, Smyth RD, Weissbach H, Toohey JI, Ladd JN and Volcani BE. Isolation and properties of crystalline cobamide coenzymes containing Benzimidazole or 5,6- Dimethylbenzimidazole. Journal of Biological Chemistry. 1960;235(2):480- 488.
2. Patil A, Ganguly S and Surana S. A systematic review of benzimidazole derivatives as an antiulcer agent. Rasayan J Chem. 2008;1(3):447-460

3. Kubo K, Oda K, Kaneko T, Satoh H and Nohara A. Synthesis of 2-(4- Fluoroalkoxy-2-pyridyl) methyl] sulfinyl]-1H-benzimidazoles as Antiulcer Agents. Chem Pharm Bull. 1990;38(10):2853-2858.

4. Grassi A, Ippen J, Bruno M, Thomas G and Bay P. A thiazolylamino benzimidazole derivative with gastroprotective properties in the rat. Eur J Pharmacol. 1991;195(2):251-9.

5. Ozkay Y, Tunali Y, Karaca H. and Isikdag I. Antimicrobial activity and a SAR study of some novel benzimidazole derivatives bearing hydrazones moiety. European Journal of Medicinal Chemistry. 2010;45(8):3293-3298.

6. Yun H, Baogen W, Yang J, Robinson D, Risen L, Ranken R, Blyn L, Eric SS. and Swayze E. 2-Piperidin-4-ylbenzimidazoles with Broad Spectrum antibacterial activities. Bioorg Med Chem Lett. 2003;13:3253-3256.

7. Metwally KA, Abdel-Aziz LM, Lashineel-SM, Husseiny MI and Badawy RH. Hydrazones of 2-aryl- -4- carboxylic acid hydrazides: synthesis and preliminary evaluation as antimicrobial agents. Bioorg Med Chem. 2006;14(24): 8675-82.

8. Spasov A, Yozhitsa L, Bugaeva I and Anisimova VA. Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties. Pharmaceutical Chemistry Journal. 33;5:232-243.

9. Arjmand F, Mohani B and Ahmad S. Synthesis, antibacterial, antifungal activity and interaction of CT-DNA with a new benzimidazole derived Cu (II) complex. Eur J Med Chem. 2005;40(11):1103-1110.

10. Preston PN. Benzimidazoles and Congeneric Tricyclic Compounds Part 2.Wiley Interscience New York, 1980:531.

11. Abbhi V., Saini L., Mishra S., Sethi G., Kumar A. P., Piplani P. (2017). Design and Synthesis of Benzimidazole-Based Rho Kinase Inhibitors for the Treatment of Glaucoma. Bioorg. Med. Chem. 25, 6071–6085. 10.1016/J.BMC.2017.09.045

12. Abd El-All A. S., Magd-El-Din A. A., Ragab F. A., ElHefnawi M., Abdalla M. M., Galal S. A., et al. (2015). New Benzimidazoles and Their Antitumor Effects with Aurora A Kinase and KSP Inhibitory Activities. Arch. Pharm. (Weinheim) 348, 475–486. 10.1002/ardp.201400441

13. Abdel-Motaal M., Almohawes K., Tantawy M. A. (2020). Antimicrobial Evaluation and Docking Study of Some New Substituted Benzimidazole-2yl Derivatives. Bioorg. Chem. 101, 103972. 10.1016/j.bioorg.2020.103972

14. Abdelgawad M. A., Bakr R. B., Ahmad W., Al-Sanea M. M., Elshemy H. A. H. (2019). New Pyrimidine-Benzoxazole/benzimidazole Hybrids: Synthesis, Antioxidant, Cytotoxic Activity, In Vitro Cyclooxygenase and Phospholipase A2-V Inhibition. Bioorg. Chem. 92, 103218. 10.1016/j.bioorg.2019.103218

15. Abou-Seri S. M., Abouzid K., Abou El Ella D. A. (2011). Molecular Modeling Study and Synthesis of Quinazolinone-Arylpiperazine Derivatives as α1-adrenoreceptor Antagonists. Eur. J. Med. Chem. 46, 647–658. 10.1016/J.EJMECH.2010.11.045

16. Abu-Bakr S. M., Bassyouni F. A., Rehim M. A. (2012). Pharmacological Evaluation of Benzimidazole Derivatives with Potential Antiviral and Antitumor Activity. Res. Chem. Intermed. 38, 2523–2545. 10.1007/s11164-012-0569-y

17. Acar Çevik U., Kaya Çavuşoğlu B., Sağlık B. N., Osmaniye D., Levent S., Ilgın S., et al. (2020). Synthesis, Docking Studies and Biological Activity of New Benzimidazole- Triazolothiadiazine Derivatives as Aromatase Inhibitor. Molecules 25, 1642. 10.3390/molecules25071642

18. Acar Çevik U., Sağlık B. N., Korkut B., Özkay Y., Ilgın S. (2018). Antiproliferative, Cytotoxic, and Apoptotic Effects of New Benzimidazole Derivatives Bearing Hydrazone Moiety. J.

19. Akhtar S., Abbas M., Naeem K., Faheem M., Nadeem H., Mehmood A. (2021). Benzimidazole Derivative Ameliorates Opioid-Mediated Tolerance During Anticancer- Induced Neuropathic Pain in Mice. Anticancer. Agents Med. Chem. 21, 365–371. 10.2174/1871520620999200818155031

20. Akhtar W., Khan M. F., Verma G., Shaquiquzzaman M., Rizvi M. A., Mehdi S. H., et al. (2017). Therapeutic Evolution of Benzimidazole Derivatives in the Last Quinquennial Period. Eur. J. Med. Chem. 126, 705–753. 10.1016/J.EJMECH.2016.12.010

21. Akkoç S., Tüzün B., İlhan İ. Ö., Akkurt M. (2020). Investigation of Structural, Spectral, Electronic, and Biological Properties of 1,3-disubstituted Benzimidazole Derivatives. J. Mol. Struct. 1219, 128582. 10.1016/j.molstruc.2020.128582

22. AlAjmi M. F., Hussain A., Alsalme A., Khan R. A. (2016). In Vivo assessment of Newly Synthesized Achiral Copper(ii) and Zinc(ii) Complexes of a Benzimidazole Derived Scaffold as a Potential Analgesic, Antipyretic and Anti-inflammatory. RSC Adv. 6, 19475–19481. 10.1039/C5RA25071D

23. Alaqeel S. I. (2017). Synthetic Approaches to Benzimidazoles from O-Phenylenediamine: A Literature Review. J. Saudi Chem. Soc. 21, 229–237. 10.1016/J.JSCS.2016.08.001

24. Alp M., Göker H., Brun R., Yildiz S. (2009). Synthesis and Antiparasitic and Antifungal Evaluation of 2'-arylsubstituted-1H,1'H-[2,5']bisbenzimidazolyl-5-carboxamidines. Eur. J. Med. Chem. 44, 2002–2008. 10.1016/j.ejmech.2008.10.003

25. Alpan A. S., Sarıkaya G., Çoban G., Parlar S., Armagan G., Alptüzün V. (2017). Mannich- Benzimidazole Derivatives as Antioxidant and Anticholinesterase Inhibitors: Synthesis, Biological Evaluations, and Molecular Docking Study. Arch. Pharm. (Weinheim) 350, e1600351. 10.1002/ardp.201600351

26. Amine Khodja I., Boulebd H., Bensouici C., Belfaitah A. (2020). Design, Synthesis, Biological Evaluation, Molecular Docking, DFT Calculations and In Silico ADME Analysis of (Benz)imidazole-hydrazone Derivatives as Promising Antioxidant, Antifungal, and Anti-acetylcholinesterase Agents. J. Mol. Struct. 1218, 128527. 10.1016/j.molstruc.2020.128527