Section: Research Paper

SYNTHESIS AND PHYSICOCHEMICAL CHARACTERIZATION OF BENZIMIDAZOLE- SULPHONAMIDE DERIVATIVES

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Abstract:

This research includes synthesis of Sulphone base different new effective compounds against multi resistant pathogens is one of the major goals in current biomedical research. Among the heterocyclic compounds known in the literature for their various bioactivities are those with benzimidazole ring and those with sulfonamide moiety, which possess a wide range of medicinal properties. A novel series of benzimidazole-incorporated sulphonamide analogues were designed and synthesized with an effort to overcome the increasing antibiotic resistance. Benzimidazole and sulphonamides plays an important role in the medical field with so many pharmacological activities such as antimicrobial, anti-viral, anti-diabetic and anti-cancer activity. The potency and these clinically useful compounds in treatment of microbial

infections and other activities encouraged the development of some more potent and significant compounds. In scheme-2 procedure are the planned reaction methodology for various derivatives of benzimidazole incorporated derivatives has been synthesized. Based on literature report about the importance of benzimidazole-sulphonamide derivatives as various drug molecules, we can expect some bioactive molecules from our synthesized compounds.

Key words: -Anti-microbial activity, Disease remonstrance, Pathogenicity, Antibiotic resistance,

INTRODUCTION

Benzimidazole and sulfonamides play an important role in medical field with so many pharmacological activities such as antimicrobial, antiviral, anti-diabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazole is remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of micro-organisms.[2]Sulfonamides are characterized by a sulfur dioxide (SO2) moiety and a nitrogen (N) moiety directly linked to a benzene ring. Many classes of drugs contain this chemical structure, including antimicrobial sulfonamides. This review is summarized to know about the chemistry of different derivatives of substituted sulfonamides and Benzimidazole along with their anti-microbial activities.[3][4][5]

EXPERIMENTAL WORK[6-19]

MATERIALS AND METHODS

The melting ranges of the synthesized compounds were performed by LAB-INDIA MS-VIS Visual melting point apparatus and are uncorrected.

The IR spectrum studies of the synthesized compound were recorded by pressed-pellet technique. IR spectra were recorded in KBr press (Shimadzu).

The ^{1}HNMR spectral study was performed by instrument AVANCE 500 MHz the solvent system used for the study was DMSO.

Mass studies of the synthesized compound were performed by using the instrument SHIMADZU QP2010 PLUS.

Table. No: 1 lists of chemicals

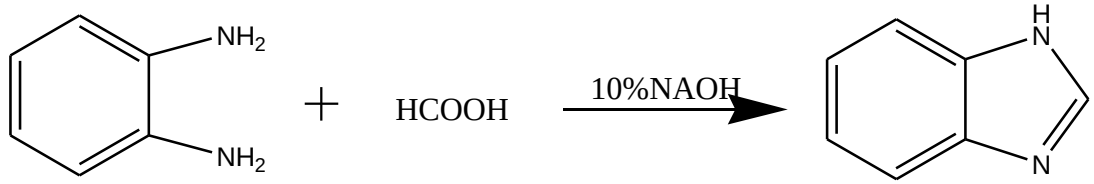
Chemical name	Required amount
o- phenylenediamine	5.48 gm
Formic acid	3 gm
NaOH	1 gm
Sulphonyl chloride	1.57gm
Triethylamine	0.97gm
Acetonitrile	0.97gm

1,4 dioxane	0.97gm
DMSO	0.97gm
Ethyl alcohol	10 ml
P-iodosulphonyl chloride	1.57 gm
P- nitrosulphonyl chloride	1.57 gm
p-carboxysulphonyl chloride	1.57 gm
3,5-bis (triflouro methyl) sulphonyl chloride	1.57 gm
3,5- bis (tertbutyl)sulphonyl chloride	1.57 gm
Toulene	10 ml
Ethylacetate	8 ml

SCHEME FOR PREPARATION:

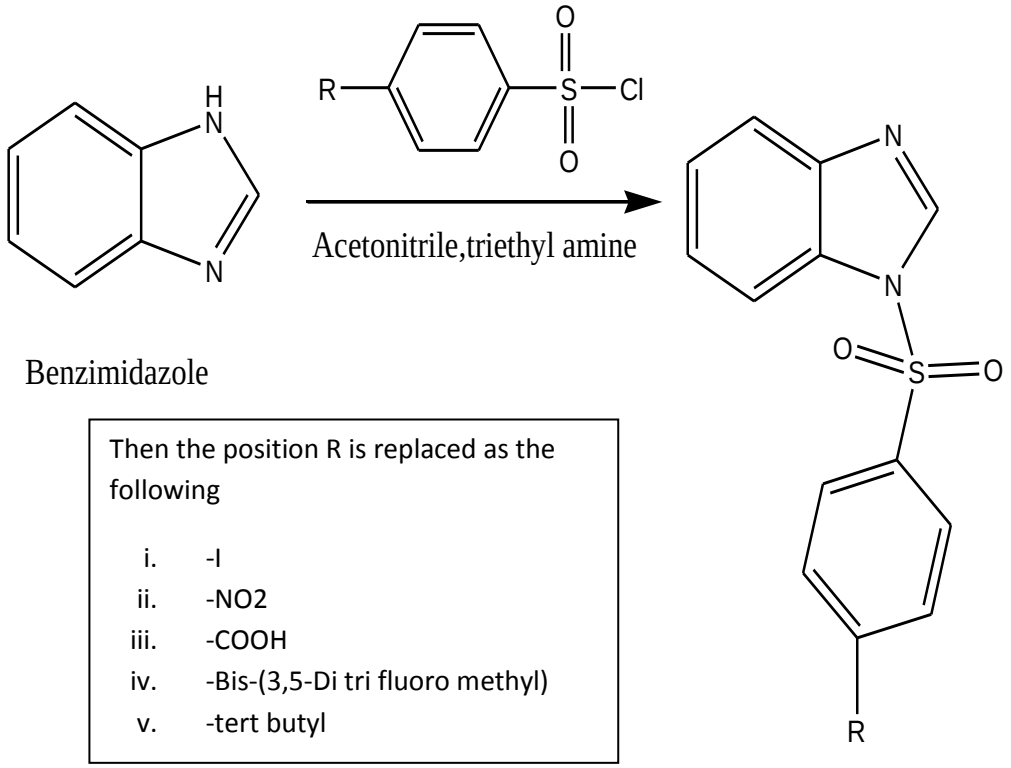
Synthesis and characterization:

Scheme -1 Synthesis of benzimidazole[7]



O- phenylene diamine formic acid benzimidazole

Scheme -2: Synthesis of benzimidazole incorporated sulfonamides derivatives [8]



Benzimidazole

Then the position R is replaced as the following

i. -I
ii. -NO2
iii. -COOH
iv. -Bis-(3,5-Di tri fluoro methyl)
v. -tert butyl

benzimidazole incorporated with sulphonyl group

SYNTHETIC METHODS:

GENERAL PROCEDURE

STEP-1: Procedure for the synthesis of Benzimidazole [7]

Benzimidazole was synthesized by the reaction of O- phenylenediamine and formic acid.5.48 grams of O-phenylenediamine in a round bottom flask (RBF). then add 3 grams (8ml) of formic acid, heat the mixture on a water bath at 100 C for 1 hour. While constant stirring of rotation of flask until the mixture is just alkaline to litmus. Finally filter the synthesized Benzimidazole wash it with it ice cold water and dry it.

STEP-2: Scheme for the synthesis of benzimidazole-sulfonamide derivatives [8](4-iodo benzene-sulfonyl) Benzimidazole

Accurately weighed 1H –Benzimidazole (1g, 5.98mmol) was dissolved in acetonitrile(MeCN) and triethylamine(TEA) (0.97g,9.54mmol) was added. The resulting mixture was poured into a salt –ice bath, and then p-iodosulphonylchloride (1.57, 8.27mmol) was added portion wise over 3hrs to the reaction medium. The mixture was stirred in a salt ice bath for 4h.at the end of the reaction the mixture filtered and evaporated. The obtained solid was dissolved in ethyl alcohol and column chromatography was carried out to obtain a substance with 90% yield.

H ^{1}NMR-Spectra: -Benzimidazole (CH-7.26, CH-7.26, CH-7.70, CH-7.70, CH-8.08), Benzene (CH-7.70, CH-7.92,CH-7.92,CH-7.70)

(4-Nitro benzene-sulfonyl) Benzimidazole [8]

Accurately weighed 1H –Benzimidazole (1g, 5.98mmol) was dissolved in 1, 4-dioxone and triethylamine (0.95g, 9.54mmol) was added. The resulting mixture was poured into a salt –ice bath, and then p-nitro sulphonyl chloride (1.57, 8.27mmol) was added portion wise over 3hrs to the reaction medium. The mixture was stirred in a salt ice bath for 4h at the end of the reaction the mixture filtered and evaporated. The obtained solid was dissolved in ethyl alcohol and column chromatography was carried out to obtain a substance with 90% yield; °C.

H ^{1}NMR-Spectra: -Benzimidazole (CH-7.26, CH-7.26,CH-7.70,CH-7.70,CH-7.70,CH-8.08) Benzene(CH-8.19,CH-8.47,CH-8.47,CH-19).

(4-Carboxy benzene-sulfonyl) Benzimidazole [8]

Accurately weighed 1H –Benzimidazole (1g, 5.98mmol) was dissolved in acetonitrile and tri-ethylamine (0.97g,9.54mmol) was added. The resulting mixture was poured into a salt –ice bath, and then p-carboxy sulphonyl chloride (1.57, 8.27mmol) was added portion wise over 3hrs to the reaction medium. The mixture was stirred in a salt ice bath for 4h at the end of the reaction the mixture filtered and evaporated. The obtained solid was dissolved in ethyl alcohol and column chromatography was carried out to obtain a substance with 90% yield.

H^{1}NMR-Spectra:-Benzimidazole(CH-7.26,CH-7.26,CH-7.70,CH-7.70,CH-8.08), Benzene(CH-8.14,CH-8.41,CH-8.41,CH-8.14)Carboxylic acid(CH-11.0)

(3,5-bistrifluoromethyl benzene-sulfonyl) Benzimidazole[8]

Accurately weighed 1H –Benzimidazole (1g, 5.98mmol) was dissolved in DMSO and tri -ethylamine (0.97g,9.54mmol) was added. The resulting mixture was poured into a salt –ice bath, then 3, 5-bis trifluoromethylsulphonyl chloride (1.57, 8.27mmol) was added portion wise over 3hrs to the reaction medium. The mixture was stirred in a salt ice bath for 4h at the end of the reaction the mixture filtered and evaporated. The obtained solid was dissolved in ethyl alcohol and column chromatography was carried out to obtain a substance with 90% yield.

H^{1}NMR-Spectra:-Benzimidazole (CH-7.26, CH-7.26, CH-7.70, CH-7.70, CH-8.08), Benzene (CH-8.12, CH-7.6, CH-8.12).

(3,5-Bis t-butyl benzene-sulfonyl) Benzimidazole[8]

Accurately weighed 1H –Benzimidazole (1g, 5.98mmole) was dissolved in DMSO and triethylamine (0.97g,9.54mmol) was added. The resulting mixture was poured into a salt –ice bath, then 3,5-bistert-butyl sulphonyl chloride (1.57,8.27mmol) was added portion wise over 3hrs to the reaction medium. The mixture was stirred in a salt ice bath for 4h at the end of the reaction the mixture filtered and evaporated. The obtained solid was dissolved in ethyl alcohol and column chromatography was carried out to obtain a substance with 90% yield.

H^{1}NMR-Spectra:-Benzimidazole(CH-7.26,CH-7.26,CH-7.70,CH-7.70),Benzene(CH-8.08,CH-7.3,CH-7.76),Methyl group(CH-1.34,CH-1.34,CH-1.34,CH-1.34,CH-1.34,CH-1.34).

CHROMATOGRAPHY STUDIES OF SYNTHESIZED COMPOUNDS

THIN LAYER CHROMATOGRAPHY:

Thin layer chromatography or TLC is a solid-liquid form of chromatography here the stationary phase is a polar absorbent and the mobile phase can be a single solvent or combination of solvents. TLC is inexpensive technique and quick that can be used for

determine the number of components in a mixture verify a substances identity, monitor the process of a reaction, determine appropriate condition for column chromatography, analyze the fractions obtained from column chromatography. [9]

Preparation of plates:

Silica gel G was mixed in a glass mortar to smooth consistency with the requisite amount of water and slurry was quickly transferred to the spreader. The mixtures have been spread over the plates in thickness of 0.2mm and allow setting into a suitable holder and after 30 minutes, plates were dried at 120 C, for further activation of the absorbent.[10]

Sample application:

About 2mm of absorbent from the edge of plate was removed to give sharply defined edge. 2-Ul volumes of synthesized compounds were spotted with the help of capillary tubes. Just above 1cm of the bottom of coated plates. [11]

Development chamber:

The chromatographic chamber was lined with filter paper dipping into mobile phase so as to maintain the atmospheric saturation with solvent vapours in the chamber saturation with solvent vapours in the chamber. The solvent front was allowed to dry in the air. [9]

Solvent system:

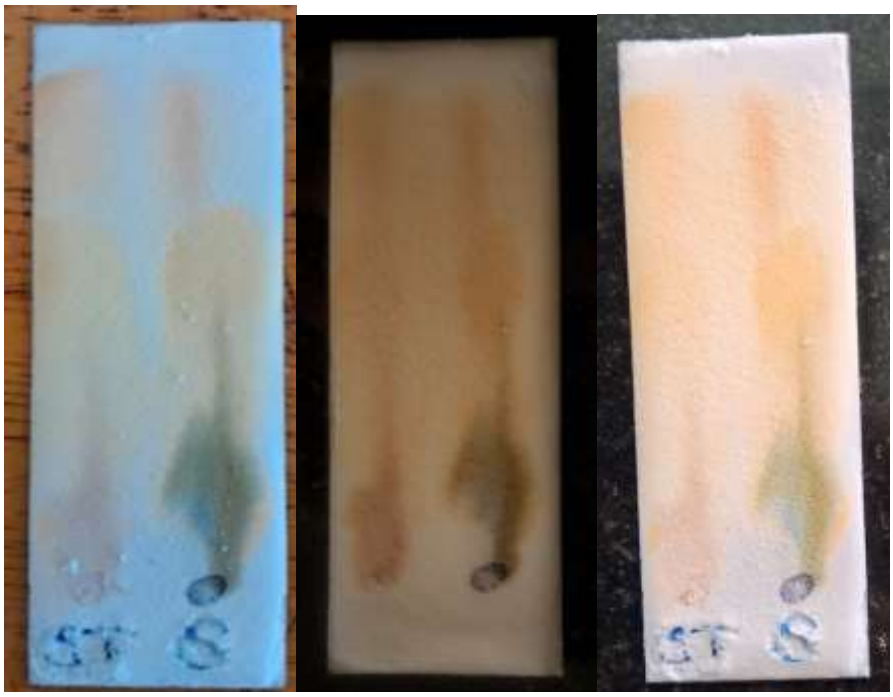
The choice of best developing solvent is one of the most important decisions in practical TLC by review of literature survey on by knowing nature of compounds, this solvent system used is toluene: ethyl acetate: formic acid (5:4:1) [9]

Detection of components:

The spots were visualized under iodine chamber.

Standard Sample Standard Sample Standard Sample

Fig. No: 1 separation of compound by TLC



Standard Sample Standard Sample Standard Sample

Fig.No:2 Separation of compound by TLC

COLLUMN CHROMATOGRAPHY [9]

Purification of synthesized derivatives was done by column chromatography.

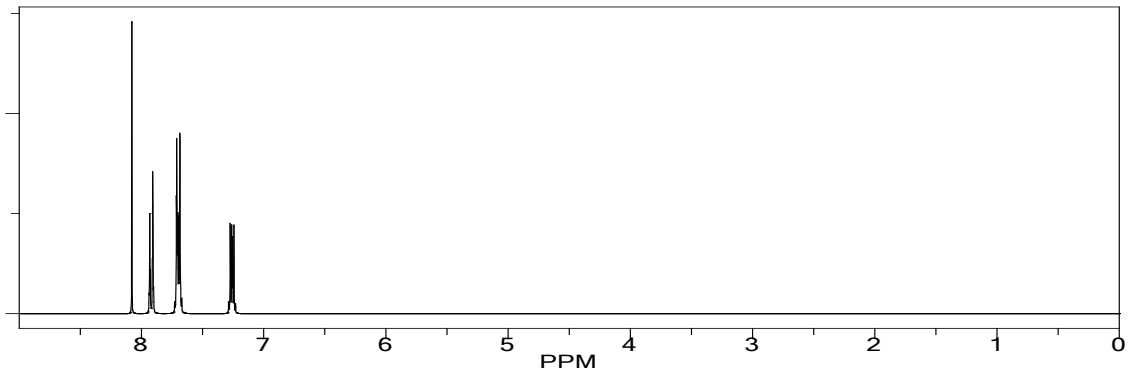
Materials

- Glass column of size 45 cm X 3cm
- Silica gel for column chromatography 60-120 mesh size.
- Eluting solvent system toluene: ethyl acetate: formic acid (5:4:1)

Preparation of column

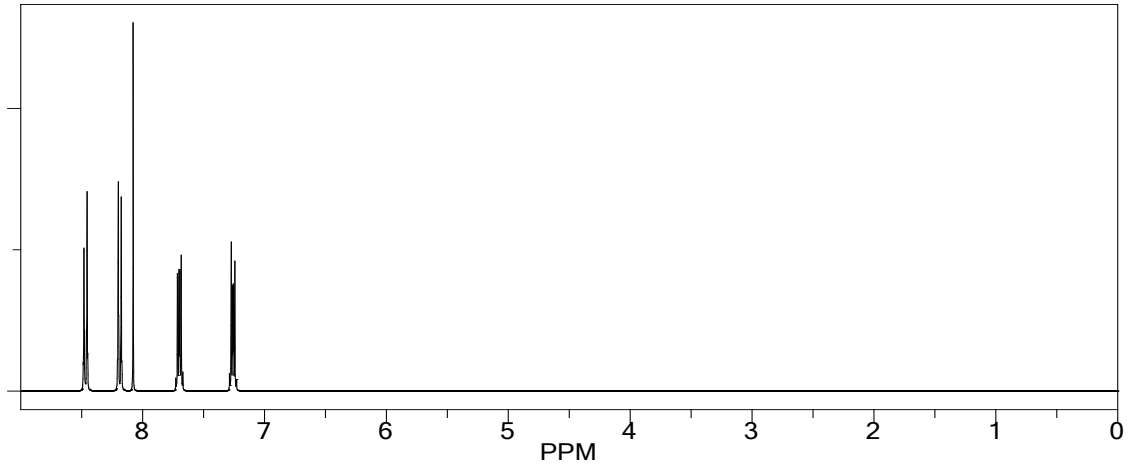
The silica gel 60-120 mesh size was made into slurry with the above solvent system. The bottom of the column was plugged with little glass wool. Then the slurry was poured into the column, which is filled with the solvent after two third of the column areas were filled with slurry. It was set aside for 30 minutes and eluting solvent was passed through column for several times ensure good packing of the column. after the adsorbents are settled, a filter paper was kept to prevent disturbance of the top layer of the adsorbent as fresh mobile phase to be added to column for the process of elution. The fractions were collected for every 5 ml and analysed for the presence of different of similar compound by running TLC and then allow evaporating to get the residual.

STRUCTURE-1: (4-iodo benzene-sulfonyl) benzimidazole



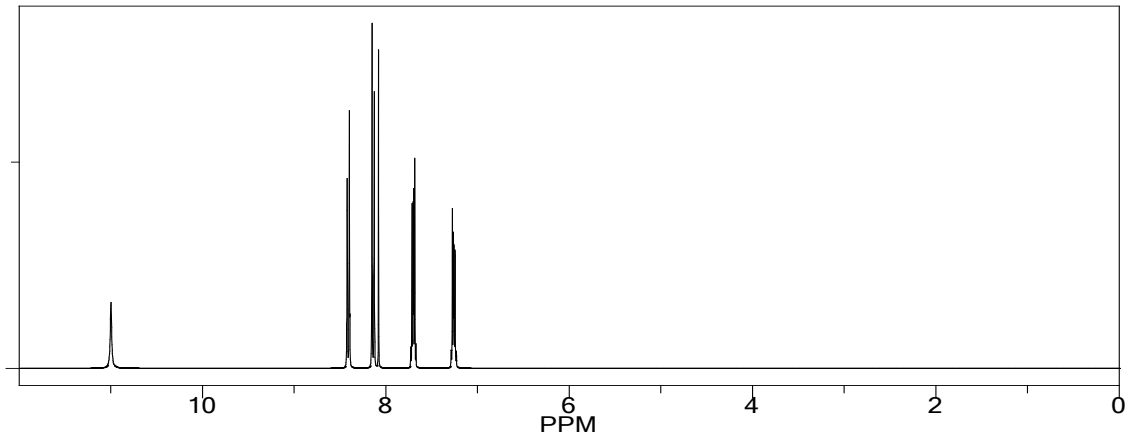
H [1]NMR-Spectra: -Benzimidazole (CH-7.26, CH-7.26, CH-7.70, CH-7.70, CH-8.08), Benzene (CH-7.70, CH-7.92, CH-7.92, CH-7.70)

STRUCTURE-2:-(4-Nitrobenzene-sulfonyl)benzimidazole



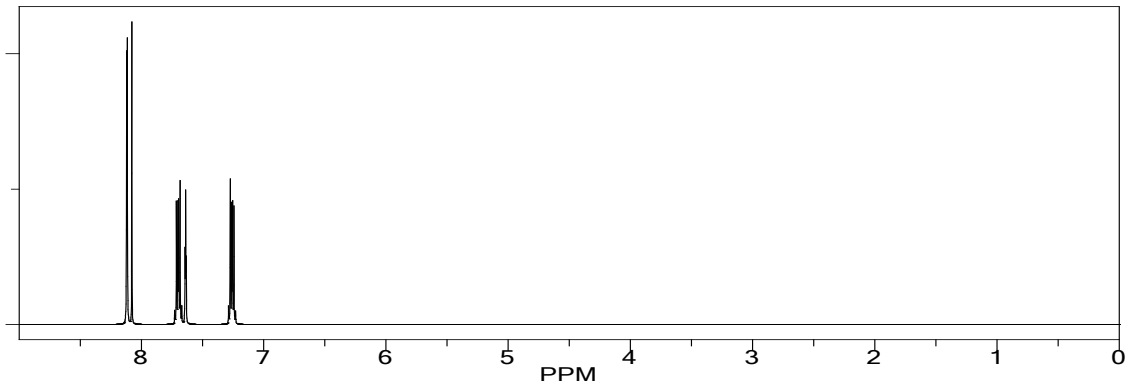
H [1]NMR-Spectra: -Benzimidazole(CH-7.26,CH-7.26,CH-7.70,CH-7.70,CH-7.70,CH-8.08) Benzene(CH-8.19,CH-8.47,CH-8.47,CH-19).

STRUCTURE-3:-(4-Carboxy benzene-sulfonyl) benzimidazole



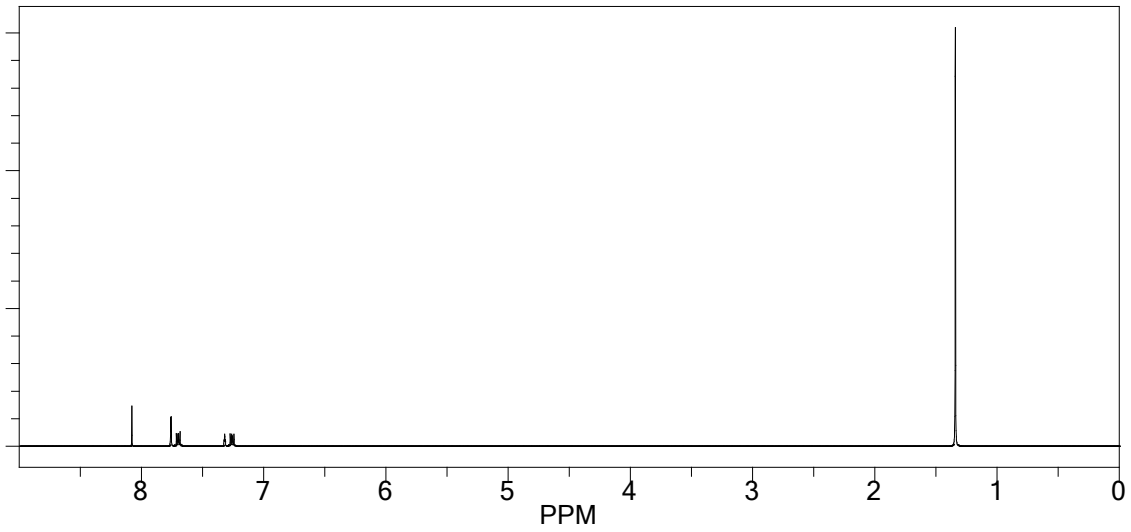
H [1]NMR-Spectra: -Benzimidazole(CH-7.26,CH-7.26,CH-7.70,CH-7.70,CH-8.08), Benzene(CH-8.14,CH-8.41,CH-8.41,CH-8.14)Carboxylic acid(CH-11.0)

STUCTURE-4:-(3,5-bistri fluoromethayl benzene-sulfonyl) benzimidazole



H [1]NMR-Spectra: -Benzimidazole(CH-7.26,CH-7.26, CH-7.70,CH-7.70,CH-8.08), Benzene(CH-8.14,CH-8.41,CH-8.41,CH-8.14)Carboxylic acid(CH-11.0)

STUCTURE-5:-(3,5-Bis tert-butyl benzene-sulfonyl) benzimidazole



H[1]NMR-Spectra:-Benzimidazole(CH-7.26,CH-7.26,CH-7.70,CH-7.70),Benzene(CH-8.08,CH-7.3,CH-7.76), Methyl group(CH-1.34,CH-1.34,CH-1.34,CH-1.34,CH-1.34,CH-1.34).

RESULS AND DISCUSSION

The targeted compound was synthesized according to schem-1 and schem-2. The yields, melting point and other related physical data of newly synthesized synthetic compounds are summarized in the table-2. The synthesized new compounds S_1, S_2, S_3, S_4 and S_5were found to exhibit good anti-biotic activity via synergism characteristic. On the basis of literature review to the novel synthetic Benzimidazole incorporated sulphonamide derivatives were synthesized and the structure will be evaluated by TLC chromatography and confirmed (or) validated through the IR, NMR spectral analytical technique. This knowledge can be used to

determine the properties in the further Benzimidazole-sulphonamide derivatives investigations which may help to find some new indications for this pharmaceutical and to avoid some more ADRs in medical use and to expand the anti-microbial activity.

On the basis of predicted Physico-chemical properties of the novel lead compounds were invented with anti-microbial, anti-fungal, anti-inflammatory like and other activities etc.,

Table. No: -5 Physico-chemical properties of synthesized compounds

Structure ID	Structure name and substitution	Molecular formula	Molecular weight	% of yield	Melting point
S_1	1N-(4-iodobenzene sulfonyl)benzimidazole	$C_{13}H_9IN_2O_2S$	387	**78%**	248 °C
S_2	1N-(benzene -4-nitro-sulfonyl)benzimidazole	$C_{13}H_9N_3O_4S$	303	**76%**	221 °C
S_3	1N-(4-carboxy-benzene sulfonyl)Benzimidazole	$C_{14}H_{10}N_2O_4S$	302	**77%**	237 °C
S_4	1N-(3,5-bis trifluoro methyl benzene sulfonyl)Benzimidazole	$C_{15}H_8F_6N_2S$	356	**75%**	253 °C
S_5	1N-(3,5-bis t-butyl benzene sulfonyl)Benzimidazole	$C_{21}H_{26}N_2S$	338.51	**76%**	281 °C

CONCLUSION:

Due to the increasing the frequency of the microbial attack on the living system of human beings there is a need to focus on the scientific survey of new synthetic lead compounds having antimicrobial activity.So, there is a continuous search for indigenous drugs, which can provide antimicrobial activity. The Benzimidazole and sulphonamide, these both are plays a major role in the showing a pharmacological action against the several microorganisms. A wide variety of several Benzimidazole & sulphonamide derivatives are currently being used as a active medicaments against the several inflammatory disease and other pathological disorders.

Several researches are focusing on the development of novel Benzimidazole–sulphonamide derivatives with better pharmaceutical& pharmacological acceptance like with better affinity, efficacy and with less side effects. This area has got the tremendous potential to come up with new lead entities of medicinal importance. This study gives the importance of Benzimidazole incorporated with sulphonamide derivatives for rational drug designing for disases.ad it serves an accepted molecule for the modification to obtain clinically useful entities up to becoming millennium.

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. BIBLIOGRAPHY

1. Prakash Prajapat1, Hasit Vaghani1, Shikha Agarwal2, and GL Talesara .,2017.
2. Fatmah A.S.Alasmary, Chemistry department, college of science, king Saud University, Riyadh 11362 Saudi Arabia. Vol 20, 2015.
3. GeetaYadav, et.al (2014)., Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities, European Journal of Medicinal Chemistry.
4. Hui-Zhen Zhang et. al (2016)., Design, synthesis and antimicrobial evaluation of novel benzimidazole-incorporated sulfonamide analogues, European Journal of Medicinal Chemistry.
5. Turgay Tunc1 et.at., Synthesis And Antimicrobial Study of New Benzimidazole Schiff Bases Bearing P-Toluene Sulfonamide Moiety.
6. Shatha Ibrahim Alaqeel, et.al., Department of Chemistry, College of Science, King Saud University (034), Riyadh 11495, Saudi Arabia Received 17 December 2015; revised 2 February 2016.
7. Z.Breijyeh, B.Jubeh, R.Karaman," Resistance of gram-negative bacteria to current antibacterial agents and approaches to reslveit", Molecules, vol.25, no6, Article ID 1340, 2020.
8. Z.A.Alagoz, S.Yildiz, E, Buyukbingol, Chemotherapy, 53, 110, (2007).
9. E. Mulugeta, Samuel. Y, department of applied chemistry, school of applied natural science, adama science and Technology University, synthesis of Benzimidazole-sulfonyl derivatives and their biological activities. , 05 Apr 2022, Volume 2022, Article ID 7255299.
10. Santosh Kumar Verma, RameshwariVerma, Fan Xue, Piyush Kumar Thakur,Y.R. Girish, K.P. Rakesh, Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its structure-activity relationships (SAR) studies. Bioorganic Chemistry, 17 October 2020.
11. Ramanpreert Walia1, Md. Hedaitullah1, Syeda Farha Naaz1, Khalid Iqbal1 and HS. Lamba 2, bezimidazole derivatives-on overview,2011, ISSN:2231-2781.
12. K.F. Ansari, C. Lal Department of Chemistry, Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives ,Harcourt Butler Technological Institute, Nawabganj, Kanpur 208002, Uttar Pradesh, India. 2009 Elsevier Masson.
13. Sumit Tahlan, Sanjiv Kumar and balasubramanaihnarasimhan Pharmacological significance of heterocyclic 1H-benzimidazole scaffolds: a review, BMC Chemistry (2019)13:101.
14. R.M. Acheson, An introduction to the chemistry of heterocyclic compounds, 3rd edition Wiley India Pvt. Ltd New Delhi (2008).
15. Zeynep Ates-Alagoz, Antimicrobial Activities of 1-H-Benzimidazole-based Molecules.2016.

16. Yogita Bansal, Manjinder Kaur, Gulshan Bansal, Antimicrobial Potential of Benzimidazole Derived Molecules, Mini Rev Med -Chem2019.
17. Umesh Kumar, Rakesh Narang, Surendra Kumar Nayak, Sachin Kumar Singh, Vivek Gupta. Benzimidazole: Structure Activity Relationship and Mechanism of Action as Antimicrobial Agent. Research J. Pharm. and Tech. 2017.
18. Garvit Satija, Barkha Sharma, benzimidazole based derivatives as anti-cancer activity relationship analysis for various targets. 28 aug 2021.
19. Shejuti Rahman Brishty, Md. Jamal Hossain, Mayeen Uddin Khandaker Mohammad Rashed Iqbal Faruque, Hamid Osman5 and S. M. Abdur Rahman, A comprehensive Account on Recent Progress in Pharmacological Activities of Benzimidazole Derivatives. 03 November 2021,