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INTEGRATED COMPUTATIONAL AND BIOLOGICAL STUDIES APPROACH TO 1H-IMIDAZOLE-1-YL OXAZOLIDINE DERIVATIVES: ANTITUBERCULAR, ANTI-BACTERIAL, AND ANTI-FUNGAL PROPERTIES

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ABSTRACT

Anti-tubercular, antibacterial and antifungal activity of synthesised oxazolidine derivatives was tested. Findings show significant antifungal activity, especially on Compound C. Compound D has the most stable electronic characteristics as per Density functional theory (DFT) calculations. It was biologically screened that Compound E is extremely active against Aspergillus niger, and Compound C has the potential activity against Candida albicans. These results imply that derivatives of oxazolidines are potential antimicrobials. The diversified biological functions of novel imidazole amide derivatives containing the imidazole moiety have been synthesised. We researched the ability of these compounds to create intermolecular hydrogen bonds in order to achieve optimal antibacterial activity. We assessed primary targets for antibacterial stains that are E. Coli, P. aeruginosa, S. aureus, and S. pyogenus to determine the enzyme inhibitory potency of generated compounds. The zone of inhibition and MIC were done to check the effectiveness of each compound in inhibiting bacterial growth. The compounds were evaluated for antifungal efficacy against Aspergillus niger, Aspergillus clavatus, and Candida albicans, along with anti-tuberculosis activity against the bacterium H37RV. Compound D showed the lowest MIC values of 125 µg/ml against the H37RV strain of tuberculosis bacteria and also have lowest total energy on DFT study. Compound A and Compound D showed considerably stronger inhibitory effects at lower concentrations, indicating their potential as candidates for additional research. It has moderate to strong antibacterial activity against the studied microorganisms, with considerable suppression of P. aeruginosa and S. aureus. Property D appears to be stable energetically.

Keywords: Substituted Anilines, Heterocyclic Synthesis, Antituberculosis, Antibacterial, Antifungal Studies, DFT.
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INTRODUCTION

Imidazole inclusion is a key synthetic technique in developing new drugs.[1] Bacterial and fungal illnesses threaten worldwide public health. N-substituted imidazole exhibits diverse valuable pharmacological properties, including anti-microbial and anti-fungal activity.[2] Nowadays, there is a rising number of multidrug-resistant gram-positive and gram-negative bacteria and infections due to Staphylococcus aureus.[3] Derivatives containing imidazoles show a wide range of pharmacological and biological characteristics, particularly anti-Alzheimer, anti-bacterial,[4,5] anti-cancer,[6] Anti-fungal,[7] anti-HCV,[8] anti-HIV,[9] and anti-TB activity profiles.[10-12] In this research paper, our objective is to review sophisticated antimicrobial approaches that aim at fungal, bacterial, and tuberculous infections. By collaborating, the study of the investigation of biological activities bridges the gap between these traditionally distinct fields of drug development perspectives on combating infectious diseases. A varied range of bacterial infections has been treated with antibiotics. However, haphazard use of antibiotics may lead to emergencies like multidrug-resistant bacterial strains and may reduce the efficacy of traditional therapies. Immunocompromised individuals are more vulnerable to fungal infections like candidiasis and aspergillosis. This comprehensive review will synthesise the existing knowledge and highlight recent advancements in multifaceted antimicrobial approaches. It will address the challenges and possible interventions to manage them, such as drug resistance and treatment adherence. In this research paper, light is shed on the possible synergies and overlaps between these areas. To conclude, approaches to antimicrobials that are discussed in this research paper have enormous potential to fill the gap in the fight

against bacterial, fungal, and tuberculosis infections. Through the synergy of various therapeutic options and addressing similar areas of weakness, the two methods provide a more holistic and efficient way of addressing the global health burden caused by multidrug-resistant pathogens. The results described in this review will be used in further research activities and new antimicrobial intervention development. This connection offers an expanded awareness of chemical reactions while making it less challenging to improve methods of synthesis for synthesizing new substances.[13] Azole inhibitors have a broad application in antifungal therapies.[14-16] N-azaaryl anilines have significant applications, such as antimicrobial,[17] anti-inflammatory,[18] and antitumor activity.[19] Marketed drugs having imidazole ring derivatives that are Clotrimazole, Miconazole, Ketoconazole, and Tinidazole.[20-21] A wide range of alterations have been made to the pyrazol and pyrazoline group to enhance the pharmacological activity of it since pyrazole-pyrazolines are actively researched to be the 5th generation of antibiotics such as broad-spectrum.[22-32] The current work aims to develop and assess a variety of oxazolidine derivatives for their antifungal, antibacterial, and anti-tubercular properties. The electrical structure, stability, and reactivity of the produced compounds were examined using density functional theory (DFT) simulations in addition to biological screening. The goal of this research is to find novel oxazolidine compounds with possible therapeutic potential by connecting computational insights with experimental antimicrobial efficacy.

EXPERIMENTAL

In vitro Antimicrobial Assay

The broth dilution method was performed to assess the antibacterial activity. It is a traditional *in vitro* assay for bacterial susceptibility. This standard method yields a quantifiable answer for the number of antimicrobial drugs required to suppress the growth of specific microorganisms. The test was carried out in tubes. The minimal inhibition concentration (MIC) and DMSO were used as a diluent/vehicle to obtain the appropriate concentration of medicines to test on standard bacterial strains. The prime advantage of the 'Broth Dilution Method' for MIC assay is that it is easily adaptable. The serial dilutions were made in screening (primary and secondary). Before inoculation, the control tube, free of any antibiotic, is first inoculated by placing a loopful of the test organism uniformly over one quarter of a plate of medium upon which the test organism will grow. It is done in the incubator overnight at 37 degrees Celsius. Tubes are then incubated overnight. MIC of the control organism is determined to ensure that the medication concentrations are accurate. The MIC represents the lowest concentration that inhibits the growth of the organism. Before incubation, the growth rate from the control tube, which serves as the initial inoculum, is compared. Primary and Secondary Screening Methods. Every synthetic drug was diluted to a stock solution concentration of 2000 micrograms per millilitre. Primary screening: The synthesised drugs were screened in concentrations of 1000 micro/ml, 500 micro/ml, and 250 micro/ml. The active synthetic medications discovered in this initial screening were tested against every species of microorganism in a subsequent phase of dilution testing. Secondary screening: The drugs identified as active in primary screening were similarly diluted to achieve concentrations of 200 micro/ml, 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, and 6.250 micro/ml. Outcome in reading is identified through the choice of maximum dilution, where the inhibition zone is that which is at least 99% in the MIC. The volume of the inoculum influences the result to a considerable extent. There are expected to be 108 organisms in the test mixture per milliliter.[33-38]

Density Functional Theory

DFT is the study of the three-dimensional electronic properties of the molecule. The DFT study of the synthesised compound was carried out using the following software: ChemDraw Professional 16.0 and GAUSS View 6.0[39] were used to create input files and visualise the structure. All DFT calculations were performed using the GAUSSIAN 09 rev. program package.[40] There was optimisation of geometry and their parameters, Frontier Molecular Orbital (FMO), Mulliken charge and Molecular Electrostatic Potential (MEP) mapping in the DFT study. The approaches to these studies were through the use of B3LYP functional- Becke three-parameter hybrid exchange functional (B3) and the correlation functions of Lee, Yang, and Parr (LYP).[41] The B3LYP /6-311G (d, p) basis set in the vacuum was used to conduct the DFT study. This paper illustrates the effectiveness of hybridised approaches such as B3LYP/6-

311G(d,p) in the study of bioactive compounds and how the approach is reliable in forecasting the electronic and structural characteristics that are important in medicinal chemistry.[42]

Chemistry

Scheme-1 summarises the synthesis of targeted 1H-imidazole-1-yl incorporated Oxazolidine derivatives. Different substituted amine taken as a starting material. Nucleophilic attack by amine 1A-E on chloro acetyl chloride gives 2A-E after removal of chlorine as a good leaving group. 2-(2-butyl-5-chloro-4-formyl-1H-imidazol-1-yl)-N-(phenyl)acetamide derivatives 4A-E was prepared according to SN2 reaction with 2-butyl-5-chloro-1H-imidazole-4-carbaldehyde 3, where an atom of carbon that is joined to a strong leaving group is attacked by a nucleophile in an SN2 (substitution nucleophilic bimolecular) reaction. The nucleophile displaces the leaving group as the reaction progresses, creating a new bond between the carbon atom and the nucleophile. The link between the carbon atom and the leaving group is also broken at this point. The final molecules substituted reaction with primary amine 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one 5 to form imines, primary amine forms imine derivatives 2-(2-butyl-5-chloro-4-((((2-oxo-3-(4-(3-oxomorpholino) phenyl)oxazolidine-5-yl)methyl)imino)methyl)-1H-imidazole-1-yl)-N-(phenyl)acetamide A-E also known as Schiff bases (Scheme-1). Aldehyde 3 derivative was prepared from valeronitrile, that undergo rection with methanolic HCl and ammonia, giving methyl pentanimidate with reacted glycine that was synthesised 3 with vilsmeier-Haack reaction, phosphorus oxychloride and N, N-Dimethyl formamide as a solvent. Oxazolidine 5 was an intermediate of rivaroxaban API. Calculations suggest that the observed chemo selectivity is kinetically controlled and results in the thermodynamically most stable product. Oxazolidines and imidazolidines produced from an amino malonate are described.[43] Although oxazolidines have variable reactivity, they are often identified by ring-opening in acidic conditions that results in the creation of iminium cations.[44] The compounds were synthesised following the procedure reported in our previous publication.[45] Promising antibacterial properties have been reported for several other oxazolidinone derivatives with C-ring alterations. For instance, an imidazole–oxazolidinone hybrid with strong activity.[46]

***In vitro* Anti-bacterial Activity**

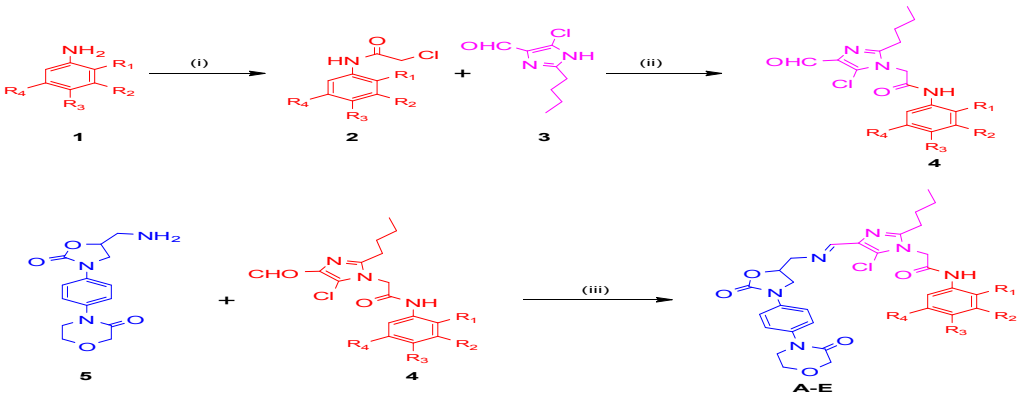
By using the broth microdilution method, the minimal inhibitory concentration (MIC) of all synthesised compounds A–E was measured in accordance with the National Committee for Clinical Laboratory Standards (NCCLS). Antibacterial activity was tested against two gram-positive (Staphylococcus aureus MTCC 96, and Streptococcus pyogenes MTCC 442) and two gram-negative (Escherichia coli MTCC 443, Pseudomonas aeruginosa MTCC 1688) bacteria by utilising Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, and Norfloxacin as the standard antibacterial drugs. The strains used in the activity were obtained from the Chandigarh Institute of Microbial Technology (MTCC-Micro Type Culture Collection). We used Mueller-Hinton broth as a nutrient medium to grow and dilute the drug suspension for the test. To achieve the appropriate concentration of chemical to test on the standard bacterial strains, 2% aqueous DMSO was used as a diluent.

***In vitro* Anti-Fungal Activity**

Using nystatin and griseofulvin as standard antifungal drugs, antifungal activity was assessed against three fungus species (Candida albicans MTCC 227, Aspergillus niger MTCC 282, and Aspergillus clavatus MTCC 1323).

***In vitro* Anti-Tuberculosis Activity**

The encouraging results from the antibacterial activity led us to do preliminary antituberculosis testing on the title compounds. Primary screening of all freshly synthesised compounds was performed using Lowenstein-Jensen medium (traditional approach) against Mycobacterium tuberculosis H37Rv strain at 250 mg/mL and 100 mg/mL, as described by Rattan. The conventional drugs were rifampicin and isoniazid. Table 2 displays the collected results in the form of percentage inhibition. Figure-1 shows a bar diagram of the antibacterial activity of the compound vs standard drugs.



Where,

Entry	R_1	R_2	R_3	R_4
A	H	H	NO_2	H
B	H	H	Cl	H
C	CH_3	Cl	H	H
D	Cl	H	H	Cl
E	H	H	H	H

Scheme-1: Preparation of Imidazole Derivatives

RESULTS AND DISCUSSION

Biological Section

Anti-bacterial Activity

By using the broth microdilution method, the minimal inhibitory concentration (MIC) of E. coli (MTCC 443): Compounds A and B show inhibitory activity against E. coli at a higher MIC than the standard drugs. Compounds C, D, and E show inhibitory activity against E. coli at a lower MIC than the standard drugs. P. aeruginosa (MTCC 1688): Compounds A, B, and D show inhibitory activity against P. aeruginosa at similar or higher MIC compared to the standard drugs. Compound E shows inhibitory activity against P. aeruginosa at a lower MIC than the standard drugs. Compound C's activity against P. aeruginosa is not provided. S. aureus (MTCC 96): Compounds A and D show inhibitory activity against S. aureus at a higher MIC than the standard drugs. Compounds B, C, and E show inhibitory activity against S. aureus at a lower MIC than the standard drugs. S. pyogenus (MTCC 442): Compounds A, B, and D show inhibitory activity against S. pyogenus at a similar or higher MIC compared to the standard drugs. Compounds C and E show inhibitory activity against S. pyogenus at a lower MIC than the standard drugs. When matched with standardised drugs, compound C and compound E consistently exhibit more inhibitory antibacterial action against tested strains of E. coli, S. aureus, and S. pyogenes. Although it has conflicting results when used against P. aeruginosa and S. aureus, compound D also exhibits encouraging inhibitory efficacy against E. coli and S. pyogenus. Compounds A and B, however, are normally of higher MIC, meaning that they do not work as well as the standard drugs. Further studies and experiments will be required to determine the overall effectiveness and safety of the said compounds as future antibacterial agents. To compare the antibacterial activity of the compounds provided in the first table with the conventional medicines provided in the second table, the value of Minimal Inhibition Concentration (MIC) of the compounds in Fig.-1). of table one against different bacterial strains can be analysed. Lower MIC values indicate higher potency and greater antibacterial action. Comparing table 1 and table 2, we can observe the following: Compared to E. coli (MTCC 443), Compound D exhibits the lowest MIC value of 62.5 5g/mL, which is stronger than the standard drugs. Compounds A, B, and E have a lower MIC value against P. aeruginosa (MTCC 1688) than compounds D and E, with Compound D having a MIC value of 125 0G/mL and Compound E having the same MIC value of 125 0G/mL as standard drugs A, B, and Ciprofloxacin. The MIC values of compounds B and C are above the standard drugs. Against S. aureus (MTCC 96): Compounds B and C have the lowest MIC values of 125 µg/mL, matching the potency of the standard drugs Chloramphenicol and Norfloxacin. Ampicillin shows a higher MIC value of 25 µg/mL compared to other compounds and standard drugs. Against S. pyogenus (MTCC 442): Compounds B, C, and E exhibit the same MIC value of 250 µg/mL, while Gentamycin shows the lowest MIC value of 0.5

µg/mL among all the compounds and standard drugs. In this case, Compound A and ampicillin both had higher MIC values than the standard drugs. Table-2 shows the MIC values of standard drugs. Escherichia coli (MTCC 443) (E. coli), Pseudomonas aeruginosa (MTCC 1688) (P. aeruginosa), Staphylococcus aureus (MTCC 96) (S. aureus), and Streptococcus pyogenus (MTCC 442) (S. pyogenus) are common bacterial strains that have been tested in this study to see how well they work against both traditional drugs and novel compounds. Minimal Inhibition Concentration (MIC) values of every compound or drug against all bacterial strains were determined. The experiment demonstrated the differences between antibacterial activity, which highlights the fact that certain compounds and widely used drugs may be used as effective antimicrobial agents. Compound D was the most active in terms of antibacterial activity. Compounds B and C were slightly active against P. aeruginosa and S. aureus strains (Table-1).

Table-1: *In vitro* Antibacterial Activity with MIC Value of Compounds A to E

Compound code	*E. Coli*	*P. Aeruginosa*	*S. Aureus*	*S. Pyogenus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
A	250	250	500	500
B	125	250	250	250
C	125	125	125	125
D	62.5	125	250	125
E	125	125	125	250

Table-2: *In vitro* Antibacterial Activity with MIC Value of the Standard Drugs

Standard Drugs	*E. Coli*	*P. Aeruginosa*	*S. Aureus*	*S. Pyogenus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
Gentamycin	0.05	1	0.25	0.5
Ampicillin	32	32	25	32
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

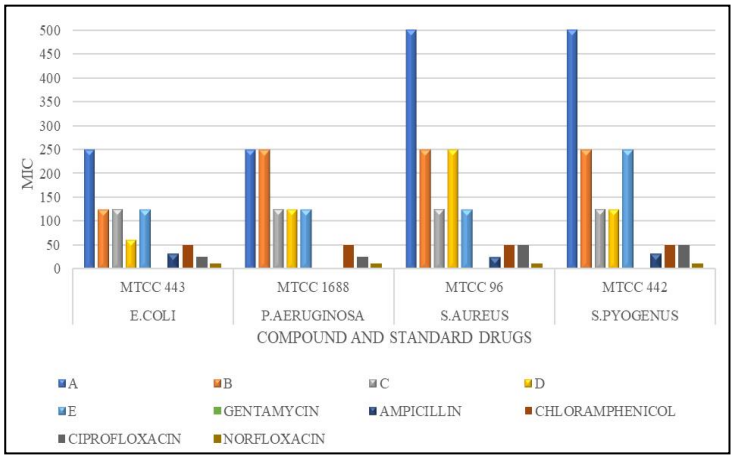


Fig.-1: Antibacterial Activity with MIC Value of Compounds A to E with the Standard Drug

Zone of Inhibition

Compounds showing better activity than the standard drug. The concentrations tested are 25 µg/ml, 50 µg/ml, 100 µg/ml, 250 µg/ml, and 500 µg/ml. The values in the corresponding cells are the zone of inhibition obtained in each compound and strain combination at that particular concentration. The standard column reflects the zone of inhibition of the standard strain at the particular concentration of the compound. The values are used as a reference point when comparing them with the values of the zone of inhibition of the other strains. According to the table, it is possible to evaluate the relative bacterial activity of each compound against various bacterial strains. Say, E. COLI, P. AERUGINOSA, and S. AUREUS exhibit moderate inhibitory activity towards compound A, whereas S. PYOGENUS and C.

ALBICANS exhibit stronger inhibitory activity. It is worth mentioning that this table gives the view of the antibacterial activity of these compounds at given concentrations. The further analysis and interpretation would have been explained by the goals and the context of the study. Strain Sensitivity: Compound B exhibits different degrees of antibacterial efficacy against different strains. As an illustration, its zone of inhibition against E. coli is the highest, with the values increasing with the increase in the concentration of Compound B. And it too shows relative activity against P. aeruginosa, S. aureus and S. pyogenus but it is comparatively less effective against C. albicans. Concentration Effect: Generally, as the concentration of Compound B is increased, the zone of inhibition values become greater, and hence a greater antibacterial effect. This is seen in the trend of increasing values of the zone of inhibition of most strains with the increase in the concentration taken between 25 and 500 micrograms per millilitre. Standard Strain Comparison: The table shows the zone of inhibition of the respective standard strains at the same concentration as well. When these values are compared with the ones of Compound B, we will be able to determine its comparative efficiency. Compound B's antibacterial activity is generally lower than that of the standard strains, indicating that it may not be as potent as the standards in inhibiting bacterial growth.

Table-3: Zone of Inhibition with MIC Value of Compounds A to E

Com. Code	Standard strain		Zone of inhibition (microgramme/ml)						Standard					
			5	25	50	100	250	500	5	25	50	100	125	150
A	*E.Coli*	MTCC 443	-	9	10	12	13	15	-	20	23	28	28	28
	P.Aeruginosa	MTCC 1688	-	10	12	14	15	17	-	20	23	24	26	27
	S.Aureus	MTCC 96	-	9	11	12	14	16	-	17	19	21	22	22
	S.Pyogenus	MTCC 442	-	10	11	12	15	16	-	16	19	21	21	22
	C.Albicans	MTCC 227	-	10	11	13	15	17	-	18	21	22	22	24
B	*E.Coli*	MTCC 443	-	12	14	15	19	20	-	20	23	28	28	28
	P.Aeruginosa	MTCC 1688	-	11	13	14	17	20	-	20	23	24	26	27
	S.Aureus	MTCC 96	-	10	11	13	14	17	-	17	19	21	22	22
	S.Pyogenus	MTCC 442	-	11	12	15	17	18	-	16	19	21	21	22
	C.Albicans	MTCC 227	-	9	10	13	14	16	-	18	21	22	22	24
C	*E.Coli*	MTCC 443	-	12	15	17	20	22	-	20	23	28	28	28
	P.Aeruginosa	MTCC 1688	-	11	14	15	18	20	-	20	23	24	26	27
	S.Aureus	MTCC 96	-	11	13	14	17	19	-	17	19	21	22	22
	S.Pyogenus	MTCC 442	-	12	13	15	16	18	-	16	19	21	21	22
	C.Albicans	MTCC 227	-	10	11	13	14	15	-	18	21	22	22	24
D	*E.Coli*	MTCC 443	-	12	15	17	21	23	-	20	23	28	28	28
	P.Aeruginosa	MTCC 1688	-	12	15	18	19	20	-	20	23	24	26	27
	S.Aureus	MTCC 96	-	10	11	13	15	18	-	17	19	21	22	22
	S.Pyogenus	MTCC 442	-	11	12	14	16	17	-	16	19	21	21	22
	C.Albicans	MTCC 227	-	10	11	13	15	16	-	18	21	22	22	24
E	*E.Coli*	MTCC 443	-	12	14	17	19	21	-	20	23	28	28	28
	P.Aeruginosa	MTCC 1688	-	11	14	15	17	20	-	20	23	24	26	27
	S.Aureus	MTCC 96	-	11	12	14	16	18	-	17	19	21	22	22
	S.Pyogenus	MTCC 442	-	10	12	13	15	17	-	16	19	21	21	22
	C.Albicans	MTCC 227	-	9	10	11	13	15	-	18	21	22	22	24

Anti-fungal Activity

The antifungal activity of Compounds (A, B, C, D, and E) against three strains of fungi: Candida albicans, Aspergillus niger, and Aspergillus clavatus. Compound A possesses MICs of 500 micrograms/mL for C. albicans, 1000 micrograms/mL for A. niger, and 1000 micrograms/mL for A. clavatus. Table-5 lists two widely used medications, Nystatin and Griseofulvin, Fig.-2), along with their MIC values when used to stain fungi. Nystatin has a MIC of 100 micrograms/mL against all three strains, but Griseofulvin has a MIC of 500 micrograms/mL against C. albicans (MTCC 227) and 100 micrograms/mL against A. niger

(MTCC 282) and A. clavatus (MTCC 1323). The relative efficacy of the compounds (A, B, C, D, and E) against the reference drugs (Nystatin and Griseofulvin) may be shown by comparing the two Tables [Table-4 & 5]. Candida albicans (MTCC 227): The lowest MIC value, 250 micrograms/mL, is displayed by compound C, followed by compounds D and E, both of which have the same MIC value. The minimum inhibitory concentrations (MIC) for compounds A and B are Stronger, at 500 micrograms/mL. These results imply that compound C is, in comparison to the other compounds, considerably more effective against Candida albicans. Aspergillus niger (MTCC 282): The MIC values for compounds A and B are 500 micrograms/mL and 250 micrograms/mL, respectively, for compound E. This shows that compound C has stronger antifungal properties. Aspergillus clavatus (MTCC 1323): The MIC value for all of the research compounds (A, B, C, D, and E) is 1000 micrograms/mL.

This implies that the substances might be less effective against this specific strain of Aspergillus clavatus. The MIC of griseofulvin was found to be 100 micrograms/mL against A. clavatus (MTCC 1323) and A. niger (MTCC 282) (Table-5). Moreover, 500 micrograms/mL versus Candida albicans (MTCC 227) Nystatin has the same MIC value as 100 micrograms/mL versus all three fungi stains. Summing up, the results of the antifungal activity tables provide insights into the comparison of the relative efficacy of the compounds and conventional drugs used to treat the analysed fungal strains. While compound E displays strong action against Aspergillus niger, compound C displays potential efficacy against Candida albicans. It's very important to keep in mind that these findings are based on the least inhibitory concentration and that additional research, such as toxicity assessments and additional assays, would be required to establish the compound's overall effectiveness and acceptability for clinical application (Table-4). Figure-2 shows a bar diagram of the antifungal activity of the compound vs standard drugs.

Table-4: *In Vitro* Antifungal Activity with MIC Value of Compounds A to E.

Compound Code	*C.Albicans*	*A.Niger*	*A.Clavatus*
	MTCC 227	MTCC 282	MTCC 1323
A	500	1000	1000
B	500	500	1000
C	100	500	500
D	250	1000	1000
E	250	250	250

Table-5: *In Vitro* Antifungal Activity with MIC Value of the Standard Drugs

Drug	*C.Albicans*	*A.Niger*	*A.Clavatus*
(Microgram/mL)	MTCC 227	MTCC 282	MTCC 1323
NYSTATIN	100	100	100
GRISEOFULVIN	500	100	100

Anti-tuberculosis activity

Table-6 represents the antibacterial activity of different compounds (identified by codes) against various standard strains of bacteria. Table-6 displays the collected results in the form of percentage inhibition. shows anti-tuberculosis activity with MIC value of compound A to E. Fig.-3. Based on the provided anti tuberculosis Activity Table and Standard drugs MIC values, the following results and discussions can be inferred: compound A showed an MIC of 125 µg/ml when tested against H37RV bacteria using the L.J. Medium method. This value indicates moderate effectiveness in restricting the growth of the bacteria. Compound B and compound C both showed an MIC of 250 µg/ml. These compounds showed similar activity to compound A, indicating moderate effectiveness against the H37RV bacteria. Compound D displayed an MIC of 125 µg/ml, similar to compound A.

This suggests that both compounds have comparable efficacy in inhibiting the growth of the bacteria. Compound E had the largest MIC value of 500 µg/ml, which means that it is not as effective as the rest of the compounds tested. It is possibly less inhibitory on H37RV growth. The antituberculosis activity using MIC value of compounds A to E. Isoniazid, as one of the standard drugs, exhibited an MIC of 0.20 µg/ml, demonstrating high inhibitory value against the bacteria. This medication is commonly applied in the treatment of tuberculosis because it is effective. The other standard medication was rifampicin; its MIC

was 0.25 µg/ml, just like isoniazid, rifampicin is also regarded as having a strong antibacterial effect against tuberculosis bacteria.

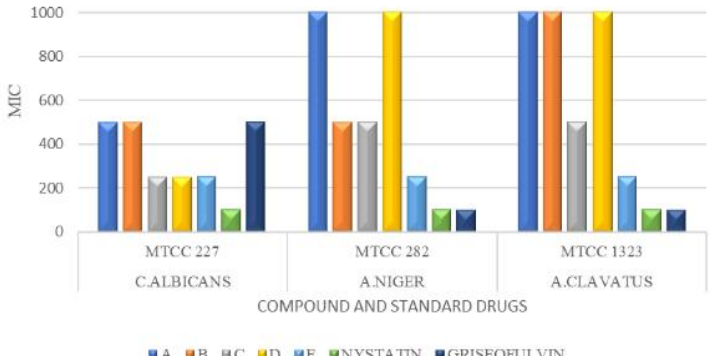


Fig.-2: Antifungal Activity with MIC Value of Compounds A to E with Standard Drugs.

When considering the treatment of tuberculosis, lower values of MIC show higher activity in the inhibition of bacterial growth. It is also shown that both isoniazid and rifampicin had greater inhibitory activity than the compounds tested. Nevertheless, it would require additional examination and assessment to understand whether the compounds are generally effective, safe, and suitable in the treatment of tuberculosis. The offered anti-tuberculosis activity Table displays the results of the testing of various compounds (A, B, C, D, and E) against the H37RV strain of tuberculosis bacteria using the L.J. Medium method. The values of MIC of individual compounds were obtained, which means the concentration at which the compounds can limit the growth of bacteria. Compound A, compound B, compound C, compound D and compound E were used in this study. Compound A and compound D had the lowest MIC values with 125 0g/ml. This indicates that these compounds had a relatively higher ability to inhibit the growth of the H37RV bacteria at lower concentrations than the other compounds tested, and compounds B and C had moderate values of 250 ug/ml, which is the MIC value. Although these compounds were not as effective as compound A and compound D, they each exhibited some effectiveness on the bacteria, with compound E having the highest MIC value of 500 µg/ml, meaning that it was not effective in containing the bacterial growth as compared to the other compounds that had been tested.

Table-6: *In vitro* Anti-Tuberculosis Activity with MIC Value of the Standard Drugs A to E

Compound Code	MIC
A	125
B	250
C	250
D	125
E	500
Isoniazid	0.2
Rifampicin	0.25

This implies that compound E might be less effective in anti-tuberculosis or might need more concentration in order to produce the intended anti-tuberculosis effect. When compared to the conventional drugs used to treat tuberculosis, isoniazid and rifampicin, the organomcompounds under test in this study tended to have a high MIC value. The MIC value of Isoniazid was 0.20 µg/ml, which showed that it is a strong inhibitor of H37RV bacteria. Another standard drug, Rifampicin, also had an MIC of 0.25 µg/ml, which shows the presence of a strong anti-tuberculosis effect. Figure-3 presents a bar diagram of the anti-tuberculosis activity of the compound compared to the standard drugs.

DFT Study

Molecule E has the lowest total energy, indicating it might be the most stable among the molecules analysed (Table-7).

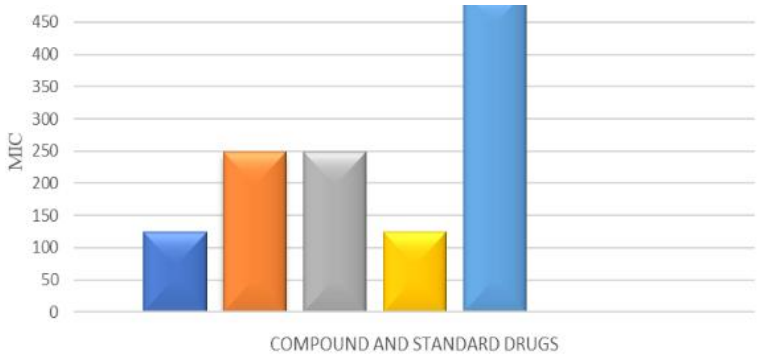


Fig.-3: Antituberculosis Activity with MIC Value of Compounds A to E with Standard Drugs (lower values)

Table-7: FMO Structure Results

S. No.	Property	A	B	C	D	E
1	Total Energy (K eV)	-68.9258	-75.8665	-76.9366	-88.3735	-63.3586
2	E_{HOMO} (eV)	-5.8573	-5.8978	-5.8064	-5.7998	-5.7925
3	E_{LUMO} (eV)	-2.7622	-1.4400	-1.6392	-1.4805	-1.5749
4	ΔE (eV)	3.0951	4.4578	4.1606	4.3193	4.2176
5	Ionisation potential (IP) (eV)	5.8573	5.8978	5.8064	5.7998	5.7925
6	Chemical potential (μ) (eV)	-4.3098	-3.6689	-3.7228	-3.6401	-3.6837
7	Electron affinity (EA) (eV)	2.7622	1.4400	1.6392	1.4805	1.5749
8	Electron Negativity (EN) (eV)	4.3098	3.6689	3.7228	3.6401	3.6837
9	Global Hardness (ɳ) (eV)	1.5476	2.2289	2.0836	2.1597	2.1088
10	Softness (S) (eV^{-1})	0.3231	0.2243	0.2399	0.2315	0.2371
11	Electrophilicity Index (ω) (eV)	6.0010	3.0196	3.3258	3.0676	3.2173
12	Dipole Moment (Debye)	4.95	3.08	5.19	3.79	3.93

Molecule C contains the lowest EHOMO and, therefore, can be susceptible to electron donation. The ELUMO of molecule B is the lowest, which means that it can be more likely to take up the electrons. Energy Gap (ΔE): Molecule B has the greatest energy gap (ΔE), implying that it may be less reactive than other molecules (Fig.-9 to 13).

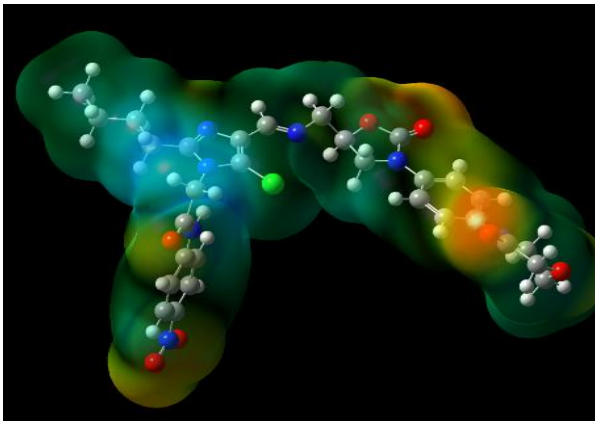


Fig.-4: Molecular Electrostatics Potential of Compound A

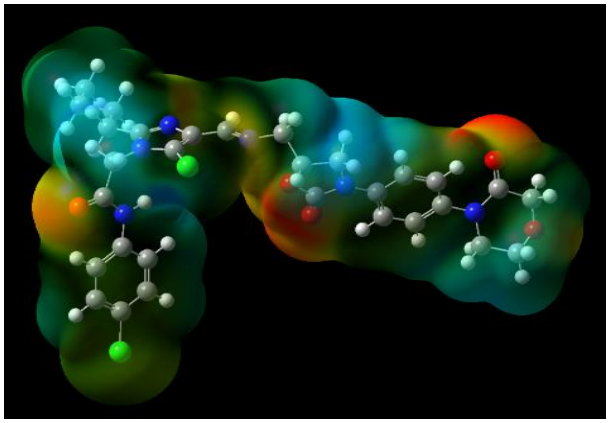


Fig.-5: Molecular Electrostatics Potential of Compound B

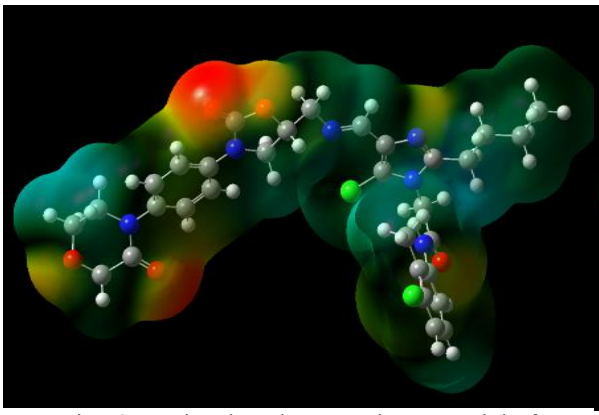


Fig.-6: Molecular Electrostatics Potential of Compound C

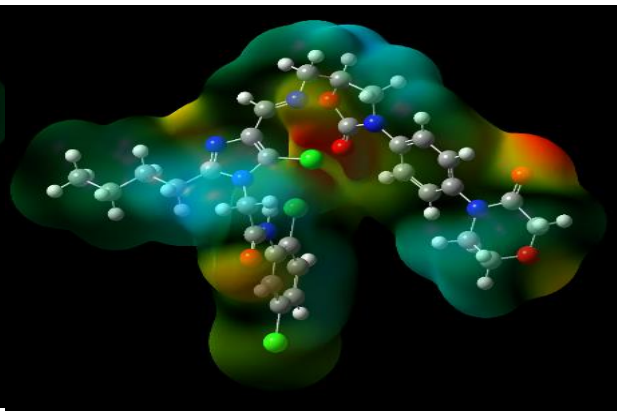


Fig.-7: Molecular Electrostatics Potential of Compound D

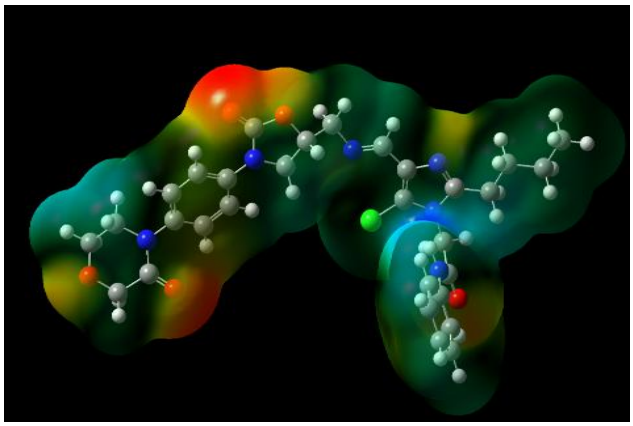


Fig.-8: Molecular Electrostatics Potential of Compound E

Ionisation Potential (IP), Chemical Potential (μ), Electron Affinity (EA), Electron Negativity (EN): These are properties that are interlinked. Molecule A always has the largest values of these properties, meaning that molecule A has a higher likelihood of donating electrons than the others. Global Hardness (∩) and Softness (S): B is the most globally hard molecule and the least soft molecule, which implies that it may be the least reactive molecule. Electrophilicity Index () A: Molecule A is most electrophilic, and this indicates that it is more likely to be attracted by electron-rich species. Dipole Moment: molecule C has the largest dipole moment, which shows that it is the most polar molecule among the molecules under analysis. To conclude, there are various electronic and structural characteristics of each molecule, and they may have consequences for the reactivity, stability, and reaction with other molecules. These conclusions made based on this table may be very important in studying their behaviour under different chemical conditions (Fig.-4 to 8).

DFT Study Related to Antifungal Activity

In structure D, the energy of the highest occupied molecular orbital (HOMO) was large, indicating it is an excellent electron donor, and the energy of the lowest unoccupied molecular orbital (LUMO) was low, indicating a high electron acceptance capacity. Due to these features, along with a medium energy gap, compound D is particularly reactive to fungal cells. Strong dipole moment and electrophilicity index also suggest that compound D has the ability to react with fungal cell membranes in an effective way, which is a requirement of antifungal action.

DFT Study Related to Anti-Tuberculosis Activity

The comparison analysis of anti-tuberculosis activity and the structure of FMO revealed the possibility of compounds D and A as promising molecules in future development as anti-tuberculosis drugs due to their high activity and good structural features.

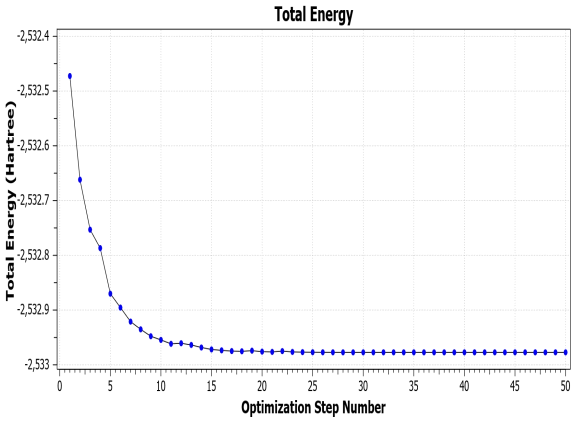


Fig.-9: Compound A Graph of Total Energy vs Optimisation Step Number

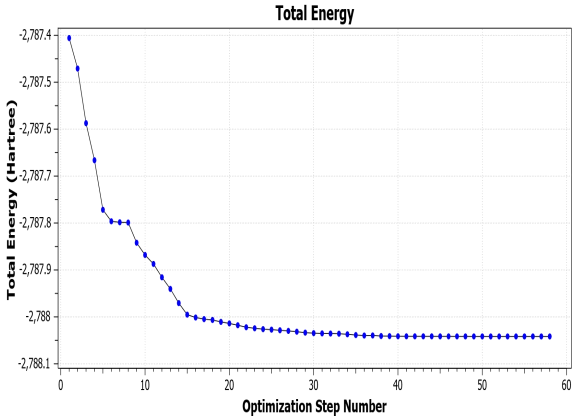


Fig.-10: Compound B Graph of Total Energy vs Optimisation Step Number

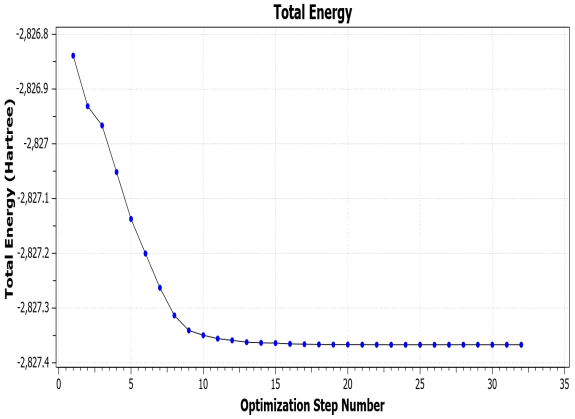


Fig.-11: Compound C Graph of Total Energy vs Optimisation Step Number

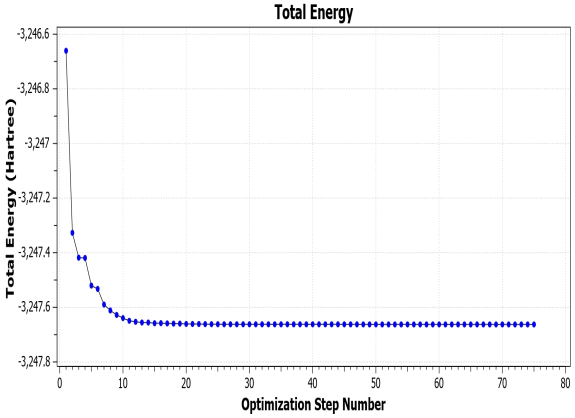


Fig.-12: Compound D Graph of Total Energy vs Optimisation Step Number

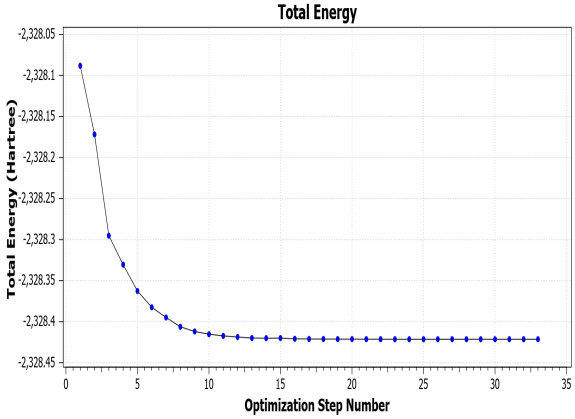


Fig.-13: Compound E Graph of Total Energy vs Optimisation Step Number

DFT Study Related to Anti-Antibacterial Activity

The HOMO-LUMO gap, electrophilicity index, and ideal chemical hardness of Compound C were lower, which means that this compound had an appropriate profile to interact with bacterial cell components. Overall, in this work, the potential of compound C is revealed as a promising one to develop it further into an antibacterial agent and underline its beneficial electrical properties and potent biological effect.

CONCLUSION

Compound D demonstrates the strongest antibacterial effect against E. coli and S. pyogenus, moderately against P. aeruginosa and S. aureus. Conclusively, the given antifungal activity tables provide the information on the minimal inhibition concentration (MIC) values of different compounds and standard drugs towards three fungi, Candida albicans (MTCC 227), Aspergillus niger (MTCC 282), and Aspergillus clavatus (MTCC 1323). According to the obtained results, the compound C shows the lowest values of MIC against Candida albicans and Aspergillus niger, and this factor suggests that compound C can be used as an effective antifungal agent against these strains. Compound E has also been found to be very active against Aspergillus niger. Nevertheless, the compounds that were tested during the study appear to have similar MIC values against Aspergillus clavatus, which indicates that the compounds might have relatively low efficacy against this strain. Nystatin and Griseofulvin, the conventional agents, have stable and effective antifungal effects, with Nystatin having 100 micrograms/mL of MICs against the three strains. Griseofulvin, on the other hand, exhibits different MIC values, where it is more effective over Aspergillus niger and Aspergillus clavatus as compared to Candida albicans. These results show the promise of compounds C and E as antifungal agents and suggest developing them further. Generally, the compounds that were tested in this study as antituberculosis agents demonstrated different levels of antituberculosis effects. Compound A and Compound D showed comparatively stronger inhibitory activity at a lower dose, which indicates that they may be considered as candidates to be used in further research. More research is required to assess their effectiveness, safety and possible modes of action. Moreover, it would be necessary to evaluate the likelihood of the compounds developing drug resistance and the potential side effects before they are considered as possible therapies against tuberculosis. According to the data of the Zone of inhibition, Compound D presents the greatest antibacterial activity compared to Compounds A, B, C, D and E. It shows moderate to good antibacterial activity on the strains tested, although there was a good inhibition on P. aeruginosa and S. aureus. Property D seems to be the most stable in terms of its energy (lowest total energy), and each of the properties has distinct electronic and reactivity properties that can be used to explain its overall behaviour. The above conclusions give insights into the molecular structure, stability, and reactivity of the substances denoted by the properties A-E.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-Being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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