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Design, Synthesis, Structural Elucidation and Biological Applications of Benzohydrazide Derivatives

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ABSTRACT

A series of benzohydrazide derivatives plays a vital role owing to their range of biological and physiological activities. Some new benzohydrazide derivatives have been successfully prepared by the condensation reaction in the present study. The reaction has been carried out at various conditions. The synthesized compounds have characteristic functional groups in the molecules are confirmed through Fourier Transform Infra-Red (FTIR), Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon 13 Nuclear Magnetic Resonance (^{13}C-NMR). Mass spectrometry provides information pertaining to the structures and molecular weight of the some selected compounds. All the compounds were screened for their antibacterial and antifungal activity in Minimum Inhibitory Concentration (MIC) levels. The antioxidant activity of Schiff base containing benzohydrazide moiety and its derivatives were investigated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method. Further, to exemplify the key structural features of the compounds, a molecular docking analysis was performed at Mycobacterium tuberculosis enoyl acyl carrier reductase InhA protein.

Keywords: FTIR, NMR, Antimicrobial activity, DPPH, Discovery studio 2.1 version

INTRODUCTION

During the past two decades, the occurrence and types of life-threatening infections has increased. A major associated crisis is that the dominance of drug-resistant inaccessible bacterial strains in the community has become quite alarming. For these reasons, the demand for new and better chemotherapy, nowadays the search for new chemicals with antibacterial and antifungal activity has become an important field of research around the world [1-5]. Azomethine group (C=N) containing compounds typically known as Schiff bases are obtained through the condensation reaction of an active carbonyl compound with a compound containing the NH_2 group. They have attracted considerable attention due to the potential industrial, analytical and pharmacological applications [6-10].

Benzohydrazide derivatives are versatile set of compounds having unique properties. A broad range of biological activities of benzohydrazones such as anticancer, antimicrobial activity, herbicidal, anticonvulscent, antioxidant, diuretic properties, anti-mycobacterial, antitumour, anti-inflammatory, antiviral and antimalarial activities have been reported [11-20]. Further, careful literature survey for functional groups which could be considered as pharmacophore for the antitubercular activities revealed that the benzohydrazone moiety is common among most of the anti-tubercular agents [21-24].

Hence the target molecules were rationalized so as to comprise the benzohydrazone pharmacophore that are assumed to be responsible for the organic importance of some relevant chemotherapeutic agents. The substitution pattern of such hydrazide derivatives was carefully selected so as to confer a different electronic environment to the molecules. Some of the more effective anti-tuberculosis drugs like iproniazide and isocarboxazide also contain hydrazide-hydrazone moieties [25-27]. The active pharmacophore (-CONH-N=CH-) of hydrazide, hydrazones is mainly responsible for the significant biological activities although the attached neighboring groups may also be responsible [28-30].

In the view of the above remarkable consideration, an attempt has been made to synthesize 4-methoxybenzohydrazide derivatives. Further the synthesized molecules be tested against antimicrobial pathogens, antioxidant activities and molecular docking study also carried out at *Mycobacterium tuberculosis* (Pdb Id: 2nsd) Protein.

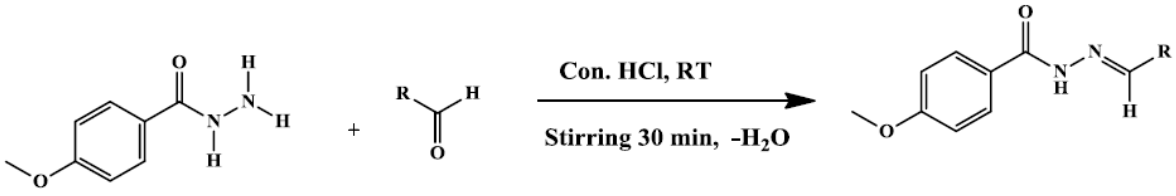
MATERIALS AND METHODS

All reagents were obtained from commercial supply and used without any further purification. Melting points were resolute on EZ-melt automatic melting point equipment without corrections.

The reactions were carried out under the open atmosphere of oxygen. TLC was carried out using silica gel coated glass plate (5 × 20 cm). Fourier Transform Infra-Red (FTIR) spectra were recorded in KBr pellets on a Shimadzu FTIR spectrometer. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on 400 MHz Bruker spectrometer in DMSO-d_6 against Tetramethylsilane (TMS) as internal reference. Carbon 13 Nuclear Magnetic Resonance (^{13}C-NMR) spectra on Bruker Advance II were recorded on 100 MHz spectrometer in Deuterated Dimethyl Sulfoxide (DMSO-d_6). Chemical Shift is reported in Parts Per Million (ppm, δ), and signals are describe as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra of some selected compounds were performed using JEOL MS mass spectrometer. 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical was used as Sigma Aldrich. The electronic spectra were measured on a Perkin Elmer UV-Vis-1800 Spectrophotometer.

General procedure for synthesis of benzohydrazide derivatives (T1-T5)

To a 10 ml aqueous solution of 4-methoxybenzohydrazide (1a, 0.17 g, 0.001 mol) 3,4,5-trimethoxybenzaldehyde (2a, 0.19 g, 0.001 mol) was added followed by concentration HCl (0.2 mmol). The reaction mixture was kept in a magnetic stirrer maintained at room temperature and stirred well for 30 min. The obtained products were filtered, then washed with petroleum ether (40-60%) and dried in a desiccator. After drying, the compound was obtained as crude solid. The crude solid was recrystallized from ethanol. The same procedure is followed for the synthesis of all the other compounds are given in Scheme 1. The physical characteristics of the synthesized compounds (T1-T5) are given in the Table 1.



Scheme 1: Synthesis of benzohydrazide derivatives (T1-T5)

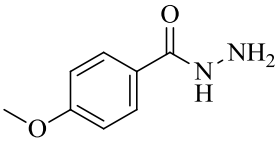
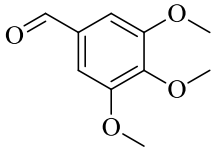
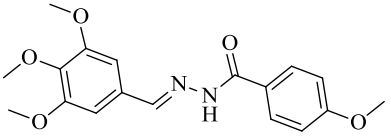
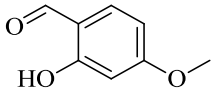
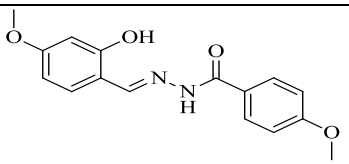
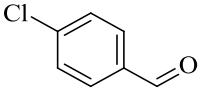
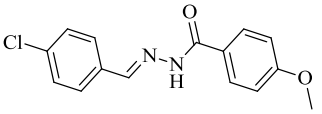
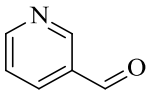
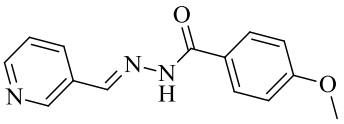
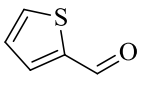
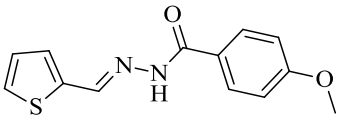
S. No.	4-methoxybenzohydrazide (1a)	Aldehydes (R) (2a-2e)	Product (T1-T5)	Yield (%)
1.	 **1a**	 **2a**	 **T1**	94
2.	**1a**	 **2b**	 **T2**	89
3.	**1a**	 **2c**	 **T3**	85
4.	**1a**	 **2d**	 **T4**	82
5.	**1a**	 **2e**	 **T5**	78

Table 1: List of products and their corresponding reactants

(E)-4-methoxy-N'-(3,4,5-trimethoxybenzylidene)benzohydrazide (T1): Synthesized from 3,4,5-trimethoxybenzaldehyde (2a) and 4-methoxybenzohydrazide (1a). The yield of product was 94%. M.p. 180-182.5°C, FTIR (ν in cm^{-1}), 3227 (NH), 2942 (Ar-CH), 2834 (Ali CH), 1637 (C=O), 1503 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6), δ(ppm)=11.7 (s, 1H, enolic NH proton), 8.4 (s, 1H, CH=N), 7.9 (d, J=8.8 Hz, 2H), 7.1 (d, J=8.8 Hz, 2H), 7.0 (s, 2H, o-Ar-3OCH_3), 3.8 (s, 9H, 3OCH_3), 3.6 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ(ppm)=162 (CO), 161 (p-ArOCH_3), 153 (m Ar3OCH_3), 147 (CH=N), 139 (p-Ar3OCH_3), 130, 129, 125, 113, 104 (ArOCH_3 & Ar3OCH_3). M/z =344.

(E)-N'-(2-hydroxy-4-methoxybenzylidene)4-methoxybenzohydrazide (T2): Synthesized from 2-hydroxy-4-methoxybenzaldehyde (2b) and 4-methoxybenzohydrazide (1a). The yield of product was 89%. M.p. 168-170°C, FTIR (ν in cm^{-1}), 3303 (NH), 2969 (Ar-CH), 2833 (Ali-CH), 1605 (C=O), 1497 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6), δ(ppm)=11.8 (s, 1H, Ar-OH) 11.7 (s, 1H, enolic NH proton), 8.5 (s, 1H, CH=N), 7.9 (d, J=8.4 Hz, 2H), 7.4 (d, J=8.4 Hz, 1H), 7.0 (d, J=8.8 Hz, 2H), 6.5 (d, 2H, Ar-o-OCH_3), 3.8 (s, 3H, Ar-o-OH-p-OCH_3), 3.7 (s, 3H, Ar-p-OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ (ppm)=162 (CO), 159 (Ar-p-OCH_3), 148 (CH=N), 131, 129, 113, 106, 101 (Ar-p-OCH_3 & Ar-o-OH-p-OCH_3), 55 (OCH_3).

(E)-N'-(4-chlorobenzylidene)-4-methoxybenzohydrazide (T3): Synthesized from 4-chlorobenzaldehyde (2c) and 4-methoxybenzohydrazide (1a). The yield of product was 85%. M.p. 146-148°C, FTIR (ν in cm^{-1}), 3272 (NH), 2829 (Ar-CH), 2726 (Ali-CH), 1600 (C=O), 1511 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6), δ(ppm)=11.8 (s, 1H, enolic NH proton), 8.4 (s, 1H, CH=N), 7.9 (d, J=8.4 Hz, 2H), 7.7 (d, J=7.6 Hz, 2H), 7.5 (d, J=8.0 Hz, 2H), 7.0 (d, J=8.4 Hz, 2d), 3.8 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ(ppm)=162.5 (C=O), 161 (p-ArOCH_3), 153 (m-Ar3OCH_3), 145 (CH=N), 139 (p-Ar3OCH_3), 134, 133, 129, 128, 125, 113, (Ar-OCH_3 & Ar-Cl), 55 (OCH_3).

(E)-4-methoxy-N'-(pyridine-3-ylmethylene)benzohydrazide (T4): Synthesized from pyridine-3-carbaldehyde (2d) and 4-methoxybenzohydrazide (1a). The yield of product was 82%. M.p. 227-229°C, FTIR (ν in cm^{-1}), 3432 (NH), 2834 (Ar-CH), 2731 (Ali-CH), 1602 (C=O), 1511 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6), δ(ppm)=11.9 (s, 1H, enolic NH proton), 8.8 (s, 1H, py) 8.5(d, J=8.0 Hz, 1H), 8.4 (s, 1H, CH=N), 8.1 (d, J=6.0 Hz, 1H), 7.9 (d, J=8.8 Hz, 2H), 7.5(t, 1H, py), 7.0 (d, J=8.8 Hz, 2H), 3.8 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ(ppm)=163 (CO), 162 (p-ArOCH_3), 148 (CH=N), 150, 144, 133, 130, 129, 125, 123, 113(py, ArOCH_3), 55 (OCH_3). M/Z=255.

(E)-4-methoxy-N'-(thiophen-2-yl-methylene)benzohydrazide (T5): Synthesized from thiophene-2-carbaldehyde (e) and 4-methoxybenzo hydrazide (1a). The yield of product was 78%. M.p. 205-207°C, FTIR (ν in cm^{-1}), 3273 (NH), 2829 (Ar-CH), 2734 (Ali-CH), 1600 (C=O), 1505 (C=N). ^{1}H-NMR (400 MHz, DMSO-d_6), δ(ppm)=11.7 (s, 1H, enolic NH proton), 8.6 (s, 1H, CH=N), 7.8 (d, 2H, o-ArOCH_3), 7.6 (d, J=4.8 Hz, 1H), 7.4 (d, J=2.8 Hz, 1H), 7.1 (t, J=8.4 Hz, 1H)7.0 (d, 2H, m-ArOCH_3) 3.8 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6), δ(ppm)=162 (CO), 161 (p-ArOCH_3), 142 (CH=N), 139, 130, 129, 128, 127, 125, 113 55 (OCH_3).

Antimicrobial evaluation

All the synthesized benzohydrazide derivatives were screened for antimicrobial activities using the following method. Standard sterilized filter paper disk (5 mm diameter) impregnated with a solution of the test compounds in DMSO (1 mg/ml) was located on agar plate seeded with the appropriate test organisms [31]. All the compounds were tested for their *in vitro* growth inhibitory activity against *Staphylococcus aureus* as Gram-positive and *Escheriea coli* as Gram-negative pathogen strains and *in vitro* antifungal potential against *Aspergillus niger* strain. The plates were incubated at 37°C for 24 h for bacteria and 48 h for fungi. Antibacterial and antifungal activities of benzohydrazide derivatives were compared with erythromycin and gentamycin are standards.

Antioxidant activity

Antioxidants in food play an essential role as a health-protecting feature. Scientific evidence suggests that antioxidants reduce the jeopardy for chronic diseases. The character of antioxidant is to remove free radicals by donating hydrogen to free radicals in its reduction to produce non-reactive species. The antioxidant activities of the synthesized compounds and the standard were measured on the basis of the radical scavenging effect using DPPH. Ascorbic acid was used as a standard and 0.002% DPPH methanolic solution was used as a blank. The assay was performed as reported by Shimada et al., [32-34]. 1 ml of blank solution was added to 1 ml sample and standard (ascorbic acid) solutions of different concentrations are kept separately. The standard and sample solutions were kept in the dark room for 30 min and absorbance of the solutions was measured at 517 nm using UV-Visible Perkin Elmer spectrophotometer. The controls contained all the reagents expect the synthetic compound or positive control substance. The experiment was carried out in triplicate. The DPPH scavenging activity was articulated as the inhibition of free radical DPPH and recorded as %, described by Teme et al., [8]. From the absorbance value, inhibition capacity of the compounds were calculated and using the formula given below.

$$\text{Radical scavenging activity } (\%) = \frac{\mathbf{A_C - A_s}}{\mathbf{A_C}} \times \mathbf{100}$$

Where, A_c-absorbance value of blank, A_s-absorbance value of sample.

Molecular docking analysis

Interaction studies were performed for the compounds (T1-T5) through *M. tuberculosis* (Protein id: 2nsd) protein by Discovery studio Accelrys software (version 2.1.). The X-ray crystallographic formation of *M. tuberculosis* (PDB ID: 2nsd) was downloaded from Protein Data Bank (http://www.rcsb.org/pdb/). The protein was prepared for docking by the elimination of water molecules and heteroatom from the downloaded protein structure. Crystallographic disorders and unoccupied valence atoms were corrected using alternate conformations and valence monitor options and were subjected to force minimize by apply CHARMM (Chemistry at Harvard Macromolecular Mechanics) force fields. Active sites the protein was explored using Discovery studio software. The 2D structures of 4-methoxybenzohydrazide derivatives were retrieved from PubChem, a Chemical database. The exact fit of the ligand to a receptor was studied using Libdock module in the Discovery Studio version 2.1 (Accelrys software corporation, San Diego; http://www.accelrys.com) USA. The interactions of 4-methoxybenzohydrazide derivatives with *M. tuberculosis* structures were analyzed using the receptor-ligand interaction protocol of the software. The receptor cavities were explored and the active sites residue selected were used for the interaction studies. Scoring functions implemented in docking programs make various assumptions and simplify in the evaluation of modeled compound, which includes in terms of hydrogen bonds employed to rank the docked bases and to evaluate the binding site and the number of rotatable bonds present. Using these criteria (Libdock score, Absolute energy) the best receptor-ligand was chosen and its stability was analyzed by the presence of hydrogen bond.

RESULTS AND DISCUSSION

Chemistry

In the present work, a series of benzohydrazide derivatives were synthesized from various aldehydes 2[a-e] and 4-methoxybenzohydrazide (1a) using different reaction condition.

Initially we attempted to synthesis using various organic/inorganic acids and organic/inorganic bases as catalysts and different types of solvents (water, methanol and ethanol) at room temperature. The inorganic acids/bases (HCl, H_2SO_4 and HNO_3/NaOH, KOH and Na_2CO_3) catalyzed reactions gave fascinating results but the reactions using organic acids/bases (HCOOH, CH_3COOH/$(CH_3)_3N$, $(C_2H_5)_3N$) gave moderate yield. It was noted that no one of the solvent other than water was productive for considerable yield. Finally the use of HCl as catalyst and water as solvent gave fascinating results.

Characterization of benzohydrazide derivatives

All the synthesized compound structures were characterized through FTIR, ^{1}H-NMR along with ^{13}C-NMR. Molecular mass spectral studies for some selected compounds. The N-H band appeared in the range of 3432-3227 cm^{-1}. From the FTIR spectra of the all synthesized compounds showed good agreement with the proposed structure at 1637-1600 cm^{-1} is due to the presence of carbonyl (C=O) functional group. The stretching frequency of (C=N) is shown in the range 1511-1497 cm^{-1}. The ^{1}H-NMR spectra of all the synthesized compounds showed good agreement with the proposed structure. A singlet appeared in the range of δ=11.9-11.7 ppm, which is assigned to imidol NH proton adjacent to (C=O) group. Compounds are exhibit amido imidol tautomerism in DMSO solution.

A singlet appeared at δ=8.8-8.4 ppm is assigned to azomethine (-HC=N-) protons. The multiplet were found at δ=7.9-6.5 ppm is due to aromatic (>C-H) protons. A singlet observed at δ=3.8-3.6 ppm is assigned to methoxy (-OCH_3) proton. The ^{13}C-NMR (100 MHz) spectra of all the compounds showed signals in the theoretical range. The peaks appeared in the range δ=163-162 ppm is assigned to carbonyl (C=O) group and peaks exhibited at δ=150-101 ppm are attributed to aromatic carbons. The peaks at δ=142-148 ppm indicate azomethine (CH=N) carbon. The peaks at δ=55-60 ppm are assigned to carbon atoms of methoxy group. The molecular weight of the compounds T1 and T4 have been fine agreement with their proposed structure, which is confirmed by mass spectral analysis.

Antimicrobial activity

The antimicrobial activities were performed by nutrient agar method at concentration level of 100 µg/ml. Erythromycin and gentamycin were used as standard. The antimicrobial activities are shown in the Table 2 and Figure 1. From the studies, the tested compounds revealed better activities against the *S. aureus* bacteria while some of the compounds showed moderate activity against *E. coli* bacteria. The compound (T1) showed greater antibacterial and antifungal activity against *S. aureus* and *E. coli* bacteria. The compound (T1) with three methoxy group of aromatic ring was found to be most effective by Satyanarayana et al., [35-37]. The remaining compounds (T2-T5) exhibited moderate activity against tested bacterial strains.

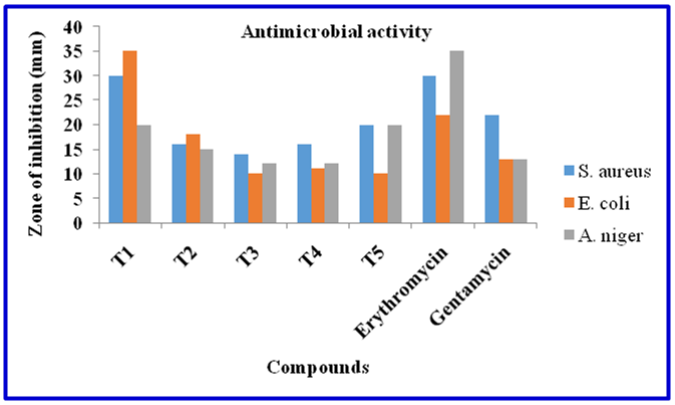


Figure 1: Antimicrobial activities of benzohydrazide derivatives (T1-T5)

Table 2: Antimicrobial activities of benzohydrazide derivatives

S. No.	Organism	*Staphylococcus aureus*	*Escheriea coli*	*Aspergillus niger*
1	T1	26	30	29
2	T2	19	14	12
3	T3	13	16	15
4	T4	16	11	12
5	T5	20	10	20
6	DMSO	-	-	-
7	Erythromycin	30	22	35
8	Gentamycin	22	13	13

Antioxidant activities

The synthesized compounds (T1-T5) were subjected to screening for their possible antioxidant activity using *in vitro* DPPH free radical scavenging technique. The major scavenging activities of all the compounds were carried based on the scavenging activity of stable DPPH free radical with a characteristic absorption at 517 nm. The results are given in the radical scavenging ability of the synthesized compounds (T1-T5) showed in Table 3. The percentage of antioxidant activities by the compounds were given in (Figure 2) graphical representation. At different concentrations of compounds, antioxidant activities were determined by comparing with ascorbic acid as standard. Generally the compounds having lower absorption value possess higher free radical scavenging activities [38,39]. The antioxidant activities of (*E*)-4-methoxy-N'-(3,4,5-trimethoxybenzylidene)benzohydrazide (T1) as well as (E)-N'-(2-hydroxy-4-methoxybenzylidene)-4-methoxybenzohydrazide (T2) are found to be more due to the presence of substituted methoxy group. All the other compounds show moderate antioxidant activities and does other compounds do not have methoxy group.

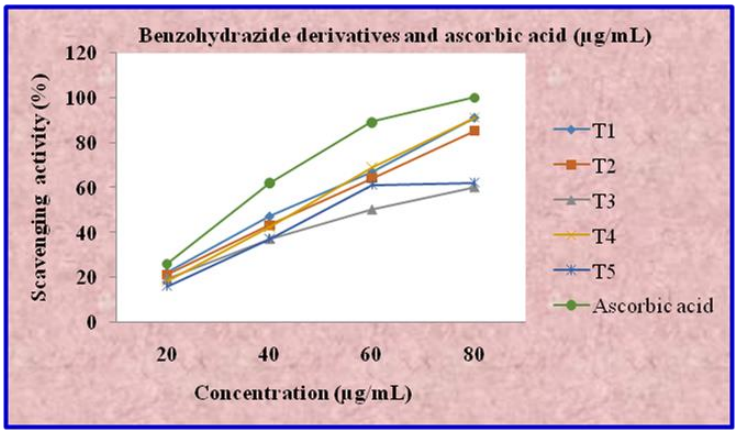


Figure 2: DPPH radical scavenging activity of benzohydrazide derivatives

Table 3: Antioxidant activity of synthesized compounds

DPPH	T1	T2	T3	T4	T5	Ascorbic acid
20 (µl/ml)	22.5 ±0.43	21.0 ± 0.34	19.5 ± 0.55	18.5 ± 0.43	16.5 ± 0.55	25.65 ± 1.79
40 (µl/ml)	47.5 ± 2.62	43.5 ± 3.32	37.0 ± 2.12	42.5 ± 2.62	37.0 ± 2.12	61.26 ± 1.28
60 (µl/ml)	67.5 ± 4.43	64.5 ± 4.27	50.5 ± 4.57	69.5 ± 4.43	50.5 ± 4.57	88.98 ± 6.22
80 (µl/ml)	91.5 ± 5.22	85.5 ± 7.11	60.0 ± 6.52	90.5 ± 5.22	62.0 ± 6.52	99.34 ± 6.95
IC_{50} Value	46.3 ± 3.5	44.62 ± 3.5	65.00 ± 3.5	46.3 ± 3.5	65.00 ± 3.5	34.91 ± 6.95

Molecular docking analysis

The binding conformation within the active site of Protein: 2NSD has been analyzed with the synthesized compounds. In order to find suitable inhibitor for *M. tuberculosis* docking studies were carried out for InhA protein. InhA catalyzes the reduction of long-chain trans-2-enoyl-ACP in the type II fatty acid cells pathway of *M. tuberculosis*. Inhibition of InhA disrupts the biosynthesis of the mycolic acids that are central constituent of the *Mycobacterial* cell wall 39]. The Libdock score values and absolute energy values for T1, T2, T3, T4 and T5 are 113.829, 103.353, 83.141, 98.707 and 93.003, and 96.816, 78.626, 62.945, 49.852 and 36.228 respectively. The hydrogen bond acceptor of the (E)-4-methoxy-N'-(3,4,5-trimethoxybenzylidene) benzohydrazide interacts with the active domain residues with stable two hydrogen bonds. This compound showed hydrogen bond interaction with GLY A: 96 and Vander Waals interaction with SER A: 20 electrostatics interaction. The docking studies revealed that ligand T1 as best ligand which showed high score of Libdock Score and absolute energy. Therefore compound T1 could be efficiently inhibit the activity and the molecule (T1) can be used as anti-mycobacterial drugs against *M. tuberculosis*. The detail interaction distance and images are shown in Table 4 and Figure 3.

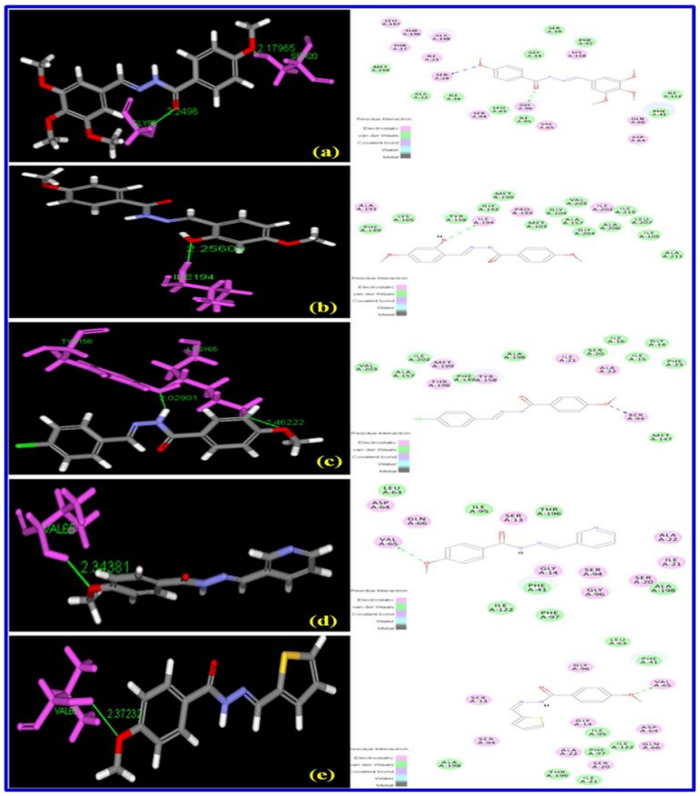


Figure 3: Molecular docking analysis of synthesized compounds

Table 4: Molecular docking results showing absolute energy and LibDock score

Compounds code	H-bond	LibDock score	Absolute energy	Length	Residues
T1	2	113.829	98.447	2.17965 2.2496	SER 20 GLY 96
T2	1	103.353	78.626	2.25609	ILE 194
T3	2	83.141	62.945	2.02901 2.46222	LYS 165 TYP 158
T4	1	98.707	49.852	2.34381	VAL 65
T5	1	93.003	36.228	2.37232	VAL 65

CONCLUSION

We have developed a simple and crucial synthetic technique of aromatic aldehydes related 4-methoxy benzohydrazide derivatives under mild conditions using water as a solvent with higher amount of yield. The antimicrobial activities of the synthesized compounds were effectively screened against gram positive *S. aureus* and gram negative *E. coli* bacterial and *A. niger* fungi strains. Most of the compounds show moderate activities and particularly compound (E) 4-methoxy-N'-(3,4,5-trimethoxybenzylidene)benzohydrazide (T1) showed better activity. The antioxidant ability of the compounds shows moderate activity which increases with increasing number of methoxy group. The binding abilities of compound T1 was found to have greater Libdock score. From the above discussions, the compound T1 has more biological activities (further this compound need to check *in vivo* level in due course).

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