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Synthesis and Biological Evaluation of Novel 1,3,4-Oxadiazole Derivatives as Antimicrobial Agents

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Abstract:

The major drawback of current treatment of infectious diseases are challenging due to resistance to antimicrobial agents and their side effects. In order to overcome this situation, it is necessary to continue the search for new antibacterial agents. In recent scenario heterocycles plays a major role in drug synthesis. In that respect oxadiazole plays a significant role among other heterocycles. From the literature survey oxadiazole was found to be having diverse activity like anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, anti-mycobacterial, anti-depressent and anticancer etc. So it was planned to synthesize a novel series of 1,3,4 oxadiazole derivatives from reaction between 4 morpholin 4-yl benzonitrile treated with hydrogen sulphide gives 4-(morpholin–4yl)benzenecarbothioamide which was cyclisation and hydrozide gives 4-methyl-2-[4-(morpholine-4-yl)-phenyl]-1,3-thiazole-5-carbohydrazide it was under goes cyclisation to yield resultant compound 1,3,4-oxadiazole derivatives (SMV-IVA-IVF). All the compounds synthesized were confirmed by spectral data and evaluated for their antibacterial and antifungal (Cup-Plate method) activity. The compounds SMV-IVD and BM-IVE have shown good antibacterial and antifungal activity and remaining shows poor activity.

Key words: 1,3,4-Oxadiazole, Antibacterial and Antifungal Biological Activity

Introduction:

Oxadiazole is a heterocyclic nucleus, which gains heavy interest by many research scholars regarding invention of novel remedial molecules. Oxadiazole is a five-member heterocyclic compound having two carbon atoms, two nitrogen atoms, one oxygen atom and two double bonds. The systematic name of 1,3,4-oxadiazole has gradually become prevalent and is used exclusively. 1, 3, 4-oxadiazoles are the class of heterocyclic compounds with a wide range of

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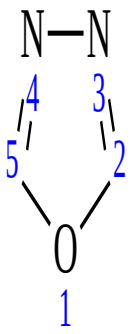
pharmaceutical and biological action. There are possibly four isomers of oxadiazole in which 1,3,4-oxadiazole have enormous importance. 1, 3, 4–Oxadiazole have attracted an interest in medicinal chemistry as ester and amide biososters for a number of biological targets. Variety of therapeutically active agents e.g. raltagravir as HIV-integrase inhibitor, furamizole as nitrofuran anti-bacterial, nesapidil as antihypertensive agents, anti-microbial, anticancer activity, anti inflammatory[1-5]. The new 1,3,4-Oxadiazole derivatives have been successfully synthesized by from reaction between 4 morpholin 4-yl benzonitrile treated with hydrogen sulphide gives 4-(morpholin–4yl)benzenecarbothioamide which was cyclisation and hydrozide gives 4-methyl-2-[4-(morpholine-4-yl)-phenyl]-1,3-thiazole-5-carbohydrazide it was under goes cyclisation to yield resultant compound 1,3,4-oxadiazole derivatives (SMV-IVA-IVF).



1,3,4 - Oxadiazole

Biazole, Oxybiazole Furo (bb') diazole

Figure No 1: Structure of 1,3,4-oxadiazole

Materials and Methods:

The entire all chemicals used were procured from Loba chemie Pvt. Ltd., Mumbai. Purity of starting materials used for reaction was confirmed by checking their melting point and by thin layer chromatography. All the reactions were monitored using thin layer chromatography. The FT-IR spectrum of the synthesized compounds has been obtained from oxygen health care and research center Pvt, Ltd Ahmadabad, Gujarat. The IR spectra were carried out by FT-IR (KBr Press Pellet) spectra were recorded on SHIMADZU Spectrophotometer (Vmax in cm^{-1}).

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Methodology:

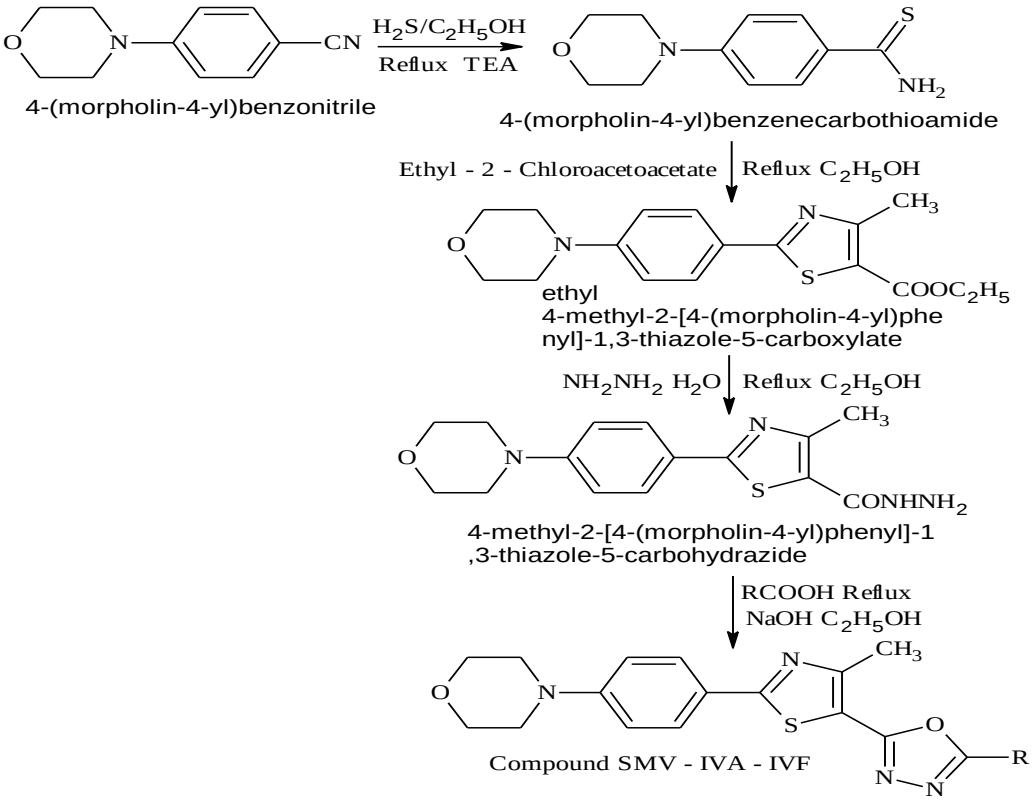
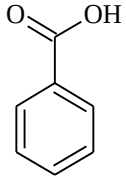
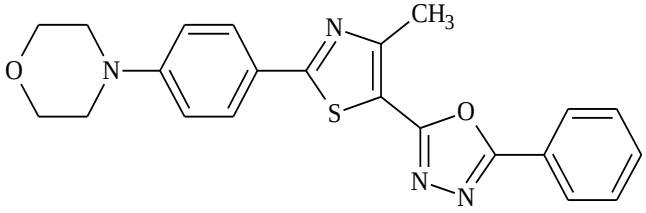


Figure No 2: Representative Scheme for the synthesis of 4-(morpholin-4-yl) benzonitrile resultant compound 1,3,4-oxadiazole derivatives (SMV-IVA-IVF)

Table 1. Derivatives of 4-methyl-2-[4-(morpholin-4-yl) phenyl]-1,3-thiazole-5-carbohydrazide (SMV-IVA-IVF)

Compound Code	Substituted Name With Structure	Derivatives of 4-methyl-2-[4-(morpholin-4-yl)phenyl]-1,3-thiazole-5-carbohydrazide (SMV-IVA-IVF)
SMV-IVA	 benzoic acid	 4-{4-[4-methyl-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-1,3-thiazol-2-yl]phenyl}morpholine

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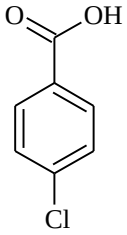
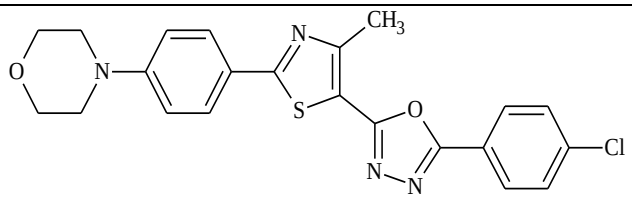
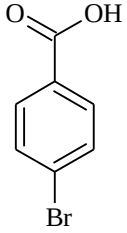
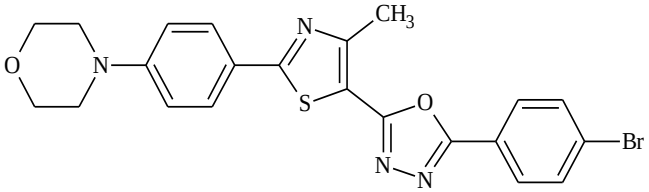
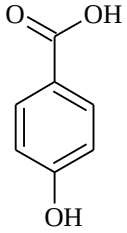
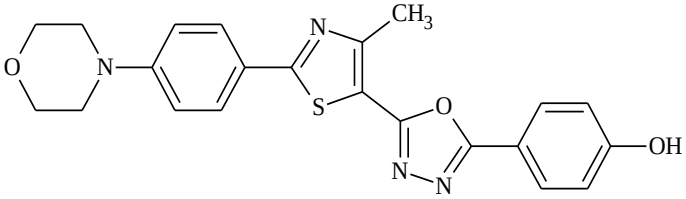
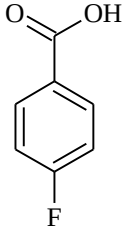
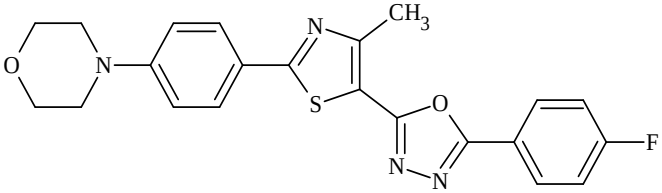
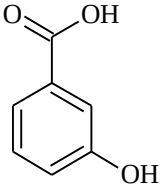
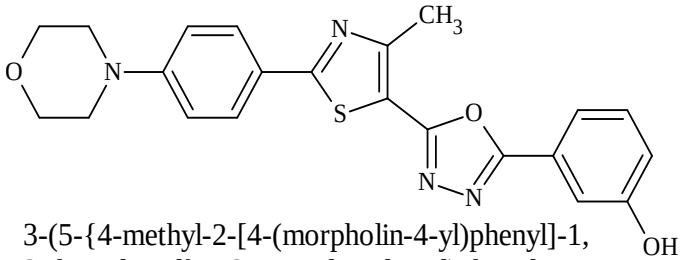
SMV-IVB	 4-chlorobenzoic acid	 4-(4-{5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] -4-methyl-1,3-thiazol-2-yl}phenyl)morpholine
SMV-IVC	 4-bromobenzoic acid	 4-(4-{5-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]-4-methyl-1,3-thiazol-2-yl}phenyl)morpholine
SMV-IVD	 4-hydroxybenzoic acid	 4-(5-{4-methyl-2-[4-(morpholin-4-yl)phenyl]-1,3 -thiazol-5-yl}-1,3,4-oxadiazol-2-yl)phenol
SMV-IVE	 4-fluorobenzoic acid	 4-(4-{5-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-4-methyl-1,3-thiazol-2-yl}phenyl)morpholine
SMV-IVF	 3-hydroxybenzoic acid	 3-(5-{4-methyl-2-[4-(morpholin-4-yl)phenyl]-1, 3-thiazol-5-yl}-1,3,4-oxadiazol-2-yl)phenol

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Biological Evaluation:

The method depends on the diffusion of an antibiotic from a cavity through the solidified agar layer in a petri dish to an extent such that growth of the added microorganisms is prevented entirely in a circular area or zone around the cavity containing a solution of test compounds. About 15-20 ml of molten nutrient agar was poured into each of the sterile petri dishes. The cups were made by scooping out nutrient agar with a sterile cork borer. The agar plates so prepared were divided into different set and each set of the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were then filled with 0.1 ml of the test solution; the plates were then incubated at 37^0C for 24 hours. The zone of inhibition (diameter in mm) developed, if any, was then measured for the particular compound with each organism. The solvent DMF was used as negative-control to know the activity of the solvent. The tested compounds are then compared with that of standard drug used i.e Amoxycillin to measure the activity of the compounds.

Antifungal Activity:

The antifungal activity of 1,3,4-Oxadiazole derivatives was carried out by **cup and plate** method in comparison with that of standard antifungal drug clotrimazole. The fungi cultures used were Aspergillus niger and Aspergillus flavous.

Cup-plate method: This method depends on the diffusion of an antifungal agent from a cavity through the solidified agar layer in a Petridis to an extent such that growth of the added microorganism is prevented in a circular area or zone around the cavity containing a solution of antifungal agent. A previously liquefied medium was inoculated appropriate to the assay with the requisite of the suspension of the microorganisms between 40-50^0C and inoculated medium was poured into petri dishes to give a depth of 3 to 4 mm. Ensured that the layer of medium were uniform in thickness by placing the dishes on a leveled surface.

With the help of a cork borer, scooped out the set agar from each petri dish. Using sterile pipettes, the standard and the sample solution (0.1 ml) of known concentrations ware fed into the bored cups. The dishes ware left standing for 1 to 4 hrs at room temperature as a period of pre-incubation diffusion. These were then incubated for 48 hr. at 37^0C. The zone of inhibition developed; if any was then accurately measured in mm. growth of the added microorganism is prevented in a circular area or zone around the cavity containing a solution of antifungal agent.

Results and Discussion:

The new 1,3,4-Oxadiazole derivatives have been successfully synthesized by from reaction between 4 morpholin 4-yl benzonitrile treated with hydrogen sulphide gives 4-(morpholin–4yl)benzenecarbothioamide which was cyclisation and hydrozide gives 4-methyl-2-[4-(morpholine-4-yl)-phenyl]-1,3-thiazole-5-carbohydrazide it was under goes cyclisation to yield resultant compound 1,3,4-oxadiazole derivatives (SMV-IVA-IVF). All the compounds synthesized were confirmed by spectral data and evaluated for their antibacterial and antifungal (Cup-Plate method) activity.

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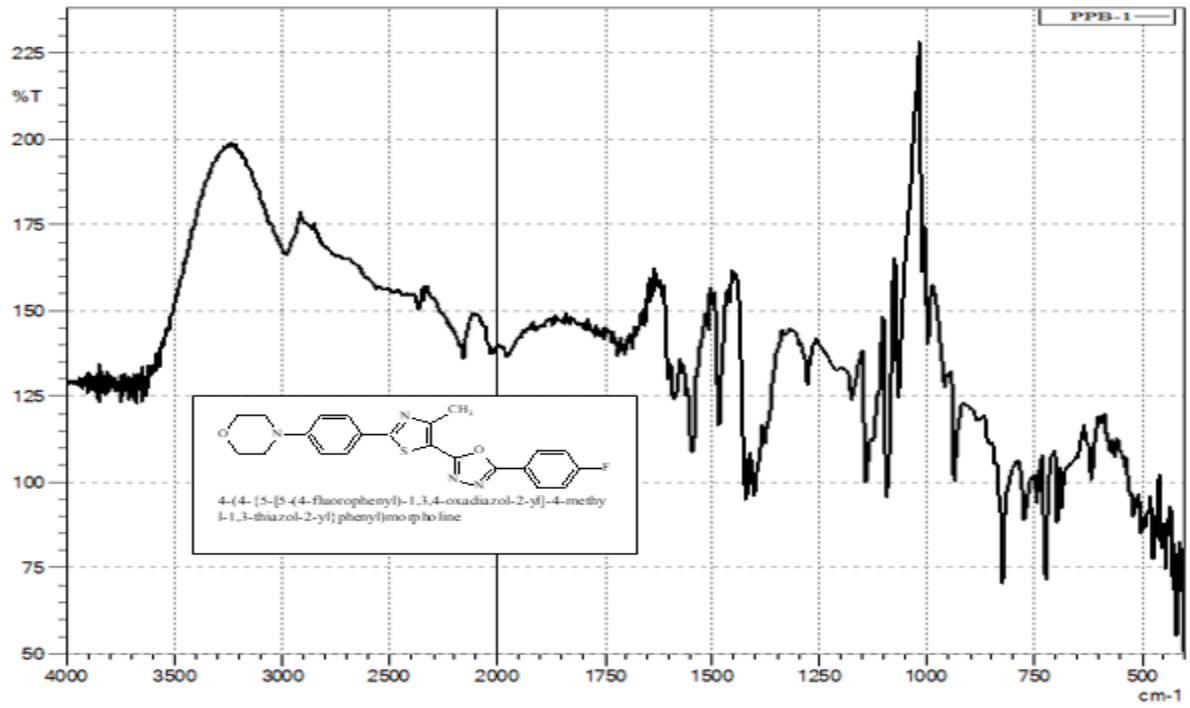

Figure No 3: FT-IR Spectrum of Compound SMV-IVE

In IR spectra 4-(4-{5-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-4-methyl-1,3-thiazol-2-yl}phenyl)morpholine the characteristic peak of -NH Stretching at 1605-1703cm^{-1}, Aromatic CH stretching at 2800-3101cm^{-1}, Aliphatic CH at 2390-2550cm^{-1}, Alkyl Group –CH_3 at 950-1010 cm^{-1}, -F Stretching at 820-910 cm^{-1} respectively confirmed the structure of the title compounds shown in figure no.3.

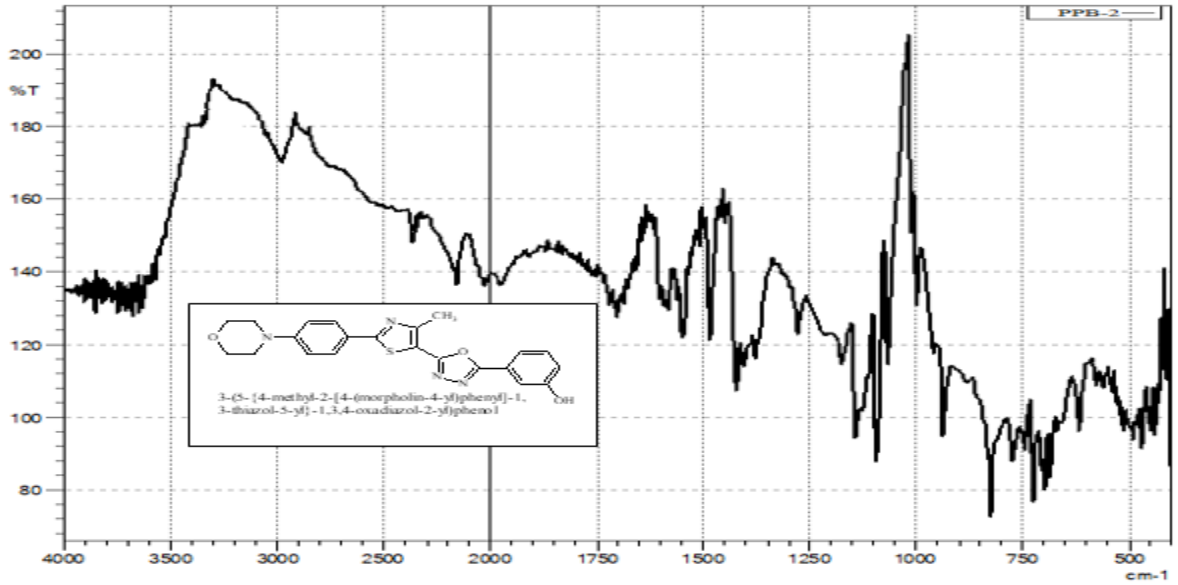

Figure No 4: FT-IR Spectrum of Compound SMV-IVF

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In IR spectra 3-(5-{4-methyl-2-[4-(morpholin-4-yl)phenyl]-1,3-thiazol-5-yl}-1,3,4-oxadiazol-2-yl)phenol the characteristic peak of -OH Hydroxy at 3000-3150cm-1, Aromatic CH stretching at 2900-3150cm^{-1}, Aliphatic CH at 2405-2550cm-1, Alkyl Group –CH_3 at 890-980 cm^{-1} respectively confirmed the structure of the title compounds shown in figure no.4.

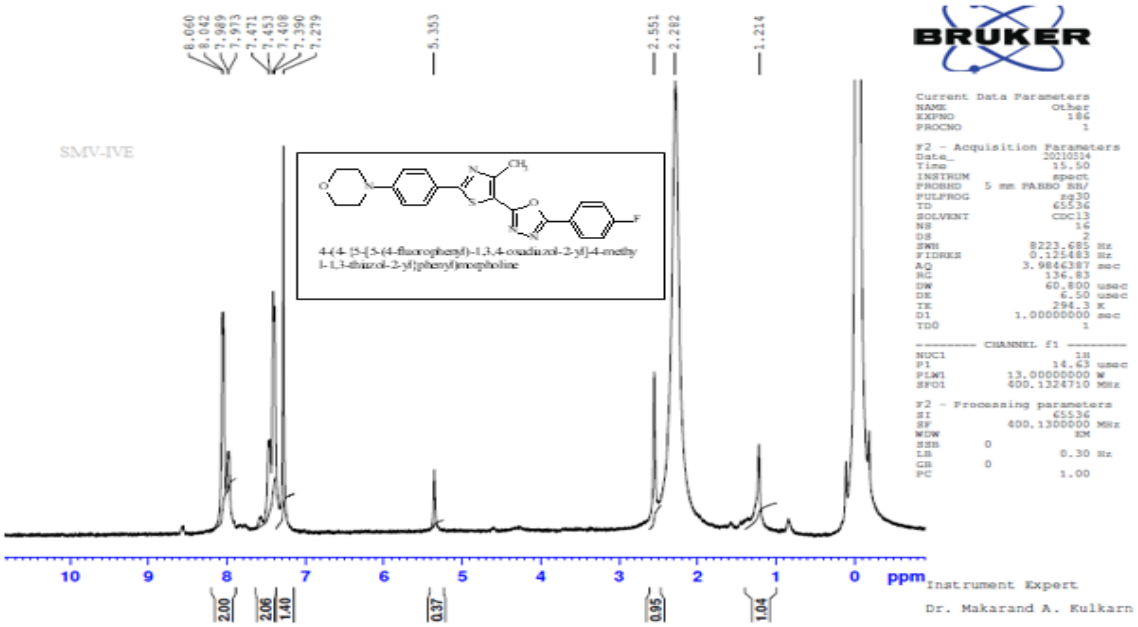

Figure No 5: 1H-NMR Spectrum of Compound SMV-IVE

In 1H-NMR spectra of 4-(4-{5-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-4-methyl-1,3-thiazol-2-yl}phenyl)morpholine the characteristic peak of δ 1.00-3.00 (-CH3), δ 4.3-5.7 (-CH morpholine doublet), δ 6.6-8.8 (Ar-H multiplate) respectively confirmed the structure of the title compounds figure no.5.

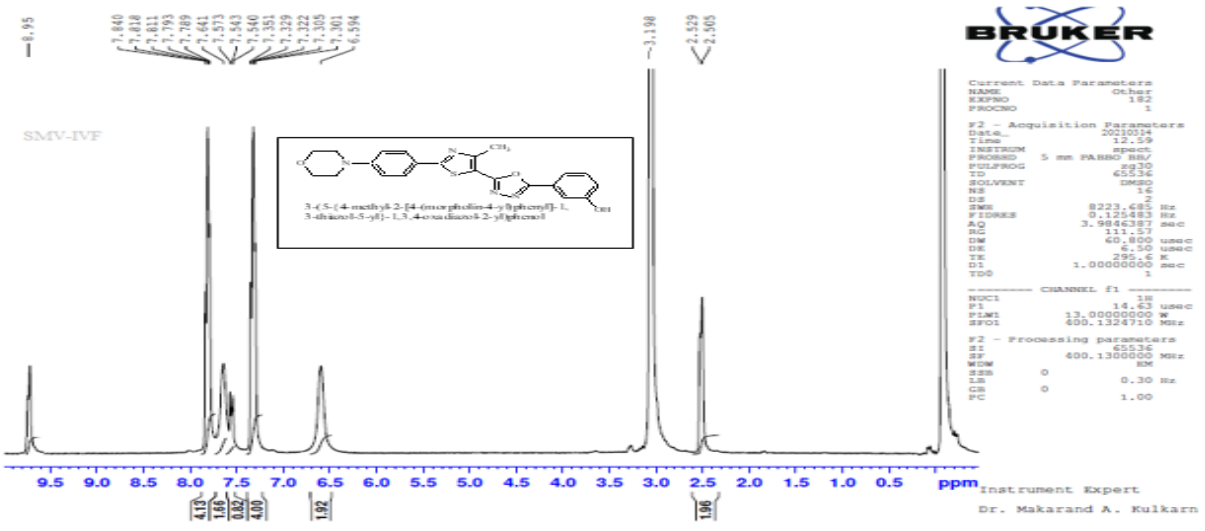

Figure No 6: 1H-NMR Spectrum of Compound SMV-IVF

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In 1H-NMR spectra of 3-(5-{4-methyl-2-[4-(morpholin-4-yl)phenyl]-1,3-thiazol-5-yl}-1,3,4-oxadiazol-2-yl)phenol the characteristic peak of δ 2.40-2.90 (-CH3), δ 3.0-3.5 (-CH morpholine), δ 6.1-8.8 (Ar-H multiplate), δ 9.31 (-OH) respectively confirmed the structure of the title compounds figure no.6.

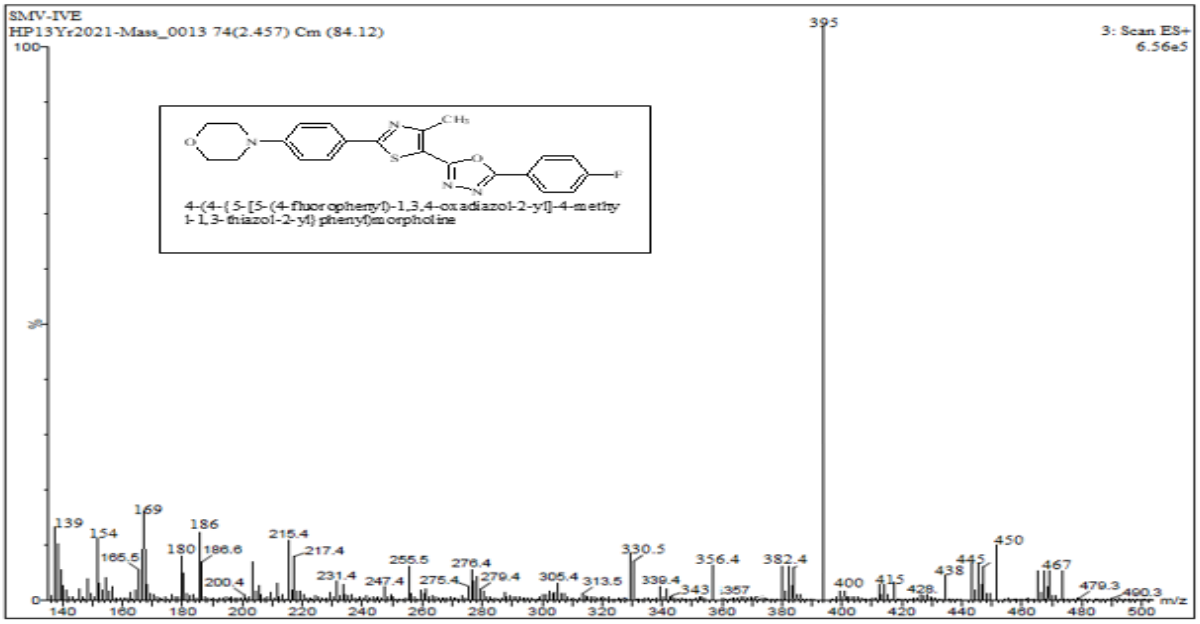

Figure No 7: Mass Spectrum of Compound SMV-IVE

- **M^+ Peaks (Mass Peak)at m/z 422 and Base Peak is 395**
- Molecular weight of compound SMV-IVE is **422** figure no.7**.**

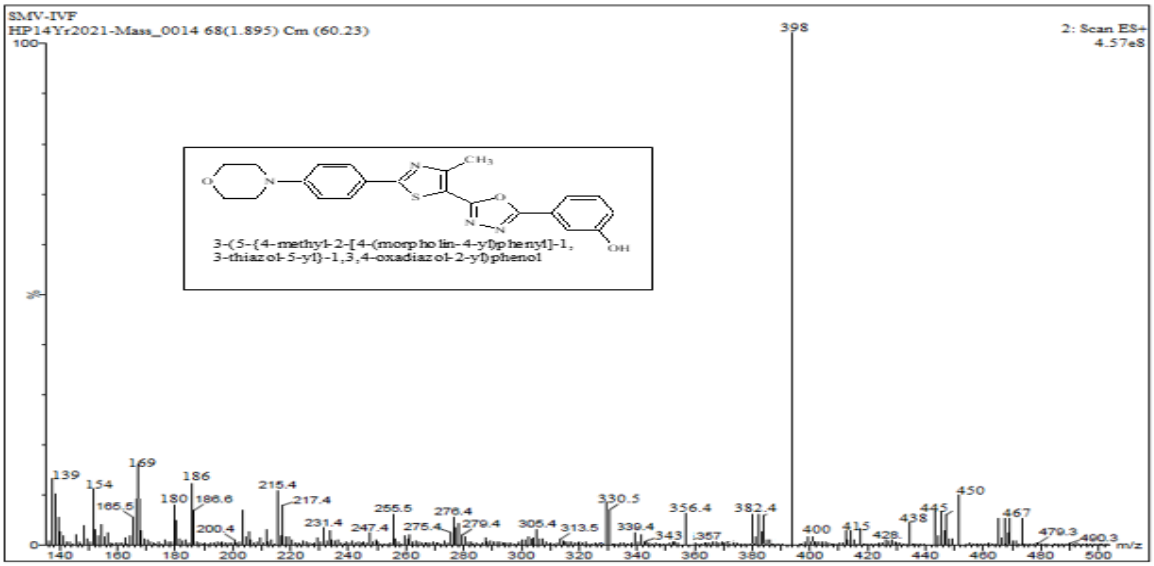

Figure No 8: Mass Spectrum of Compound SMV-IVF

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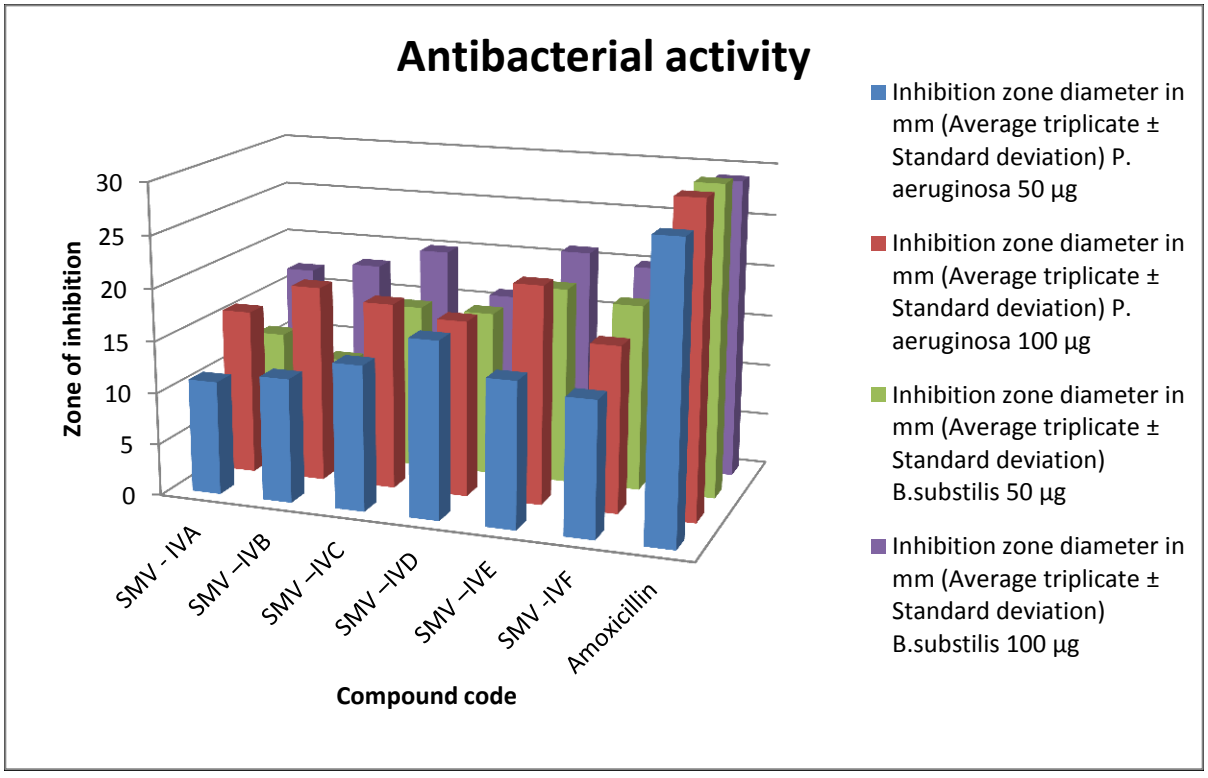
- **M^+ Peaks (Mass Peak)at m/z 420 and Base Peak is 398**
- Molecular weight of compound SMV-IVF is **420** figure no.8**.**

Table No 2: Antibacterial Activity

Compound Code	Inhibition zone diameter in mm (Average triplicate ± Standard deviation)			
	P. aeruginosa		B.substilis	
	50 µg	100 µg	50 µg	100 µg
SMV - IVA	11	16	12	17
SMV –IVB	12	19	10	18
SMV –IVC	14	18	16	20
SMV –IVD	17	17	16	16
SMV –IVE	14	21	19	21
SMV -IVF	13	16	18	20
Amoxicillin	28	30	30	29



Graph No 1: Antibacterial Activity

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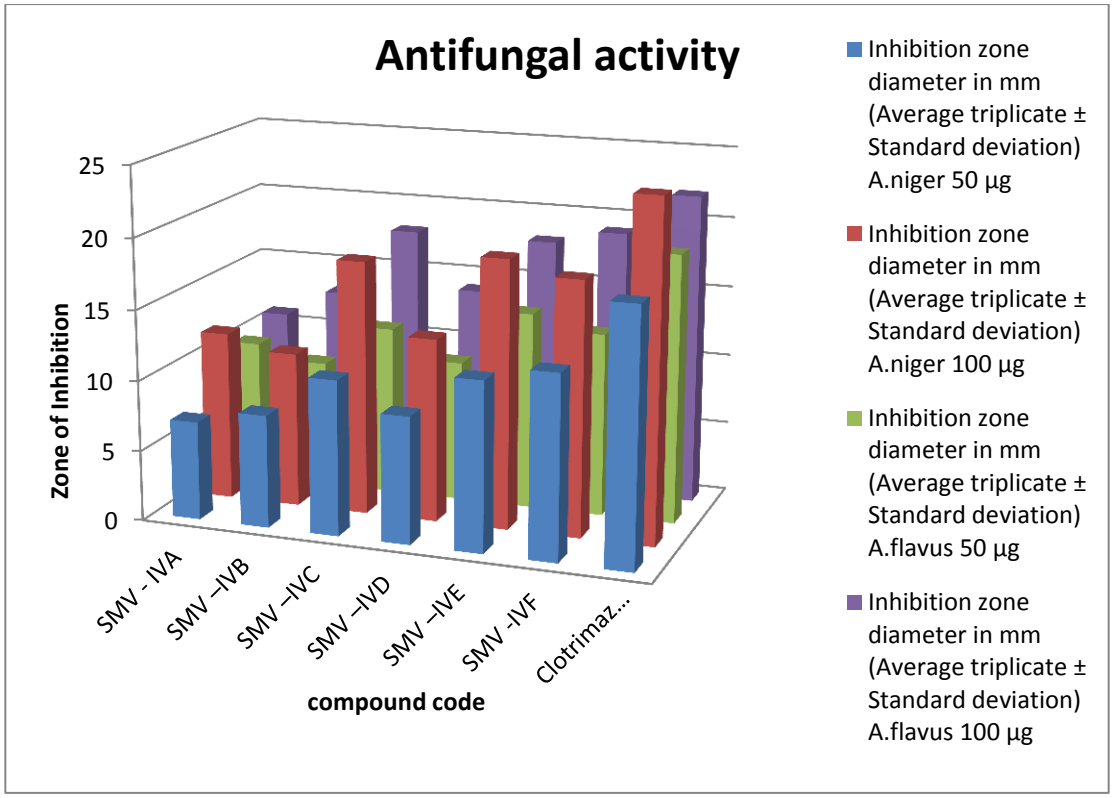
Table No 3: Antifungal Activity

Compound Code	Inhibition zone diameter in mm (Average triplicate ± Standard deviation)			
	A.niger		A.flavus	
	50 µg	100 µg	50 µg	100 µg
SMV - IVA	7	12	10	11
SMV –IVB	8	11	9	13
SMV –IVC	11	18	12	18
SMV –IVD	9	13	10	14
SMV –IVE	12	19	14	18
SMV -IVF	13	18	13	19
Clotrimazole	18	24	19	22



Graph No 2: Antifungal Activity

CONCLUSION

All the compounds synthesized were confirmed by spectral data and evaluated for their antibacterial and antifungal (Cup-Plate method) activity.

Antibacterial activity:

All the synthesized compounds were screened for antibacterial activity studies at a

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concentration of 100 µg/ml and 50 µg/ml using DMSO as a control against Pseudomonous aeruginosa and Bacillus substilis by cup- plate method on nutrient agar media, The standard drug used was Amoxycillin 50 µg/ml and 100 µg/ml used for comparison against Gram positive and Gram negative bacteria. The data in Table indicates that most of the synthesized compounds are active against bacteria. The compounds SMV-IVC, SMV-IVE and SMV-IVF has shown good antibacterial activity were remaining shown poor antibacterial activity.

Antifungal activity:

All the synthesized compounds were screened for antifungal activity studies at a concentration of 100 µg/ml and 50 µg/ml using DMSO as control against Aspergillus niger and Aspergillus flavus on potato dextrose agar media. Clotrimazole were used as standard. The data in Table indicates that most of the synthesized agents are significantly active against fungal strains used for the study. The compounds SMV-IVC, SMV-IVE and SMV-IVF have shown good antifungal activity and remaining shows poor antifungal activity.

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