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Synthesis and biological activity of some various aldehyde and 1,2,3-triazole containing heterocyclic compounds

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ABSTRACT

As heterocyclic compounds show good biological activity, we have synthesized nitrogen containing compounds among them 6b, 6d, 8a and 8b have shown very good antimicrobial activity with remarkable inhibition zones N'-(anthracen-9-ylmethylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4 carbohydrazide and N'-(3-(benzyloxy)benzylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (6a-d, 8a-d) was synthesized from various aldehyde and 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbohydrazide by condensation in acidic media. All intermediates and final compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR, Mass Spectroscopy methods and IR analysis.

***Keywords*:** Hydrazones, Azides, aldehyde, antibacterial, anti-fungal, triazoles

1. INTRODUCTION

The compound having biological activity are most probably contain heterocyclic like pyrazole, thiazole, quinolins, triazoles, oxadiazole, tetrazole, coumarin etc. this work is planed basically on pyrazole and triazole containing molecules because these heterocycles show

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different types of biological activity like, antimicrobial [1-3, 11-13], antitubercular [4, 5], antioxidant [6] anti-TMV activity [7], antibacterial [8], Antiproliferative Activity [9, 14], anti-allergenic [10], anti-HIV [11], cytostatic, anti-depressant, gastric secretion stimulatory, and anti-filarial agents. As pyrazole [15, 16] and 1,2,3-triazole [17-19] are mostly water soluble so that they can be used in different prospect of life due to different kind of biological activity. The pyrazole ring is found within a variety of pesticides as fungicides, insecticides and herbicides, including chlorfenapyr, fenpyroximate, fipronil, tebufenpyrad [20-32].

Triazole and its derivatives represent an important class of heterocyclic compounds. They are having biological importance and are used in the synthesis of drugs. Triazole derivatives are also used in the synthesis of antibiotics, fungicides, herbicides, and plant growth hormone insulators and are potentially good corrosion inhibitions 3-5. The vicinal triazoles, also known as 1,2,3-triazoles, are five membered, unsaturated heterocyclic, the ring consists of three sequentially linked nitrogen atoms and two carbons. The parent compound has one unlocated hydrogen atom, as indeed do all derivatives with hydrogen joined to a ring. Triazoles refer to either one of a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$.

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not very useful due to the resistance developed by microbes. In continuation to this, it is an ongoing effort to synthesize new antimicrobial agents. A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of heteroatoms or grouping imparts preferential specificities in there biological responses.

The number of heterocyclic derivatives containing nitrogen atom possess broad spectrum of biological activities1. B-lactam is a cyclic amide with nitrogen atom in its ring. The contemporary name for this ring system is azetidinones. β-Lactam comes to be a generic descriptor for penicillin family. The ring ultimately proved to be the main component of the pharmacophore. So the term β-lactam possesses medicinal as well as chemical significance2. Penicillin, cephalosporin, & norcordicine antibiotics, which have been widely used as chemotherapeutics agents to treat bacterial infections and microbial diseases contains 2-azetidinone (β-lactam) 3-4.

Furthermore, interest in the chemistry, synthesis and biology of the 2-azetidinone pharmacophore continues to be fuelled by their wide range of biological properties such as antimicrobial, anti-tumour, anti-hyperglycaemic, anti-HIV, anti-inflammatory, analgesic and enzyme inhibitory activities 5-21. Quinazoline system possesses positions 2 and 3 which can be suitably modified by the introduction of different heterocyclic moieties to yield potential anticonvulsant agent.

As various aldehyde and triazoles are very useful compounds in drug synthesis and there is lots of work done on this scaffolds that is why synthesis of this intermediates is quite easy. There are different methods available for synthesis and among them one was selected here.different derivatives of intermediate were synthesized by taking different substituted anilines.

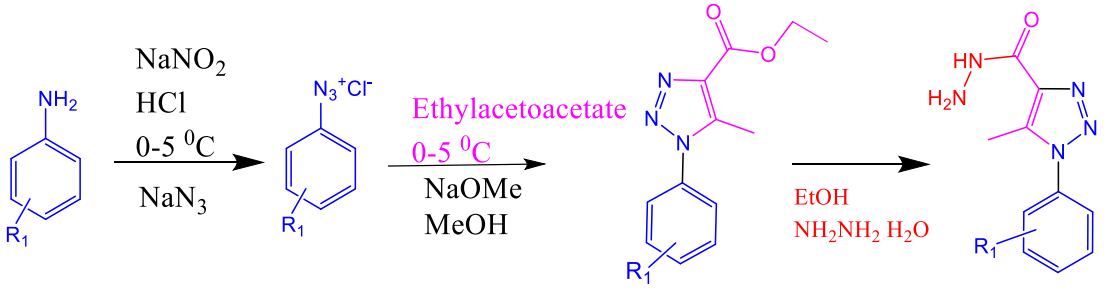
Aniline was diazotized to give diazonium salt which was converted into triazole by cyclisation. This triazoles were further reacted with hydrazine hydrate to give intermediate. The final product was synthesized by the reaction of various aldehyde and triazole in presence of acidic media. All final products were confirmed by ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy.

2. EXPERIMENTAL PROCEDURE

A: general introduction

For all these conversions, progress of reaction was carried out on TLC plate silica gel GF^{254} and the melting points were recorded by open capillary method. Mass spectra were recorded on Shimadzu GCMS-QP-2010 model using Direct Injection Probe technique. ^1H NMR was determined in $CDCl_3$/DMSO solution on a Bruker AVANCE II 400 MHz.

B: general method of synthesis



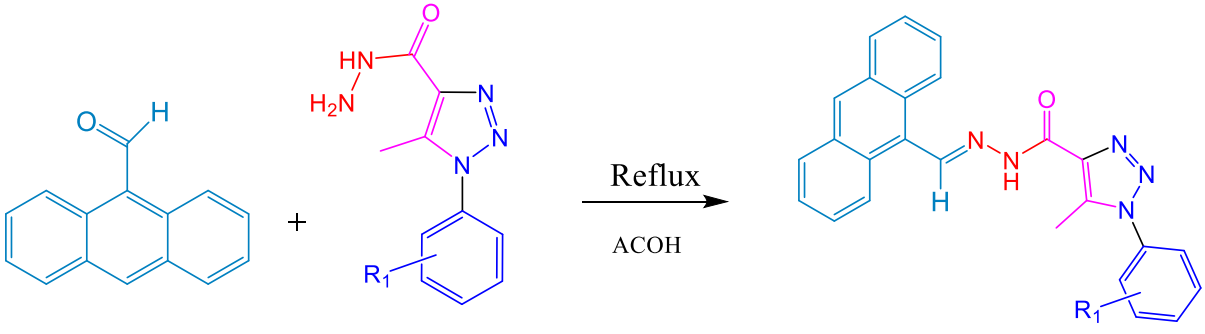
1a; R_1 = 4- Cl
1b; R_1 = 4- F
1c; R_1 = 2,4 di Cl
1d; R_1 = 2,3 di Cl

2a; R_1 = 4- Cl
2b; R_1 = 4- F
2c; R_1 = 2,4 di Cl
2d ; R_1= 2,3 di Cl

3a; R_1 = 4- Cl
3b; R_1= 4- F
3c; R_1 = 2,4 di Cl
3d ; R_1= 2,3 di Cl

4a ; R_1= 4- Cl
4b; R_1 = 4- F
4c; R_1 = 2,4 di Cl
4d; R_1 = 2,3 di Cl

Scheme 1. Rout of synthesis for compounds 4a-d



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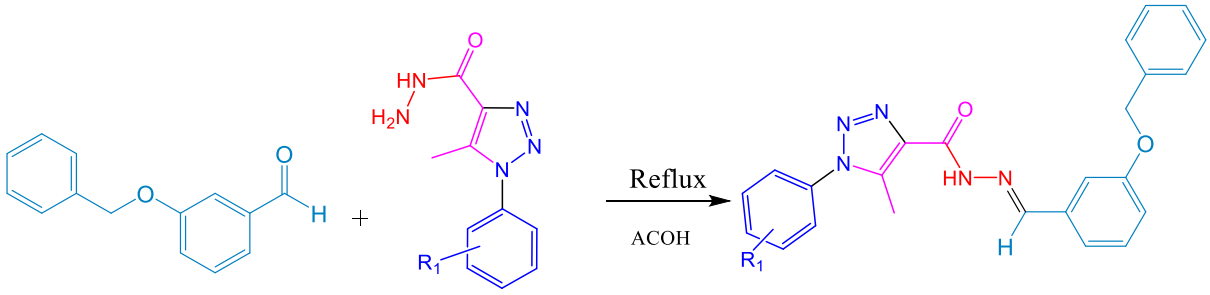
4a ; R_1= 4- Cl
4b; R_1 = 4- F
4c; R_1 = 2,4 di Cl
4d; R_1 = 2,3 di Cl

6a ; R_1= 4- Cl
6b; R_1 = 4- F
6c; R_1 = 2,4 di Cl
6d; R_1 = 2,3 di Cl

Scheme 2. Rout of synthesis for compounds 6a-d



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4a ; R_1= 4- Cl
4b; R_1 = 4- F
4c; R_1 = 2,4 di Cl
4d; R_1 = 2,3 di Cl

8a ; R_1= 4- Cl
8b; R_1 = 4- F
8c; R_1 = 2,4 di Cl
8d; R_1 = 2,3 di Cl

Scheme 3. Rout of synthesis for compounds 8a-d.

2. 1. Antibacterial activity

The antibacterial activity of N'-(anthracen-9-ylmethylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide and N'-(3-(benzyloxy)benzylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (5a-d,7a-d) was appraised against *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei* (anti-fungal bacteria) using Furacin and ltraconozoleas standard drugs. Minimum bacterial inhibitory concentration (MIC) values were resolved by Broth dilution technique. Dimethyl sulfoxide was used as diluent. MIC values of the appraised compounds are recorded in (Table 1).Majority of the prepared compounds displayed less activity than standard drug Furacin and ltraconozole against *E. coli, P. aeruginosa, Kl. pneumoniae, S. aureus, P. marneffei.*

Table 1. Antibacterial / fungal activity table [microgramme/ml]

MINIMAL INHIBITION CONCENTRATION						
SR. NO	**CODE**	*E. coli*	*P. aeruginosa*	*Kl. pneumoniae*	*S. aureus*	*P. marneffei*
		MTCC 443	MTCC 1688	MTCC 109	MTCC 96	WILD STAIN
1	**6a**	25	50	100	50	500
2	**6b**	12.5	25	25	100	100
3	**6c**	50	50	100	25	250
4	**6d**	100	25	50	50	100

5	**8a**	25	50	100	25	50
6	**8b**	12.5	50	25	100	50
7	**8c**	50	50	25	50	100
8	**8d**	25	12.5	25	100	250
9	**Furacin**	25	25	50	50	-
10	**Itraconozole**	-	-	-	-	100

All the synthesised compounds were screened for their in-vitro antimicrobial activity against 24h old cultures of bacterial and fungal pathogens. Antimicrobial activity was determined against *Escherichia coli, Salmonella typhimurium, Klebisiella pneumoniae* and *Aspergillus niger, Aspergillus fumigatus, Curvularia lunata* strains using the disc diffusion assay. For this, a sterile filter paper disc (5 mm) impregnated with fixed doses (600 µg/mL) of the synthesized compounds Antibacterialnder investigation were placed upon the seeded petridishes. Similar disc were prepared for the standard drugs, chloramphenicol, fluconazole and the solvent control, dimethyl formamide. The plates were incubated for 24h at 37 ºC for the bacterial and fungal strains. The zone of inhibition, observed around the disc after incubation was measured. The results are represented in Table 1.

2. 2. Experimental Section

Synthesis of Various azide derivatives of Aniline (2a-d)

For the formation of various azide derivatives, HCl (6 ml) and water (20 ml) were placed in three necked round bottom flask. The solution was cooled at 0 ºC. then aniline derivatives (5.0 g,0.053 mol) was added drop wise and temperature kept constant between 0-5 ºC then sodium nitrite solution (3.65g, 0.053 mol) and sodium azide (3.44 g,0.053 mol) was added drop wise at 0-5 ºC. Then allow the reaction mass to stirred for 30 min. after the completion of reaction the residue extracted using chloroform and washed with water to give 2a-d (4.2g, 70.42%).

Synthesis of ethyl 5-methyl-1-phenyl-1H-1, 2, 3-triazole-4-carboxylate (3a-d)

The formation of ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate derivatives azide (4.2g, 0.035 mol) derivatives treated with ethyl acetoacetate (9.1g, 0.07 mol) then reaction mixture cooled at 0 ºC and then sodium methoxide (3.78g, 0.07 mol) was added under inert atmosphere in methanol as a solvent. The reaction mixture was stirred at ambient temperature and the progress of the reaction was monitored using TLC. after the completion of reaction the

reaction mass was poured into the ice cold water, the residue obtained are dry and separated and washed with water and recrystallized from ethanol to give 3a-d (6.2g, 76.68%).

Synthesis of 5-methyl-1-phenyl-1H-1, 2, 3-triazole-4-carbohydrazide (4a-d)

The carbohydrazide derivatives prepared by dissolving ethyl 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (6g, 0.0259 mol) into ethanol (30 ml) and then hydrazine hydrate was added drop wise and reflux the reaction mass for 6 hrs. at 80 ºC. After the completion of reaction, the reaction mass was colled and residue was separated are filtered and washed with water to give 4a-d (5g, 88.80%).

Synthesis of N'-(3-(benzyloxy)benzylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide derivatives (6a-d)

or

N'-(anthracen-9-ylmethylene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide derivatives (8a-d)

The various aldehyde (5,7) (6.5g,0.0295 mol) was dissolved in acetic acid (30ml) and methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (0.902g, 0.0036 mol) was added to it and allowed to stir at reflux temperature for 4-5 hrs. The reaction was monitored by TLC. After completion, the reaction mixture was poured to water and extracted by ethyl acetate. The organic layer was washed with cold water and dried over Na_2SO_4, concentrated under reduced pressure to obtained pure product. (7.2g, 87.69 %)

N'-(anthracen-9-ylmethylene)-1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (8a)

White coloured, Yield: 82% m.p: 182-184 ºC, ^{1}H NMR: (400 MHz, $CDCl_3$-d) δ 9.09 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 7.94 – 7.75 (m, 4H), 7.51 – 7.42 (m, 2H), 7.41 – 7.34 (m, 4H), 7.34 – 7.21 (m, 2H), 2.41 – 2.37 (m, 3H). ^{13}C NMR (100 MHz) δ 172, 159, 156, 150, 138, 137, 134, 133, 129, 129, 127, 126, 126, 122, 117, 113, 70, 11. LC mass m/z: 439 (M.F: $C_{25}H_{18}ClN_5O$).

N'-(anthracen-9-ylmethylene)-1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (8b)

White coloured ,Yield: 77% compound, m.p: 173-175 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 9.10 (s, 1H), 8.42 (s, 1H), 8.33 (s, 1H), 7.93 – 7.75 (m, 4H), 7.52 – 7.48 (m, 2H), 7.41 – 7.35 (m, 4H), 7.11 – 7.05 (m, 2H), 2.42 – 2.38 (m, 3H). ^{13}C NMR (100 MHz) δ 172, 160, 159, 156, 150, 138, 137, 131, 129,127,127, 126, 122, 117, 116, 113, 70, 11.LC mass m/z: 423.45 (M.F $C_{25}H_{18}FN_5O$)

N'-(3-(benzyloxy)benzylidene)-1-(4-cholorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (6a)

White coloured, Yield: 81% compound, m.p: 182-185 ºC, ^{1}H NMR (400 MHz, Chloroform) δ 9.16 (s, 1H), 7.76 (s, 1H), 7.60 – 7.45 (m, 2H), 7.45 – 7.31 (m, 2H), 7.30 – 7.12 (m, 7H), 6.96 (s, 1H), 6.78 (s, 1H), 5.21 – 5.17 (m, 2H), 2.48 – 2.44 (m, 3H), ^{13}C NMR (100 MHz) δ 172, 159, 156, 150, 138, 137, 134, 133, 129,129,127, 126, 126, 122, 117, 113, 70, 11. M/z: 446 ($C_{24}H_{20}ClN_5O_2$)

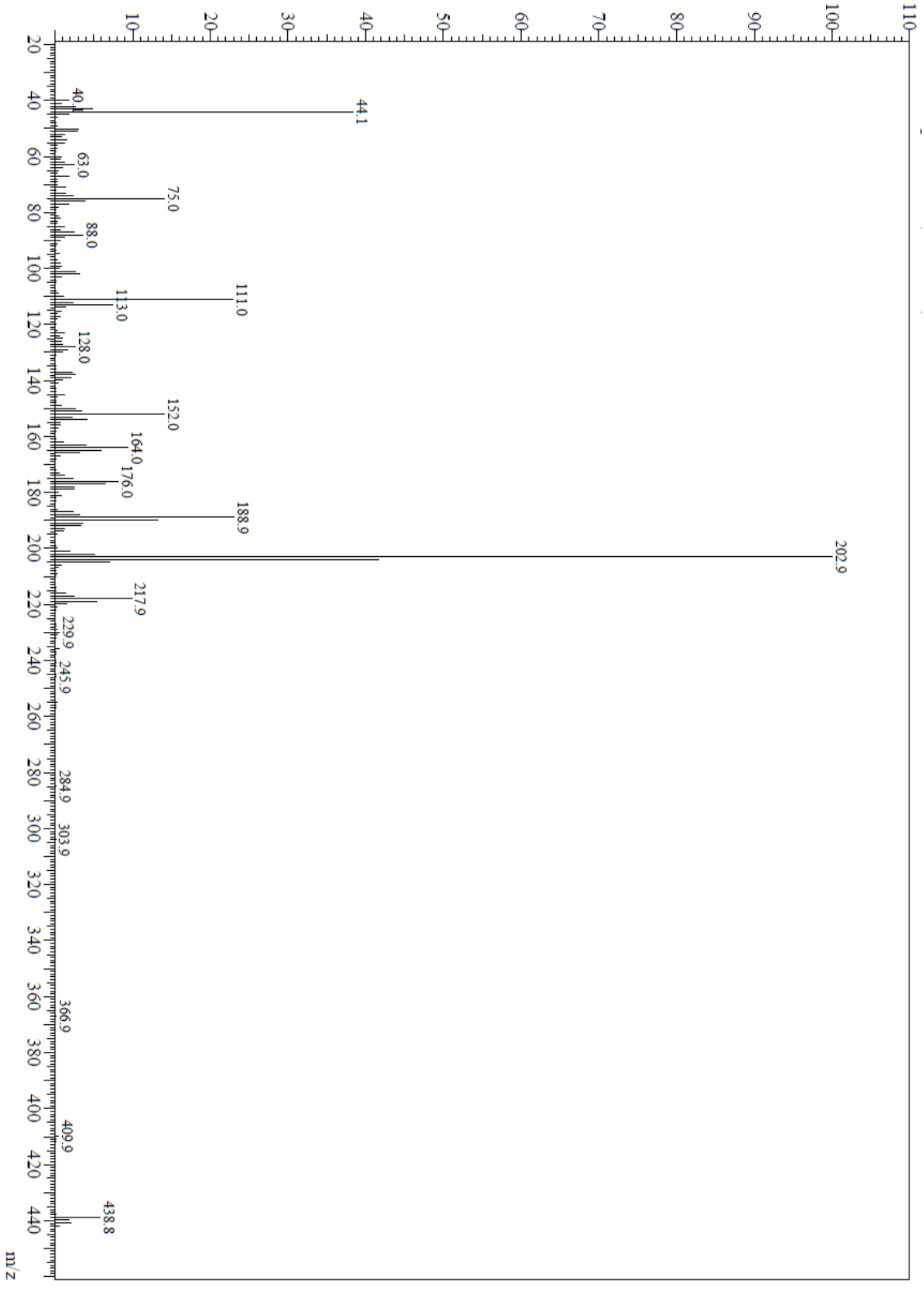

Fig. 1. Mass spectra of 8a

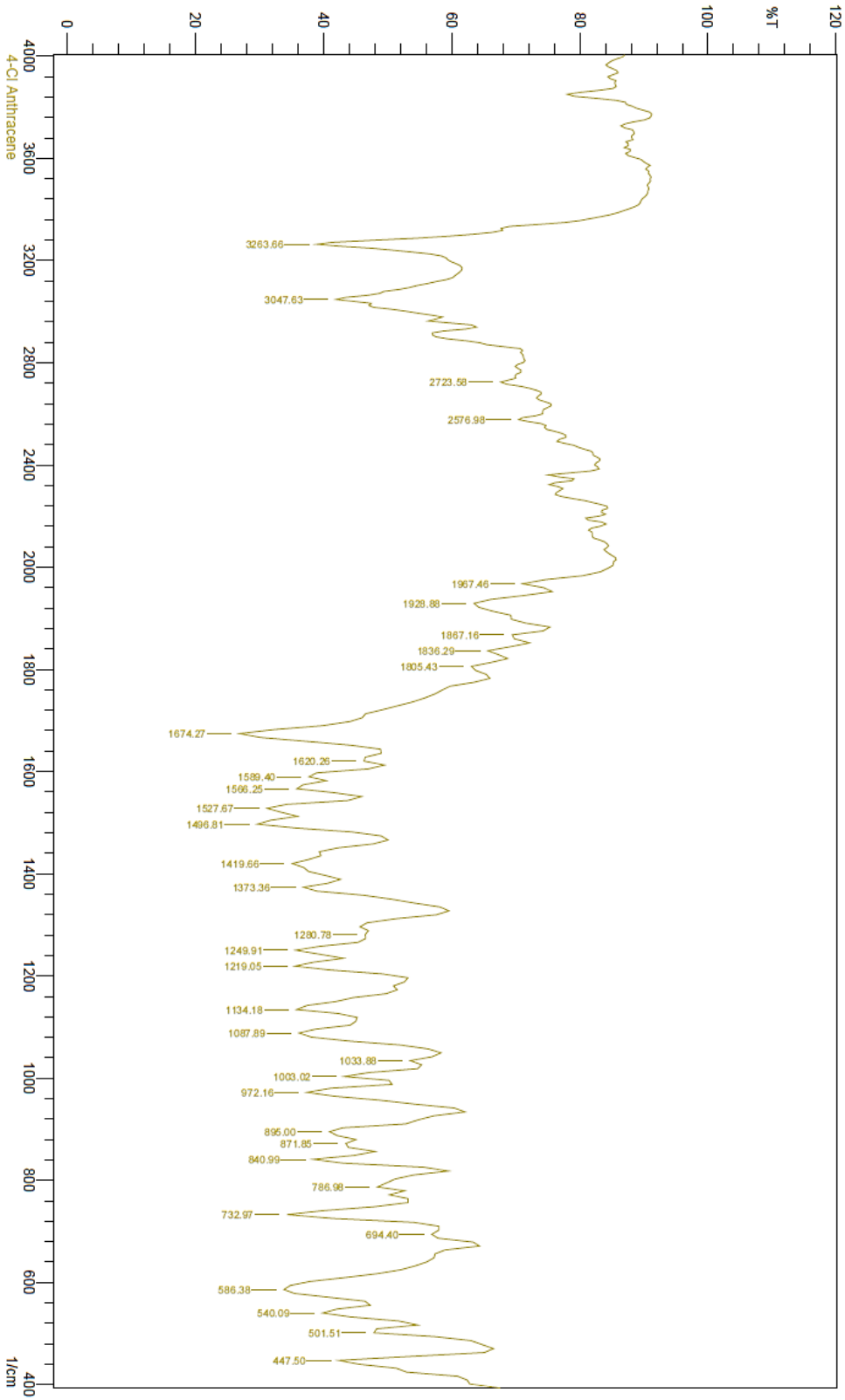

Fig. 2. IR spectra of 8a

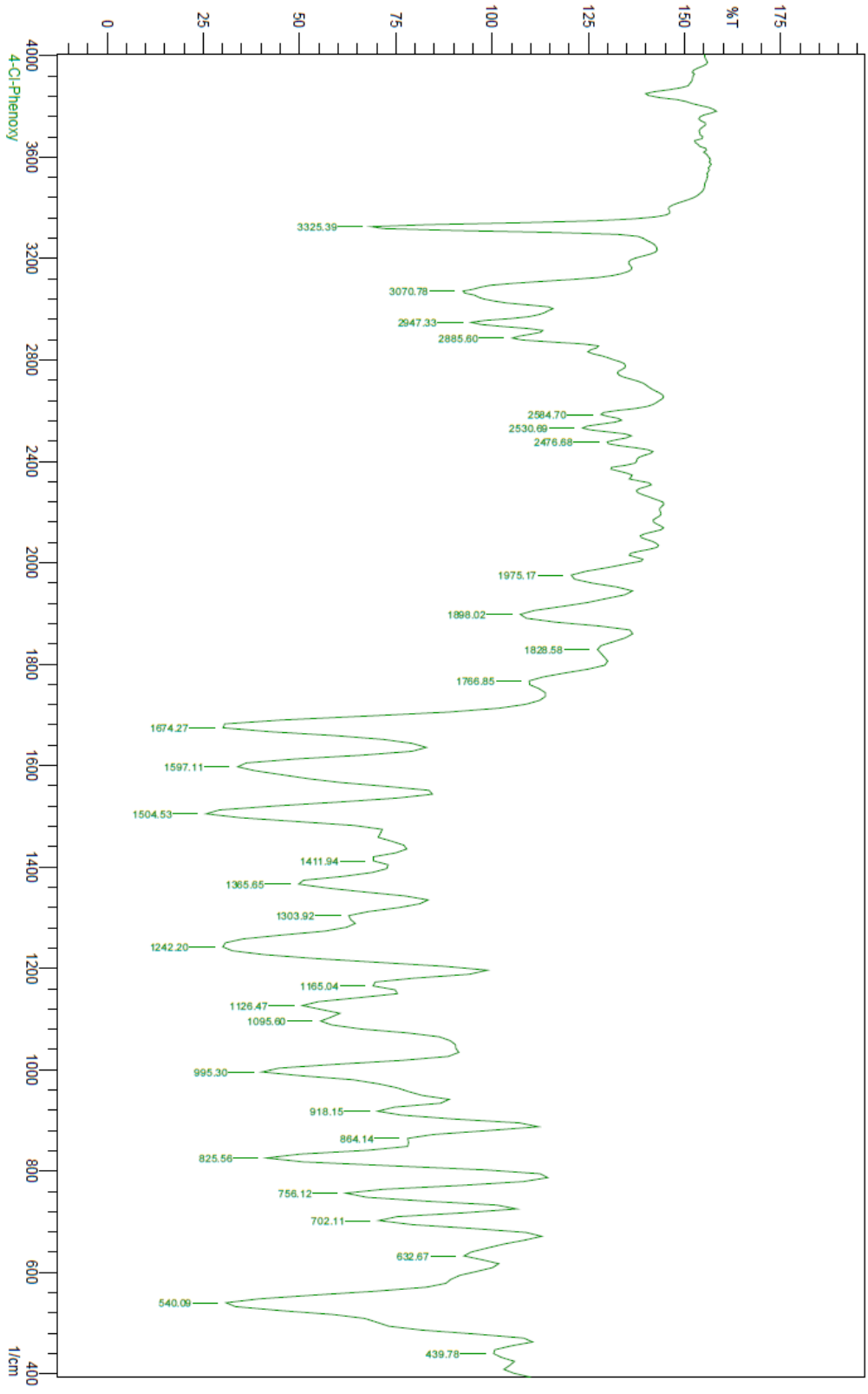

Fig. 3. IR Spectra of 6a

N'-(3-(benzyloxy)benzylidene)-1-(4-florophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (6b)
White coloured, Yield: 85% m.p: 181-184 ºC, 1H NMR:(400 MHz) δ 8.46 (s, 1H), 8.06 – 7.97 (m, 3H), 7.97 – 7.87 (m, 2H), 7.53 – 7.49 (m, 2H), 7.46 – 7.38 (m, 4H), 7.11 – 7.04 (m, 2H), 2.54 – 2.50 (m, 3H), ^{13}C NMR (100 MHz) δ 160, 156, 150, 142, 132, 131, 130, 130,128, 127, 127, 127, 126, 126, 116, 11..LC mass m/z :423 (M.F $C_{25}H_{18}FN_5O$)

3. CONCLUSIONS

All the final compounds 6a-d, 8a-d were successfully synthesized. purified by Column chromatography and characterized by different spectroscopically techniques like ^{1}H NMR, ^{13}C NMR and MS analysis, all the compounds were carried out for their antibacterial and anti-fungal activity using 2 gram positive and 2 gram negative bacteria's as well as one fungal stain, from this study we came to know that all the compounds emerged out as potent antibacterial and anti-fungal agents expect 6c and 8a.

Acknowledgements

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