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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF UNDEC-10-ENOIC ACID DERIVATIVES

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ABSTRACT

Antimicrobial agents are effective in treatment of many types of infections, but their overuse promotes the spread of resistant microorganisms that refuse to obey conventional treatments and complicate patient care. One way to overcome the problem of antibiotic resistance is by synthesizing new and effective antimicrobial agents. Long chain fatty acid hydrazide derivatives possess antibacterial, antifungal, antimycobacterial and antiviral activities. Undec-10-enoic acid (Undecylenic acid) is an eleven carbon straight chain unsaturated fatty acid. It is a natural fungicide used against fungal skin infections, such as athlete's foot, ringworm and jock itch. Inspired by above facts, in present study a series of undec-10-enoic acid hydrazide derivatives have been synthesized successfully in appreciable yield (50-80%) and characterized by their physicochemical (Mp/Bp and Rf value) and spectral (IR and NMR) data. Synthesized derivatives were evaluated for their *in vitro* antimicrobial activities against Gram-positive *S. aureus, B. subtilis* and Gram-negative *E. coli* and antifungal activity against *A. fumigatus* and *A. niger* by tube dilution method. Antimicrobial screening results indicated that compounds having NO2 (**4** and **15**), alkoxy (**9**, **11** and **12**), hydroxyl (**7**, **8**, **10**, **11** and **13**) groups and phenyl substituted azetidinone ring (**15-17**) were more active against tested strains, but none of them have antimicrobial activity comparable to standard drug Ciprofloxacin and Fluconazole. Further, the presence of electron-withdrawing *p*-fluoro phenyl group in azetidinone moiety (**16**) improved the growth inhibition potency specifically against tested fungal strains, *A. fumigatus* and *A. niger*.

KEYWORDS: Undec-10-enoic acid, Hydrazide derivatives, Antimicrobial activity.

INTRODUCTION

1.1 Antibiotics

The term antimicrobial agent has been defined as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kills or inhibits the growth of microorganisms).[1]

Antibiotics: These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. 1st antibiotics discovered by Fleming in 1929 is Penicillin from *Penicillium notatum.*[2]

Antibiotics were originally considered as "wonder drugs" mainly because they were introduced at a time when only surgical waste or spontaneous cures were available to treat serious microbial (bacterial, fungal etc.) infections.[1] Traditionally, these are defined as natural compounds, produced by microorganisms, with selective antibacterial activity that does not have any strong effects on human cells. The term antimicrobial agents are now used to include both synthetic and natural compounds.[2]

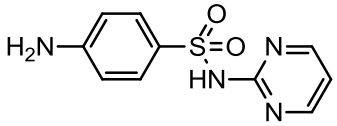
On the basis of their mechanism of action antibiotics are classified as:

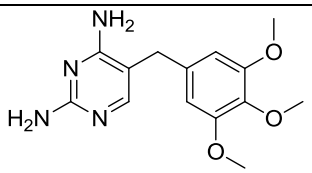
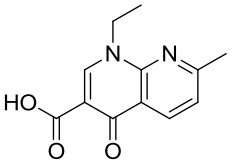
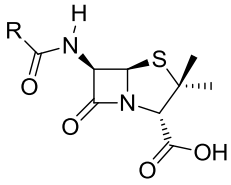
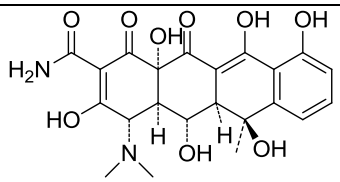
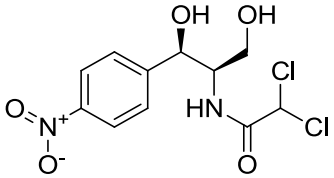
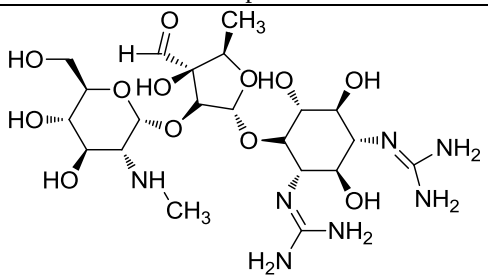
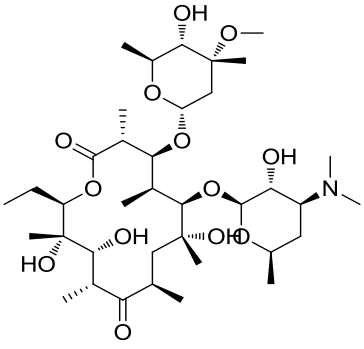
(1) Bactericidal *(i.e.* kill the organism).

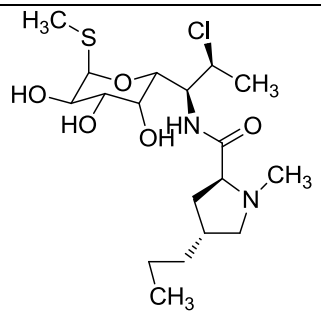
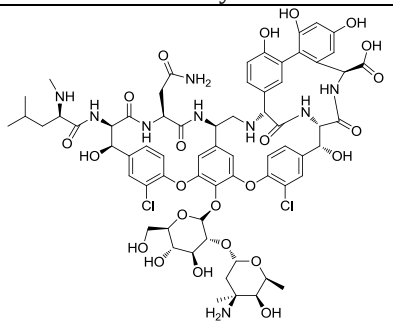
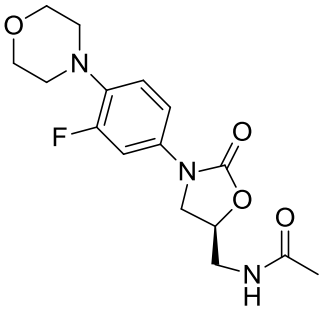
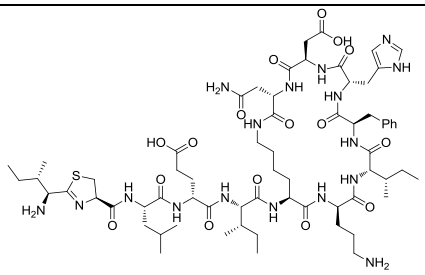
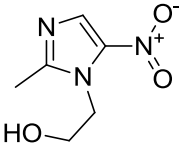
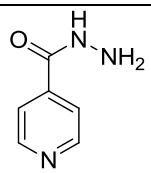
(2) Bacteriostatic (*i.e.* inhibit growth of the organism).[3]

1.1 Classification

Table 1 Classification of antimicrobial agents based on their chemical structure.

S. No.	Class	Examples	Basic Nucleus
1.	Sulfonamides and related drugs	Sulfadiazine, Dapsone(DDS), Paraaminosalicylic acid (PAS).	 Sulfadiazine

2.	Diaminopyrimidines	Trimethoprim, pyrimethamine.	 Trimethoprim
3.	Quinolone	Nalidixic acid, Norfloxacin, Ciprofloxacin, Gatifloxacin.	 Nalidixic acid
4.	β-Lactam antibiotics	Penicillins, Cephalosporins, Monobactams, Carbapenems.	 Penicillin R – Variable group
5.	Tetracyclines	Oxytetracycline, Doxycycline	 Oxytetracyclin
6.	Nitrobenzene derivatives	Chloramphenicol	 Chloramphenicol
7.	Aminoglycosides	Streptomycin, Gentamycin, Amikacin, Neomycin, etc.	 Streptomycin
8.	Macrolide antibiotics	Erythromycin, Clarithromycin, Azithromycin,	 Erythomycin

9.	Lincosamide antibiotics	Lincomycin, Clindamycin.	 Clindamycin
10.	Glycopeptide antibiotics	Vancomycin, Teicoplanin.	 Vancomycin
11.	Oxazolidinones	Linezolid	 Linezolid
12.	Polypeptide antibiotics	Polymyxin-B, Colistin, Bacitracin, Tyrothricin.	 Bacitracin
13.	Nitroimidazoles	Metronidazole, Tinidazole.	 Metronidazole
14.	Nicotinic acid Derivatives	Isoniazide, Pyrazinamide, Ethionamide.	 Isoniazide

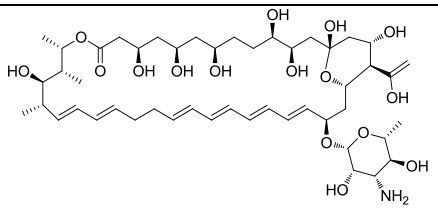
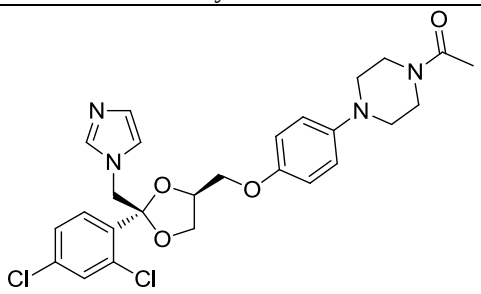
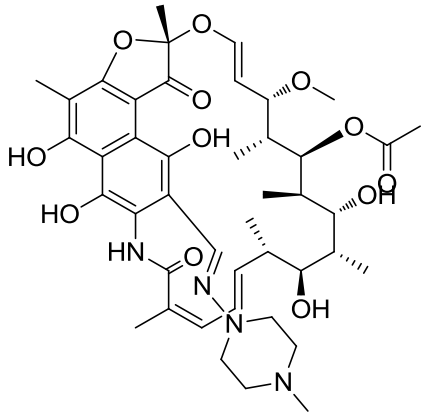
15.	Polyene antibiotics	Nystatin, Amphotericin-B, Hamycin.	 Nystatin
16.	Azole Derivatives	Miconazole, Clotrimazole, Ketoconazole, Fluconazole.	 Ketoconazole
17.	Others	Rifampin, Spectomycin.	 Rifampin

Table 2: Classification of antimicrobial agents based on their mechanism of action.

S. No.	Class	Examples
1.	Inhibit cell wall synthesis	Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.
2.	Cause leakage from cell membrane	Polymyxins, Colistin, Bacitracin, Amphotericin B, Nystatin, Hamycin.
3.	Inhibit protein synthesis	Chloramphenicol, Erythromycin, Clindamycin, Linezolid
4.	Cause misreading of m-RNA code and affect permeability	Streptomycin, Gentamycin.
4.	Cause misreading of m-RNA code and affect permeability	Streptomycin, Gentamycin.
5.	Inhibit DNA gyrase	Ciprofloxacin.
6.	Interfere with DNA function	Rifampin, Metronidazole
7.	Interfere with DNA synthesis	Acyclovir, Zidovudine
8.	Interfere with intermediary metabolism	Sulfonamide, Sulfones, PAS, Trimethoprim, Pyrimethamine, Ethambutol

Table 3: Classification of antimicrobial agents based on their spectrum.

S.No.	Class	Examples
1.	Narrow-spectrum	Penicillin G, Erythromycin, Streptomycin
2.	Broad-spectrum	Chloramphenicol, Tetracyclines

1.2 Mechanism of action of hydrazone derivatives

Thiazolidinones inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall of bacteria.[3] MurB enzyme (reduction of enolpyruvyl uridine diphosphate N-acetylglucosamine (EP-UNAG) to uridine diphosphate N-acetylmuramic acid (UNAM)[4], is a unique target for antibacterial activity of thiazolidinones.

2-azetidinones containing beta-lactams ring are most prescribed chemotherapeutic agents used in medicine to treat bacterial infections and microbial diseases. 2-

azetidinone molecules are operated by forming a covalent adduct with membrane-bound bacterial transpeptidase, which are also known as penicillin-binding proteins(PBPs), involved in the biosynthesis of cell walls. On the basis of this mechanism, inhibitors prevent the construction of cell wall and eventually lead to cell lysis and death. Moreover, due to their beta-lactamase inhihibitory action, 2-azetidinones based heterocycles represent an attractive target of contemporary organic synthesis.[5]

1.3 Antibiotic Resistance

Resistance: Resistance is the failure of microorganisms to be killed or inhibited by antimicrobial treatment. Resistance can either be intrinsic (exist before exposure to drug) or acquired (develop subsequent to exposure to a drug) and cross resistance.[6]

Intrinsic resistance: Intrinsic resistance, inherent to all the strains of a bacterial species or genus, is acknowledged as having a minimal potential for horizontal spread, although any gene responsible for intrinsic resistance may spread provided that it is flanked by insertion sequence.[7] The example of intrinsic resistance are penicillin's, cephalosporin's, Aminoglycosides and the Macrolide.[8]

Acquired resistance

It is the development of resistance by an organism (which was sensitive before) due to the use of an antimicrobial agents over a period of time. This can happen with any microbe and is a major clinical problem. However, development of resistance is dependent on the microorganism as well as the drug. Some bacteria are notorious for rapid acquisition of resistance, e.g. staphylococci, coli forms, tubercle bacilli.[2]

Cross resistance

It is produced by mutations or by the acquisition of resistance genes affecting antimicrobials agents from the same class. An excellent example is the *methicillin resistant Staphylococcus aureus* (MRSA).[9]

1.4 Cause of Resistance: The cause of resistance is as follow:

The other cause of bacterial resistance is irrational use of antibiotics.[10]

The development, acquisition and spread of the resistance gene itself and specific biochemical mechanism conveyed by this resistance gene.[11]

1.5 Removal of antibiotic resistance

1) Prudent antibiotic use: In medicine, prudent antibiotic use dictates that we should not use antibiotics unless they improve patient outcome. Not all bacterial infections need antibiotic therapy. For example, in acute bacterial bronchitis and sore throat, any benefit to the patient from antibiotic therapy is small and counterbalanced by the risk of drug side effects, such as rash.

2) Preventing infections: Use of antibiotics can also be reduced by preventing infections in the first place. For example, since the introduction of an effective vaccine for *Homophiles influenza* type B.[12]

3) Diagnose and treat infection effectively: Diagnose and treat infection effectively helps to remove antibiotic by using following steps:-

a) Target the pathogen

1. Obtain appropriate cultures.
2. Target empiric therapy to likely pathogens.
3. Target definitive therapy to known pathogens.
4. Optimize timing, regimen, dose, route and duration.

b) Access the experts

Consult the appropriate expert for complicated infections.

4) Use antimicrobials wisely

a) Use local data

1. Know your local antibiogram.
2. Get previous microbiology results when patients transfer to your facility.

b) Treat infection, not contamination or colonization

1. Use proper antisepsis for drawing blood cultures.
2. Get one peripheral vein blood culture, if possible.
3. Avoid culturing vascular catheter tips.
4. Treat bacteria, not the catheter tip.

c) Stop antimicrobial treatment

1. When infection is treated.
2. When infection is not diagnosed.

5) Prevent transmission: Follow Infection Control Precautions can be used to prevent transmission:

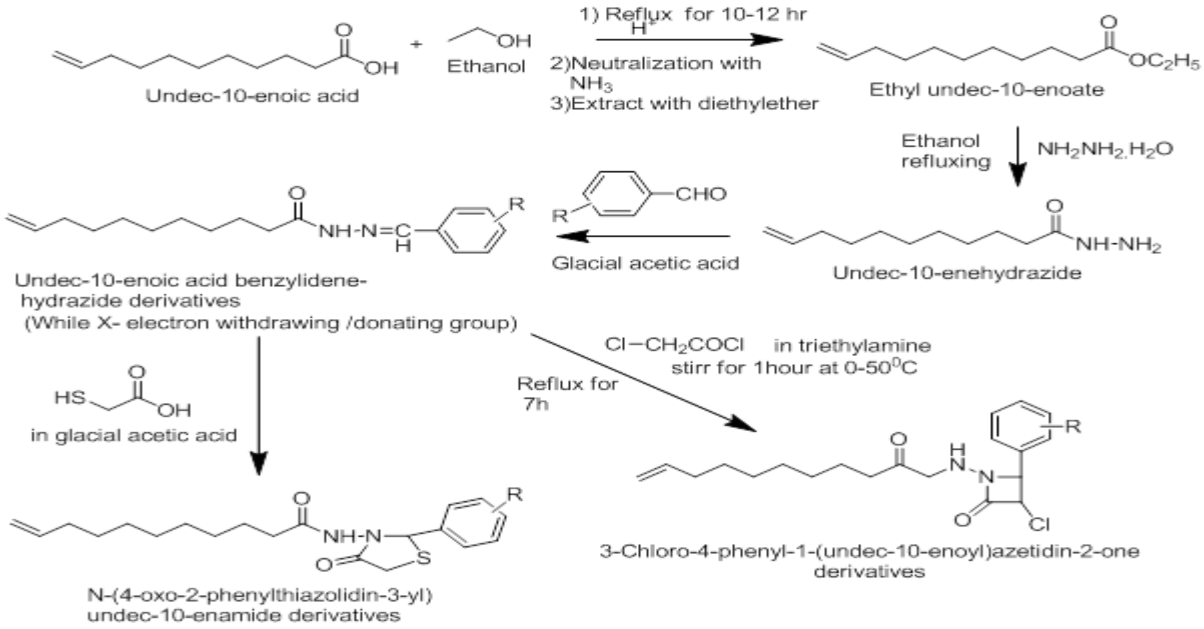
1. Use standard infection control precautions for dialysis centers.
2. Consult local infection control experts.
3. Wash your hands or use an alcohol-based hand rub.
4. Educate on access care and infection control measures
5. Re-educate regularly.[13]

6) Blocking the efflux: The cellular organization contains the presence of various protein channels involved in the transport, uptake or efflux, of a large variety of compounds, nutrients or toxic molecules (sugars, drugs, small peptides, chemicals).

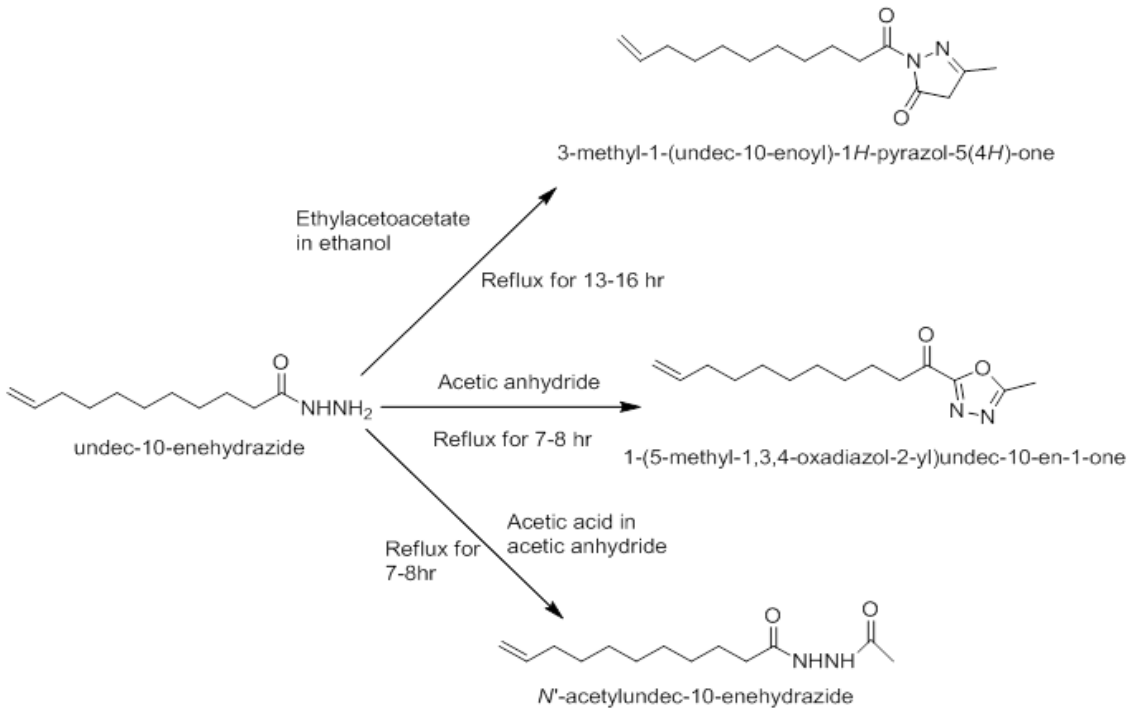
Because of the clear involvement of the resistance nodulation cell division (RND) transporters in the increased frequency of MDR clinical bacteria, efflux pumps are now considered as an attractive target for the development of a combinational therapy using antibiotic/efflux pump inhibitor (EPI) as adjuvant of usual antibiotics.[14]

2. Research methodology

2.1 General scheme



Scheme 1. General scheme for synthesis of hydrazide derivatives of undec-10-enoic acid.

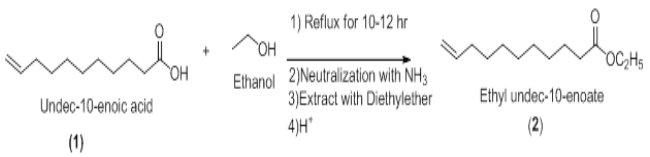


Scheme 2. General scheme for synthesis of hydrazide derivatives of undec-10-enoic acid.

3. Experimental work done

3.1 Synthesis of ethyl ester of undecylenic acid

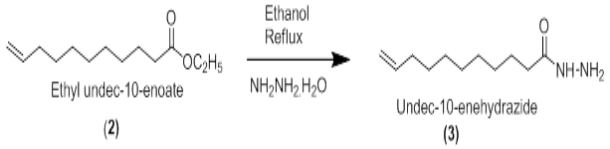
A mixture of 0.05 mole (10 gm) of undecylenic acid and methanol (45 ml) was refluxed in presence of conc. sulphuric acid (4-5 drops) for 10-12 hr. The completion of reaction was confirmed by TLC. The excess of acid was neutralized with ammonia. Then, synthesized ester was extracted by adding diethylether and water. Ester was obtained by evaporating diethylether layer. R_f value of synthesized ester = 0.71, mobile phase (hexane-ethylacetate–9.5 ml: 0.5ml). Yield = 80%.



Scheme 3. Scheme for synthesis of ethyl undec-10-enoate from undec-10-enoic acid.

3.2 Synthesis of undec-10-ene hydrazide from ester

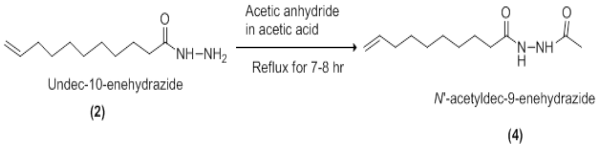
The solution of ethyl undec-10-enoate (0.02 mol) in ethanol was refluxed with hydrazine hydrate (0.058 mol). The mixture was refluxed for 14-16 hr. Completion of the reaction was confirmed by TLC. Reaction mixture was cooled and the precipitate of undec-10-enehydrazide was collected. R_f value of synthesized hydrazide = 0.52, mobile phase (hexane- ethyl acetate – 8 ml: 2ml). Yield= 72%.



Scheme 4. Synthesis of undec-10-ene hydrazide from ester.

3.3 Synthesis of *N*'-acetyldec-9-enehydrazide from undec-10-ene hydrazide

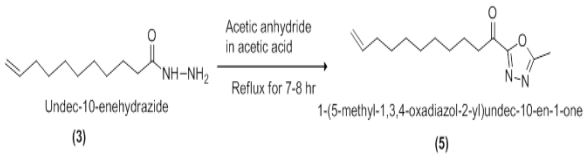
The solution of undec-10-enehydrazide (0.005 mol) in ethanol was refluxed with acetic acid (mol) in acetic anhydride (0.049 mol). The mixture was refluxed for 7-8 hr. Completion of the reaction was confirmed by TLC. Reaction mixture was cooled and the precipitate of *N*'-acetyldec-9-enehydrazide was collected. R_f value of synthesized hydrazide = 0.70, mobile phase (hexane-ethyl acetate – 8 ml: 2ml). Yield= 65%.



Scheme 5. Synthesis of N'-acetyldec-9-enehydrazide from undec-10-ene hydrazide.

3.4 Synthesis of 2-Methyl-5-(non-8-en-1-yl)-1,3,4-oxadiazole from undec-10-ene hydrazide

The solution of undec-10-enehydrazide (0.0015 mol) in ethanol was refluxed with acetic anhydride (0.048 mol). The mixture was refluxed for 7-8 hr. Completion of the reaction was confirmed by TLC. R_f value of synthesized hydrazide = 0.8, mobile phase (hexane- ethylacetate – 8 ml: 2ml). Yield= 64%.



Scheme 6. Synthesis of 2-Methyl-5-(non-8-en-1-yl)-1,3,4-oxadiazole from undec-10-ene hydrazide.

4. RESULTS AND DISCUSSION

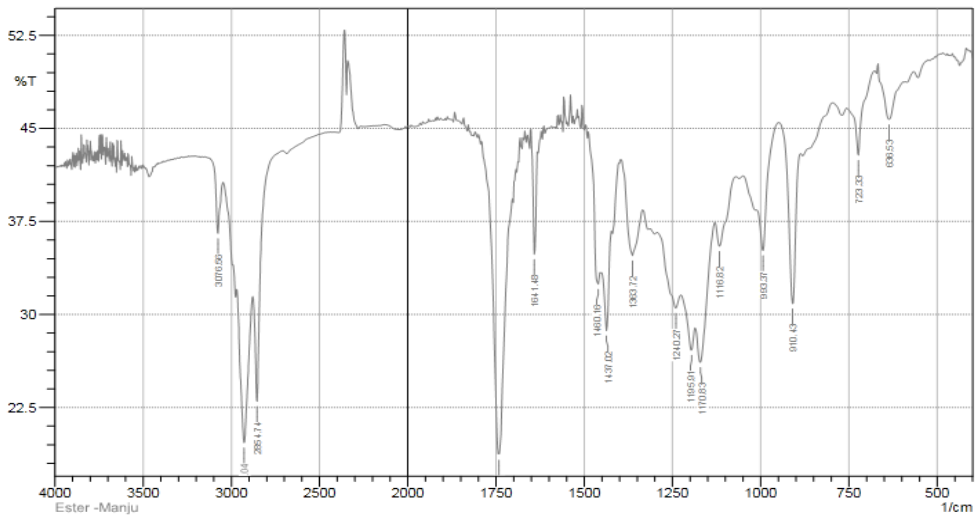
Different derivatives of undec-10-enoic acid have been successfully prepared. The physicochemical properties of prepared derivatives are as follow:-

Table 4 Physicochemical properties of synthesized compounds

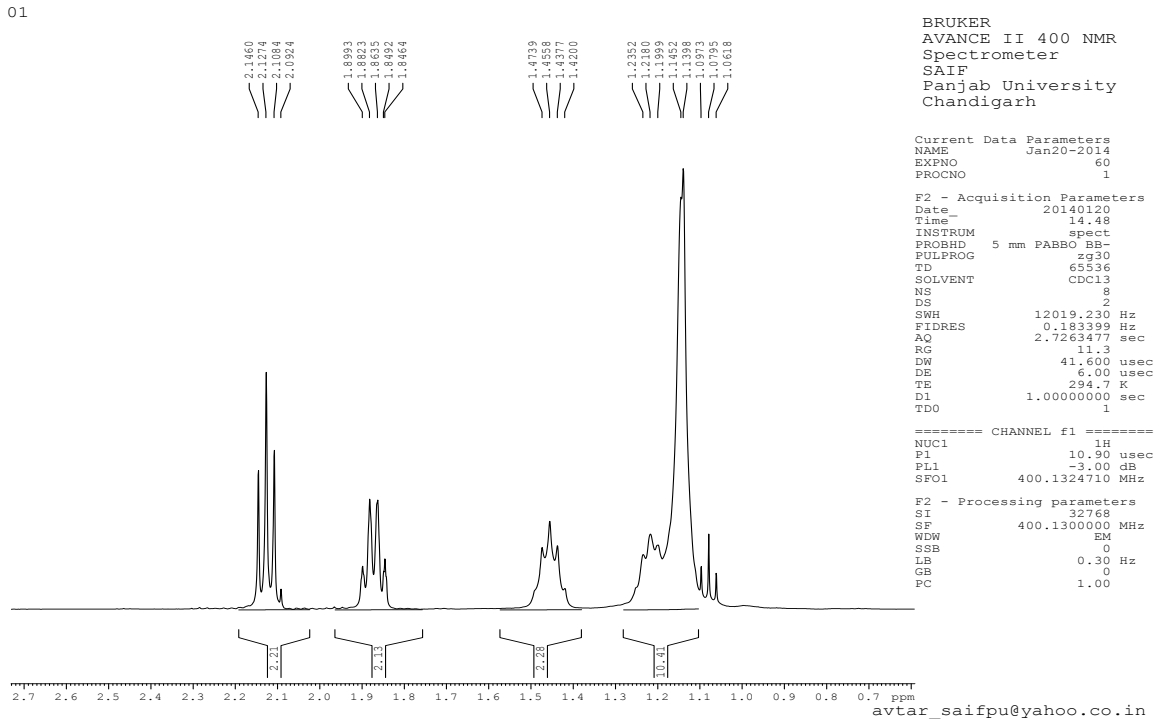
Compound	Mol. formula	Mol. Wt.	M.Pt/ B.Pt.* (℃)	R_f	Percentage yield
2	$C_{13}H_{24}O_2$	212.18	103-108*	0.71[a]	80.0
3	$C_{11}H_{22}N_2O$	198.17	88-93	0.52[b]	72.0
4	$C_{12}H_{22}N_2O_2$	226.17	45-51	0.70[b]	63.0
5	$C_{14}H_{22}N_2O_2$	250.17	184-189*	0.80[b]	65.0

(Solvent system used: (a) hexane – ethyl acetate -9.5 ml : 0.5 ml, (b) hexane – ethylacetate – 8ml: 2ml).

Spectral data (IR and NMR) of synthesized derivatives
Ethylundec-10-enoate

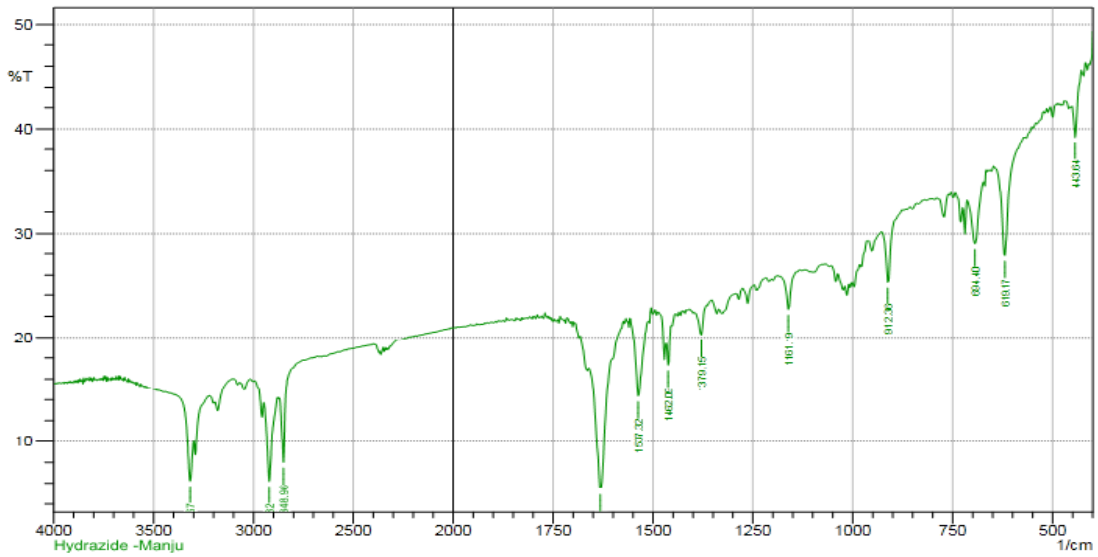


1741.78 (C=O str.), 1641.48 (C=C str., alkenes), 3076.56 (C-H str., alkenes), 2928.04 (C-H str., aliphatic), 993.37 (C-H bending, alkenes), 1460.16 (C-H bending, aliphatic).

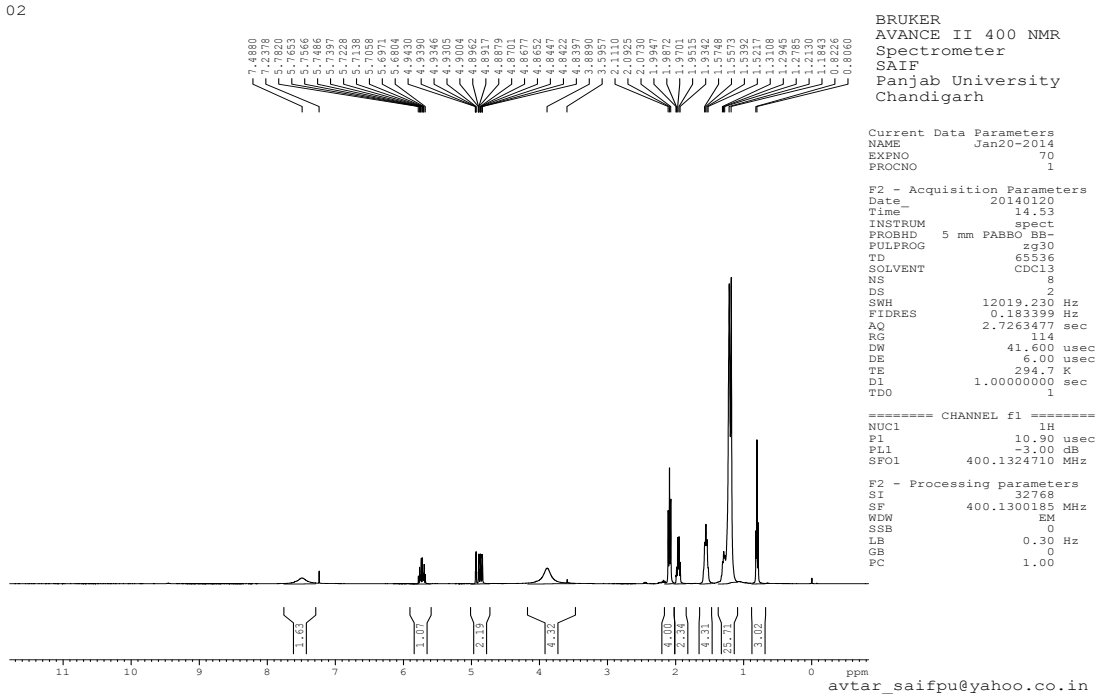


^{1}H NMR ($CDCl_3$): δ = 5.57-5.67 (m, 1H, CH), 4.73- 4.83 (m, 2H, CH_2), 3.48 (s, 3H, CH_3), 2.09-2.15 (q, 2H, CH_2), 1.85-1.90 (p, 2H, CH_2), 1.42-1.47 (q, 2H, CH_2), 1.06-1.24 (m, 10H, CH_2).

Undec-10-enehydrazide

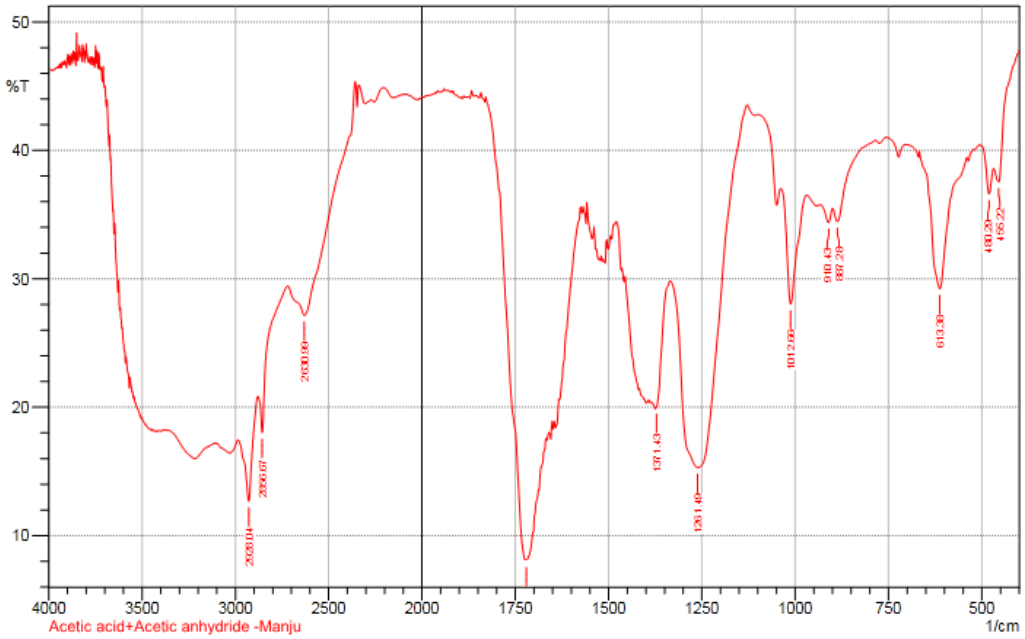


3317.61(NH str.), 3045.70(C-H str., alkenes), 2920.32(C-H str., aliphatic), 1664.27(C=C, alkenes), 1631.83(C=O str.), 1537.32(NH bending), 1462.02(C-H bending, aliphatic), 912.36(C-H bending, alkenes), 1161.19(C-N str.).

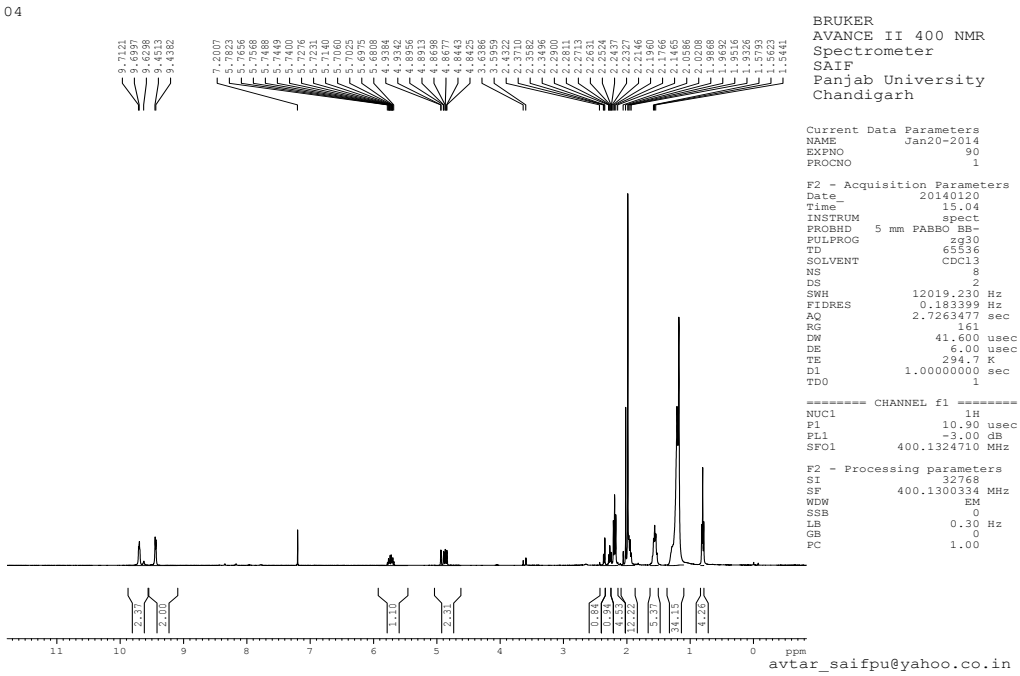


^{1}H NMR($CDCl_3$): δ 5.68-5.78(m, 1H, CH), 4.83-4.94(m, 2H, CH_2), 3.88(s, 2H, NH_2), 7.49(s, 1H, NH), 2.07-2.11(t, 2H, CH_2), 1.93-1.99(p, 2H, CH_2),1.18-1.31(p, 10H,CH_2).

***N*'-acetyldec-9-enehydrazide**

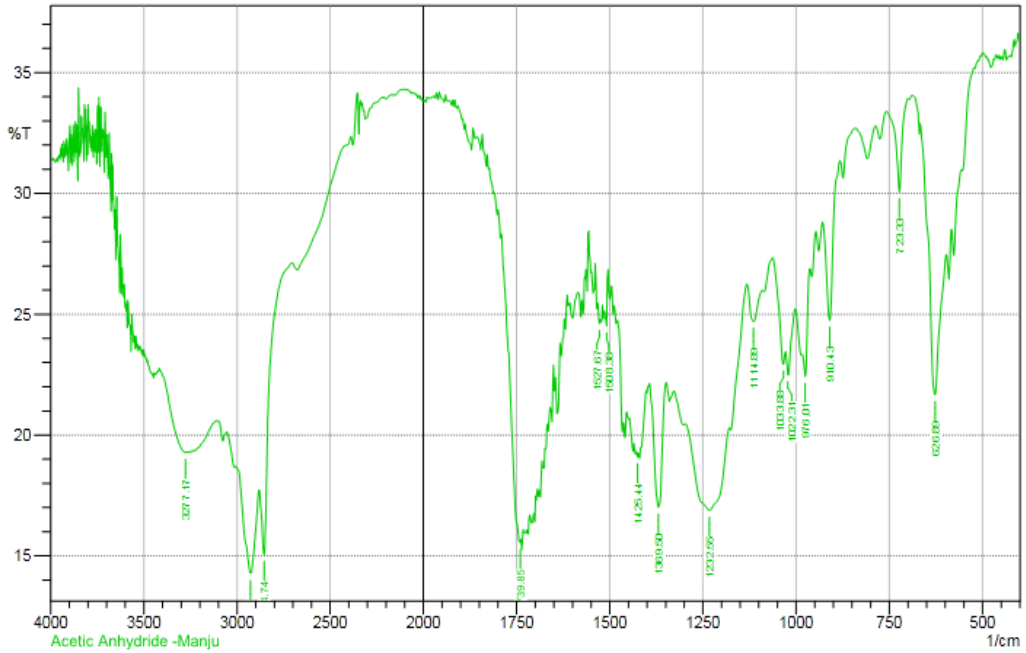


1654.98(C=C, alkenes), 1720(C=O str.), 3032.20(C-H str., alkenes), 910.43(C-H bending, alkenes), 2856.67(C-H str., aliphatic), 1371.43(C-H bending, aliphatic), 3462.34 & 3221.23(NH str.), 1641.48(NH bending).

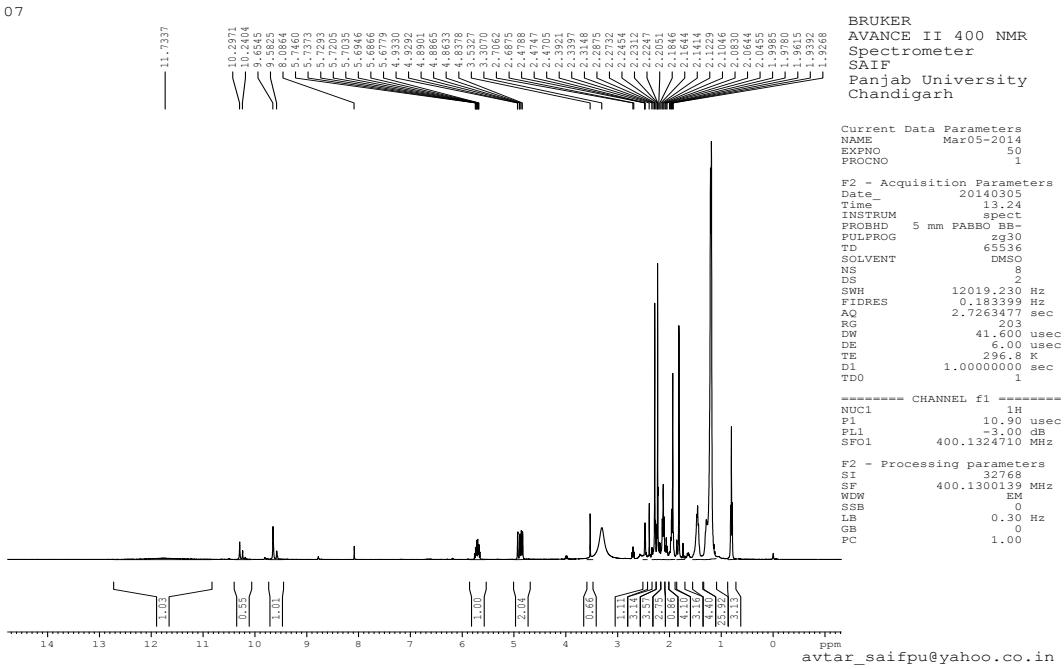


^{1}H NMR($CDCl_3$): δ 9.63-9.71(d, 1H, NH), 9.43-9.45 (d, 1H, NH), 5.68-5.78(m, 1H, CH), 2.02-2.43(m, 2H, CH_2), 1.53-1.99(m, 10H, CH_2), 1.21(s, 2H, CH_2).

2-Methyl-5-(non-8-en-1-yl)-1,3,4-oxadiazole



1641.48(C=C, alkenes), 2254.86(C=N str.), 3076.56(C-H str., alkenes), 2928.04(C-H str., aliphatic), 1458.23(C-H bending, aliphatic), 976.01(C-H bending, alkenes).



^{1}H NMR ($CDCl_3$): δ 5.67-5.74 (m, 1H, CH), 4.83-4.93 (m, 1H, CH_2), 1.44-1.47(t, 2H, CH_2), 1.92-1.99 (q, 2H, CH_2), 2.04-2.70 (m, 10H, CH_2), 1.21-1.29 (m, 10H, CH_2), 11.73 (s, NH).

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