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Synthesis and biological activity of some maleimide derivatives

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Abstract

This study included the preparation of four compounds of maleimide derivatives. Novel compounds (N1-N4) were resulting from the reaction between N-substituted maleimide and benzohydrazide. It has been identified the novel maleimide derivatives by using infrared spectroscopy (FT-IR), 1H-NMR spectroscopy and mass spectrometry as well as measured the melting point for the preparing compounds. The synthesized compounds were screened for their in vitro antibacterial activity against five bacterial strains.

Keywords: synthesis, malemides, benzohydrazide and antibacterial activity.

ntroductionI

Cyclic imides are an important class of compounds having bis-amide linkages with common nitrogen. They are useful building blocks in the synthesis of natural products[1] and other heterocyclic[2] as well.Maleimides are the important class of compounds among cyclic amides.

Maleimide and its derivatives are prepared from maleic anhydride by treatment with amines followed by dehydration[3]. A special feature of the reactivity of maleimides is their susceptibility to additions across the double bond in ppm. Infrared spectra were obtained an FT-IR-1600 Perkin-Elmer spectrophotometer.Thin layer chromatography (TLC) was performed on aluminum sheets silica gel from merk. The TLC spots were visualized in UV and I_2. Mass spectra recorded on High-resolution mass spectra were recorded on an ESI-TOF Mariner Spectrometer (Perspective Biosystem).

either by Michael addition[4,5] or via Diels-Alder reaction[6] and 1,3-dipolar cycloaddition reaction.[7,8]

A new method for the C=C bond of N-aryl substituted maleimide using Michael reaction was developed.[9]

Maleimides are an important class of compounds known for biological, pharmacological and chemical applications. Their derivatives have been extensively used in industry as antibacterial agents[10-12]pharmaceutical intermediate[13,14]across linking reagents for natural rubbers.[15,16]

Experimental

General methods:

Melting points were determined by using a Gallenkamp melting point apparatus. Proton NMR spectra was recorded on a Bruker DRX 500 Advance spectrometer at 500 MHz, using deuterated solvents and TMS as an internal standard Chemical shifts are reported as δ values

Procedure for synthesis maleanilic acid

The method used as same as in literature[17,18] with some modification, where moles from maleic anhydride and substituted aniline equal was dissolved in acetone or diethyl ether and stirring for 1-2 hours after that the precipitate was filtered and dried.

Procedure for synthesis maleimides (M1-M4):

The same method was used as in literature[17,18] with some modification, where maleanilic acids derivatives were dissolved in acetic anhydride and added anhydrous sodium acetate (10%-20%) by weight, the mixture was refluxed on water bath until the colour was changed, then cooled the solution and poured in ice bath with vigorously stirring. Where the maleimide was precipitated, filtered and dried and recrystallized with suitable solvent, (See Table1).

General procedure the synthesis of compounds (N1-N4):[19]

A mixture of differently substituted maleimides (0.01mol) and benzohydrazide (0.01mol) in ethanol (20 ml) were brought to reflux under magnetic stirring for 4-6 hours. The white precipitate formed was filtered and recrystallized in ethanol.

Ń-(2,5-dioxo-1-phenylpyrrolidin-3-yl)benzohydrazide (N1):

Reaction phenylmaleimide (0.003 mol) with benzohydrazide (0.003 mol) in 15 ml ethanol gave a white solid (65% yield), m.p.= 235-237 ºC. (See table 2).

Ń-(1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)benzohydrazide (N2):

Reaction p-bromophenyl maleimide (0.0023 mol) with benzohydrazide (0.0023 mol) in 15 ml ethanol gave a white solid (75% yield), m.p.=264-266 ºC. (See table 2).

Ń-(2,5-dioxo-1-(p-tolyl)pyrrolidin-3-yl)benzohydrazide (N3):

Reaction *p*-methylphenyl maleimide (0.001 mol) with benzohydrazide (0.001 mol) in 15 ml ethanol gave a white solid (50% yield), m.p.= 241-244 ºC. (See table 2).

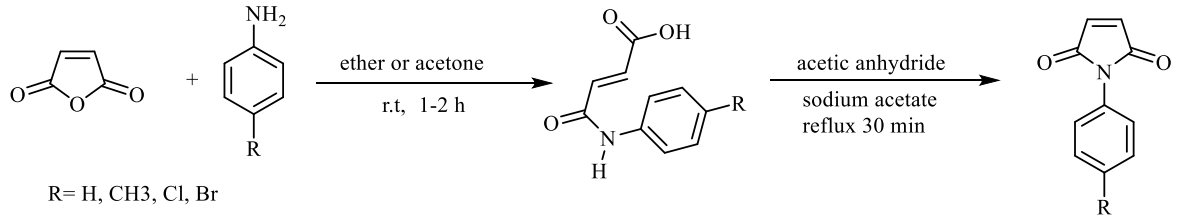
Ń-(1-(4-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)benzohydrazide (N4):

Reaction *p*-chlorophenyl maleimide (0.001 mol) with benzohydrazide (0.001mol) in 15 ml ethanol gave a white solid (60% yield), m.p.= 258-260 ºC. (See table 2).

Results and Discussion

The N-substituted maleimides described herein were synthesized followed two main routs: The first one (scheme1) involves as substituted aniline and maleic anhydride as building blocks, whereas the second one requires benzohydrazide and maleimide (scheme 2).

The N-substituted maleimides (M1-M4) were readily obtained by using method through reacting the desired substituted aniline with maleic anhydride in solvent such as diethyl ether or acetone leading to the corresponding substituted maleanilic acid without any further purification. This intermediate was subsequently cyclized in acetic anhydride in the presence of sodium acetate to the N-substituted maleimide of interest (M1-M4).[17,18](See scheme 1 and Table 1)



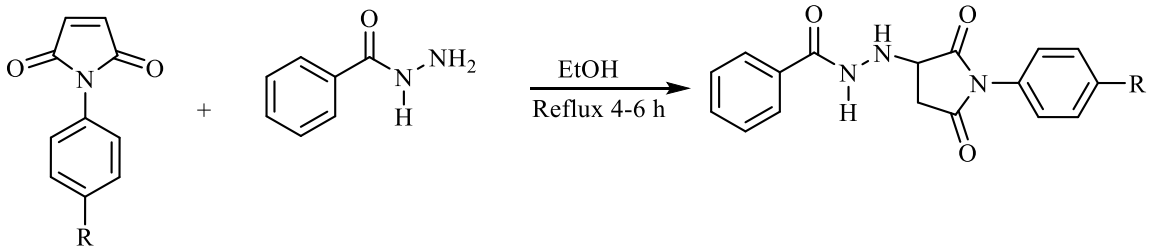
Scheme 1: Synthesis of maleimides (M1-M4)

Table 1: physical data of maleimides (M1-M4)

Compound Symbol	R	Chemical Formula	Molecular Weight	Colour	%Yield	Melting point (C°)
M1	H	$C_{10}H_7NO_2$	173	Yellow	80	88-89
M2	CH_3	$C_{11}H_9NO_2$	187	Yellow	65	149-151
M3	Cl	$C_{10}H_6ClNO_2$	207	Yellow	70	115-117
M4	Br	$C_{10}H_6BrNO_2$	252	Yellow	75	126-129

Conversion of N-substituted maleimides into corresponding maleimide derivatives were achieved by Michael addition with aromatic primary amine. After preparation of N-substituted maleimides, synthesis of maleimide derivatives was undertaken. The desired maleimide derivatives were prepared by Michael addition according to the literature.[19]

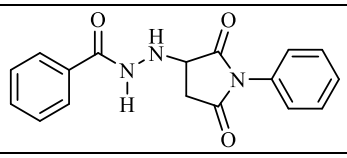
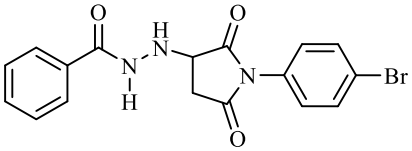
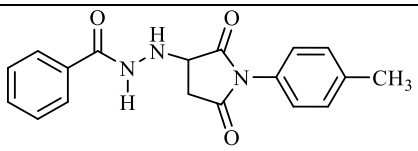
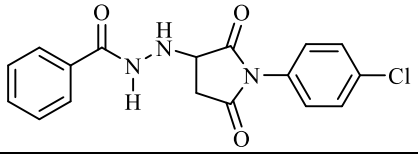
Compounds (M1-M4) were reacted with benzohydrazide in dry ethanol to afford a product (N1-N4). (See Scheme2 and Table 2).



R= H, CH_3, Cl, Br

Scheme 2: synthesis of maleimide dreivatived (N1-N4)

Table2: preparation and physical data of maleimidesderivatives

Comp. symbol	structure	Yield %	M.P (ºC)	Colour
N1		65	235-237	white
N2		75	264-266	white
N3		50	241-244	white
N4		60	258-260	white

The characteristic of IR absorption bands of (N1-N4) were determined in KBr disk. The functional groups of these compounds have been identified from the infrared spectrum. The bands in the region (3325-3302) cm^{-1} and (3217-3197) cm^{-1} attributed to the N-H vibrations. The bands in the region (1782-1635) cm^{-1} were assigned to the C=O. The band in range (1600-1543) cm^{-1} was assigned to the C=C aromatic stretching.[20,21](See Table 3and Figures 1-4)

Table 3: FT-IR data of synthesized maleimide derivatives (N1-N4).

Comp. symbol	N-H Amide cm-1	NH cm-1	C-H Aromatic cm-1	C=O Sym. cm-1	C=O Asym. cm-1	C=O cm-1	C=C Aromatic cm-1	C-N cm-1
N1	3309 m	3194 w	3059 w	1782 w	1720 s	1635 s	1600	1400
N2	3317 m	3213 w	3089 w	1782 w	1716 s	1635 s	1543	1400
N3	3325 m	3217 w	3062 w	1782 w	1708 s	1635 s	1543	1400
N4	3321 m	3217 w	3062 w	1782 w	1712 s	1635 s	1543	1400

s= strong, m= medium, w= weak

The 1H-NMR spectra were shown in figures (5 to 8) for maleimides derivatives (N1-N4). Peaks at 2.5 ppm and 3.3 ppm are belonging to the solvent DMSO-d6 and water respectively.
The doublet of doublets peaks at around (2.80-2.79) ppm and (3.08-3.06) ppm belong to H_a and H_b protons respectively, because they attached to carbon adjacent to chiral centre. Pentet peaks at around (4.25-4.23) ppm belong to H_c. Quartet peaks at around (6.03-6.01) ppm belong to H_d. Doublet peaks at around (10.21-10.18) ppm belong to H_e. Multiplet peaks at around (7.8-7.1) ppm belong to H-aromatic. Singlet peak at around 2.3 ppm belong to CH_3. (See the Table 4).

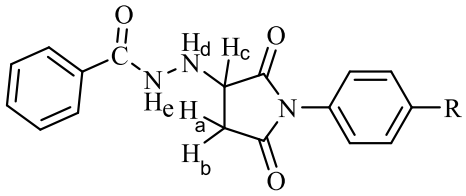


Table 4: ^{1}H-NMR chemical shift (ppm) of N1-N4

Comp. Symbol	R	H_a	H_b	H_c	H_d	H_e	H-Aromatic	CH_3
N1	H	2.80 (1H,dd,J=18,3Hz)	3.07 (1H,dd,J=18,9Hz)	4.25 (1H,Pent,J=9Hz)	6.02 (1H,q,J=6Hz)	10.18 (1H,d,J=9Hz)	7.8-7.2 (10H,m)	–
N2	Br	2.81 (1H,dd,J=20,5Hz)	3.08 (1H,dd,J=20,10Hz)	4.25 (1H,Pent,J=10Hz)	6.03,1H (1H,t,J=5)	10.19 (1H,d,J=5Hz)	7.8-7.2 (9H,m)	–
N3	CH3	2.8 (1H,dd,J=15,5Hz)	3.06 (1H,dd,J=20,10Hz)	4.24 (1H,Pent,J=10Hz)	6.01,1H (1H,q,J=5,5)	10.21 (1H,d,J=10Hz)	7.8-7.1 (9H,m)	2.3 (s,3H)
N4	Cl	2.79 (1H,dd,J=18,3Hz)	3.06 (1H,dd,J=18,9Hz)	4.23 (1H,Pent,J=9Hz)	6.02 (1H,q,J=6Hz)	10.18 (1H,d,J=6Hz)	7.8-7.3 (9H,m)	–

The mass spectra of the (N1-N4) (Fig.9-12) showed a molecular ion $[M]^+$:309, 389, 323, 343 respectively. The mass spectra is confirmed the correct of the prepared structures.

Biological activity

The study of biological activityincluded the effect of one concentration of compounds prepared on five types of bacteria: *Staphylococcus aureus, Escherichia coli , Pseudomonas, Chryseobacterium indologenes, Kocuria rosea*.[22] All prepared compounds gave positive inhibitors at low concentration against the bacteria under investigation. The results were compared with pharmaceuticals. The results showedthat the prepared compounds were more effective than the pharmaceuticals substances as indicated in tables (5 and 6).

Table 5: Anti-bacterial activity of molecules **N1-N4** (zone size, mm).

Compound	Conc. (ppm)	Diameter of inhibition zone (mm)				
		S-auerus	*Pseudomonas*	*E-coli*	*K-rosea*	*C-indologenes*
N1	200	26	31	36	10	14
N2	200	20	29	27	8	13
N3	200	15	20	30	12	10
N4	200	25	25	20	12	10

Note: control treatment (DMSO) had no inhibitory effect on tested bacteria.

Table 6: Values of inhibition area (mm) for pharmaceuticals

Compound	Conc. (ppm)	Diameter of inhibition zone (mm)		
		Staphylococcus aureus	*Pseudomonas*	*Escherichia coli*
Azibru	600	15	9	5
Lincodar	600	11	12	14
Tzide	600	19	7	20

Conclusion

In conclusion, a series of maleimide derivatives were successfully synthesized from N-substituted maleimides with benzohydrazide and characterized by FT-IR, 1H-NMR and mass spectra. The synthesized compounds were screened for their in vitro antibacterial activity against five bacterial strains. All prepared compounds gave positive inhibition and low concentration.

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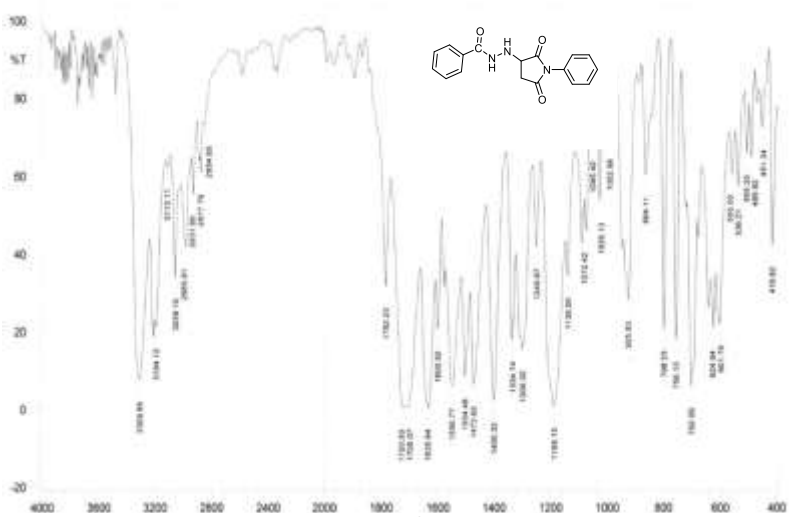

Fig.1: IR spectra of compound (N1)

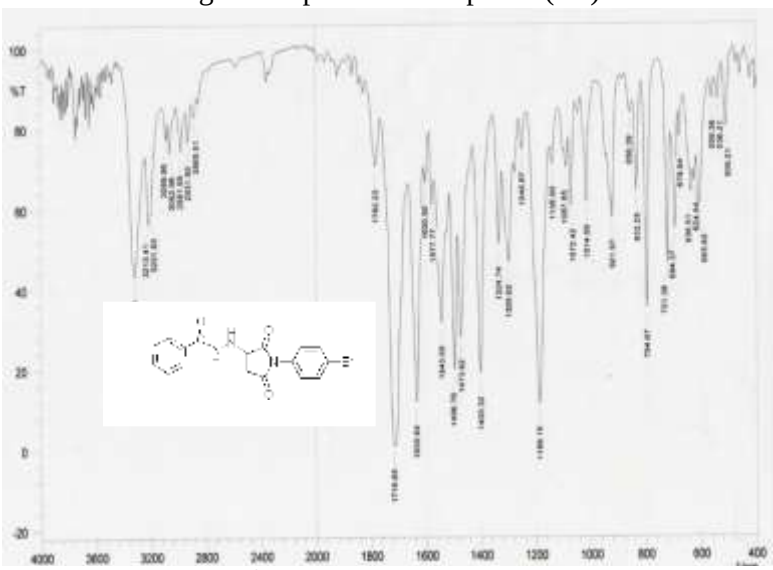

Fig.2: IR spectra of compound (N2)

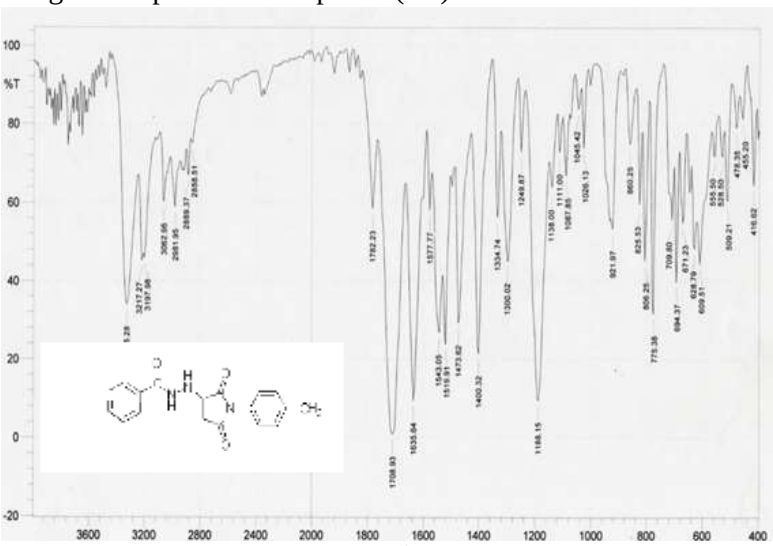

Fig.3: IR spectra of compound (N3)

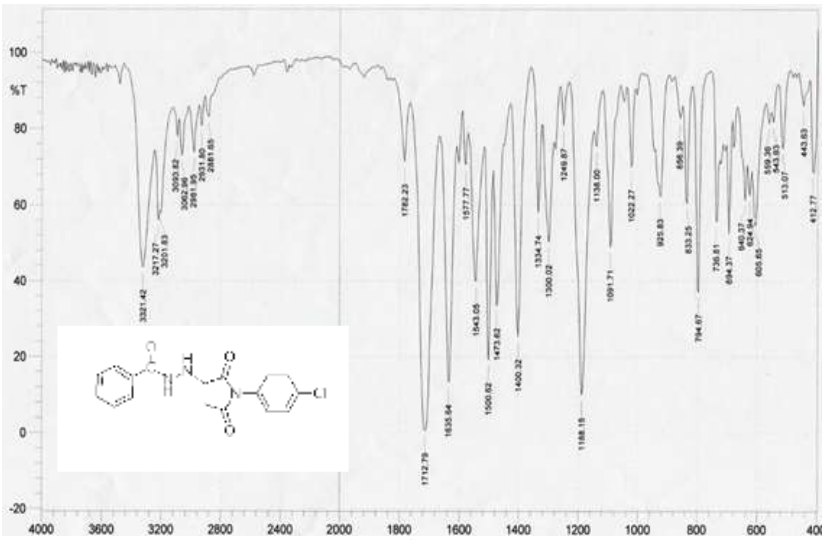

Fig.4: IR spectra of compound (N4)

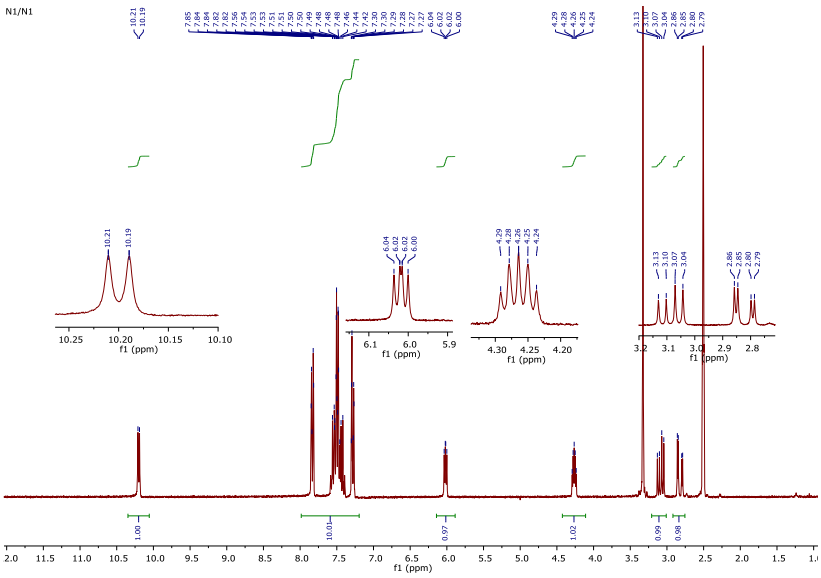

Fig.5: 1H-NMR spectra of compound (N1)

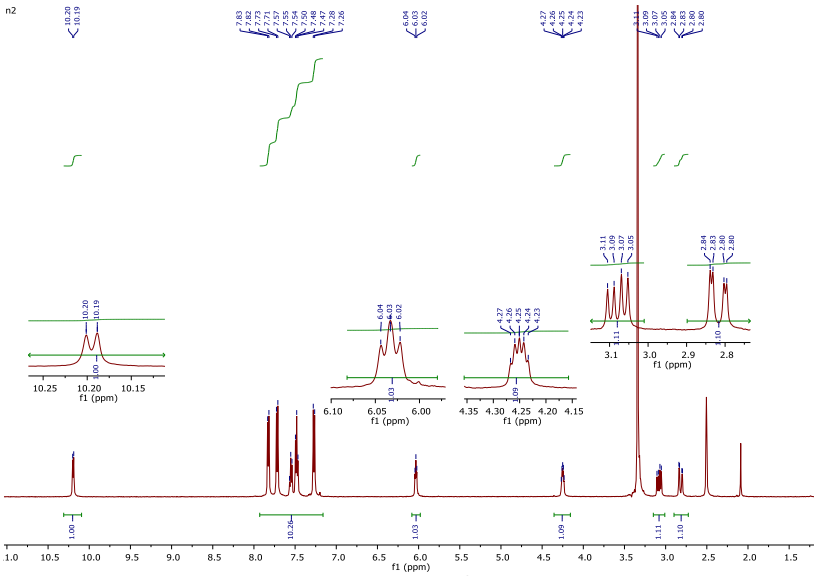

Fig.6: 1H-NMR spectra of compound (N2)

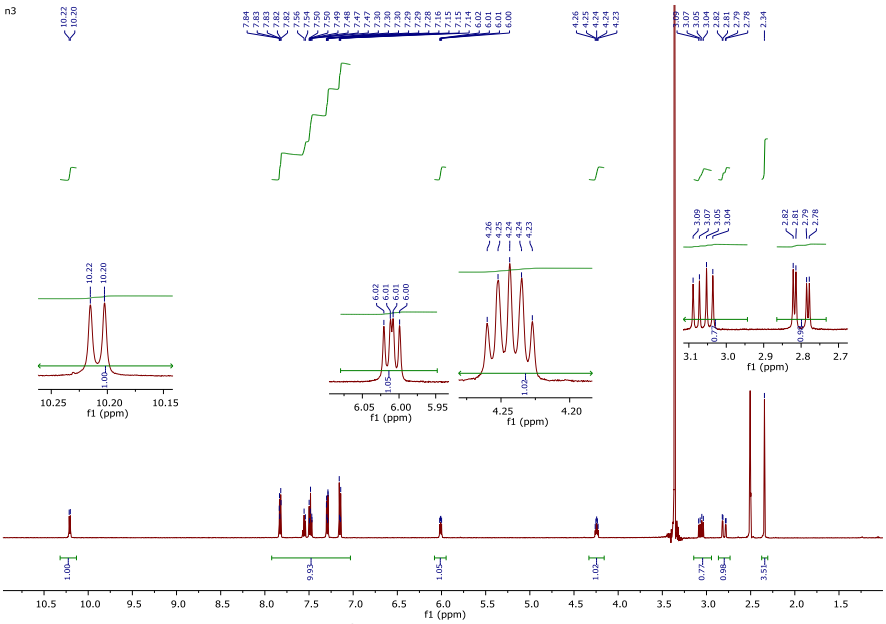

Fig.7: 1H-NMR spectra of compound (N3)

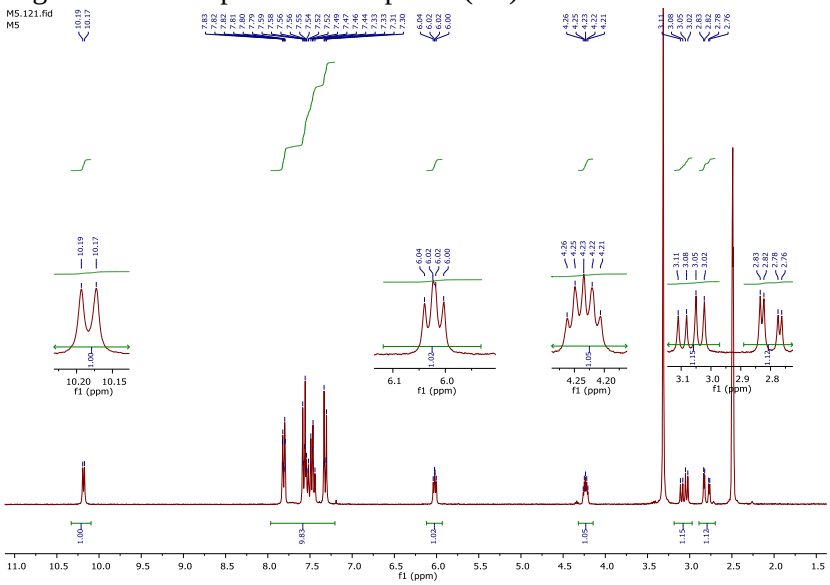

Fig.8: 1H-NMR spectra of compound (N4)

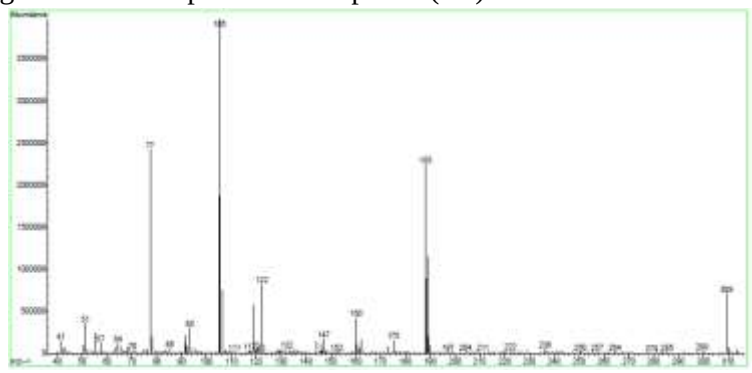

Fig.9: Mass spectra of compound (N1)

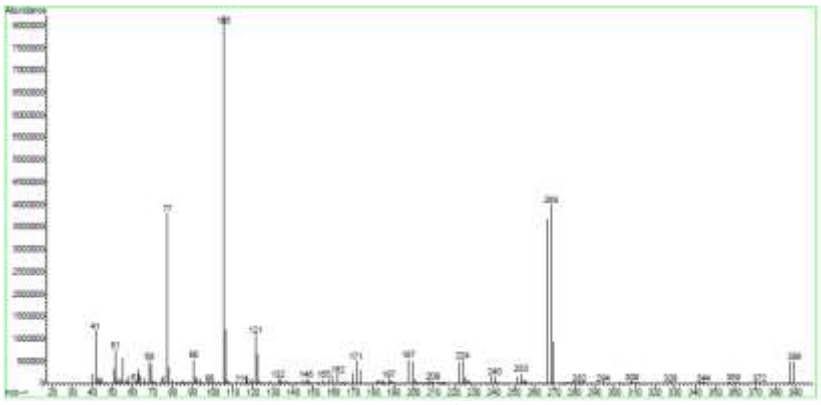

Fig.10: Mass spectra of compound (N2)

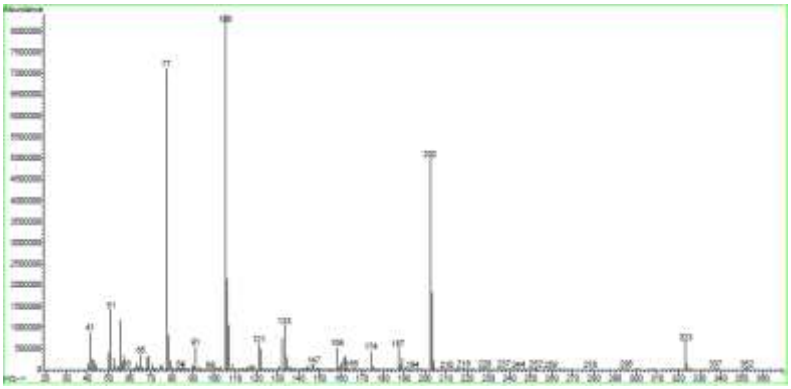

Fig.11: Mass spectra of compound (N3)

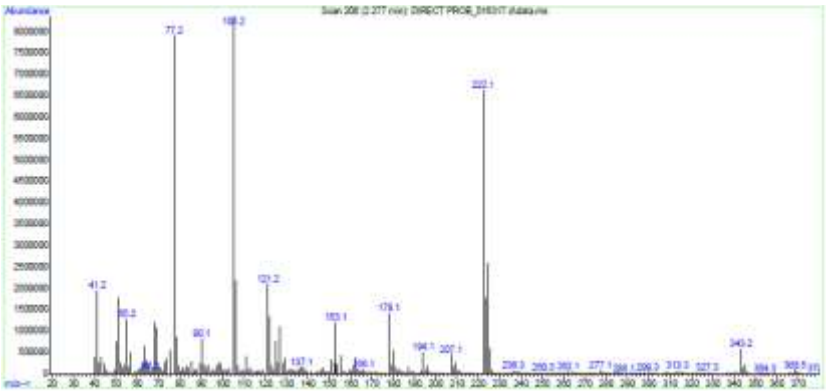

Fig.12: Mass spectra of compound (N4)