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Design, Synthesis and Characterization of Some 5-Nitroimidazole Derivatives

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ABSTRACT

Medicinal chemistry is a science whose roots lie in all branches of chemistry and biology. The intellectual goal of the medicinal chemist is to know the mode of action of drugs at the molecular level. Antiprotozoal drugs are medicines that are used to treat a variety of diseases caused by protozoa. 5-Nitroimidazole is an imidazole derivative that contains a nitro group. The treatment of protozoal diseases is important and challenging problems as the pathogenic microorganism has found to become resistant against the drug. So there is a constant need to synthesize new drugs for the treatment for the pathogenic microorganism. In this study, the 5-nitroimidazole derivatives (IIA-F) were synthesized from various heterocyclic compounds in the presence of cool temperature and physicochemical data of substituted 5-nitroimidazole derivatives were studied. In which**,** Molecular formula, Molecular weight, Nature, Yield, M.P.^{o}C, and solubility was studied. The purity of all the synthesized derivatives was checked by thin layer chromatography (TLC). IR spectra of the 5-nitroimidazole derivatives were recorded using KBr pellets and Shimadzu Fourier Transform Infrared Spectrophotometer (FTIR- 8400s). The mass spectra were obtained by Micromass Quattro II triple quadrupole Mass Spectrometer. In our protocol, the agar diffusion technique was used to assess antibacterial activity of new compounds. It can be concluded that all compound possess appreciable antibacterial and antifungal activities against gram-positive and gram-negative bacteria and fungi. So among six synthesized derivatives, compound **IIA, IIB, IID and F** are potent than compound **IIC and IIE.**

INTRODUCTION

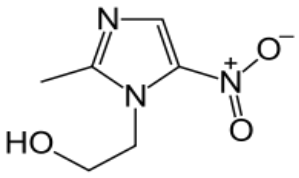
Medicinal chemistry concerns the discovery, development, the identification, and the interpretation of the mode of action of biologically active compounds at the molecular level.[1]The intellectual goal of the medicinal chemist is to know the mode of action of drugs at the molecular level.[2] Antiprotozoal drugs are medicines that are used to treat a variety of diseases caused by protozoa. Some commonly used antiprotozoal drugs are metronidazole (Flagyl), eflornithine (Ornidyl), furazolidone (Furoxone), hydroxyl chloroquine (Plaquenil), iodoquinol (Diquinol, Yodoquinol, Yodoxin), and pentamidine (Pentam 300).[3]The immune system plays a crucial role in protecting against the pathological consequences of protozoal infections. 5-Nitroimidazole is an imidazole derivative that contains a nitro group. Several derivatives of nitroimidazole constitute the class of nitroimidazole antibiotics that have been used to combat anaerobic bacterial and parasitic infections.

They entered the cell by diffusion; the antimicrobial toxicity of the nitroimidazoles is dependent on the reduction of the nitro moiety to the nitro anion radical and other highly active compounds, including nitroso and hydroxylamine derivatives. These reduction products are damaging to macromolecules and have been shown to cause DNA degradation and strand breakage. In the structure of 5 nitroimidazole substitutions at the 2 position of the imidazole ring that enhances the resonance conjugation of the chemical structure increase antiprotozoal activity.[4]

Drug Profile[4,5,6]

Metronidazole Formula: $C_6H_9N_3O_3$

Mol. Mass: 171.15 g/mol



Systematic (IUPAC) name: 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol

Metronidazole is used as primary therapy for *Clostridium difficile* infection, the major cause of pseudomembranous colitis. Given at doses of 250-500 mg orally, three times daily for 7-14

days (or even longer). Metronidazole is also used in the treatment of patients with Crohn's disease who have perianal fistulas, and it can help control colonic (but not small bowel) Crohn's disease.

LITERATURE SURVEY

Kraft *et al* (1989) had synthesized 2-(2 methyl-5-nitro-1H-imidazole-1-yl) ethanol.[7] Vardanayan *et al* (2006) had synthesized 2-(2 methyl-5-nitro-1H-imidazole-1-yl) ethanol and analyzed comparatively with the other alternative drugs.[8] Abdul Kadir *et al* (2009) had synthesized and analyzed new cyclic amines-linked metronidazole derivatives.[9]

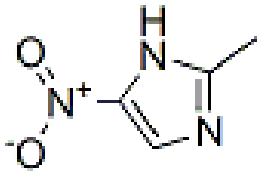
RATIONAL

There are numerous antiprotozoal drugs that were bitter in taste. In order to ensure patient compliance bitterness masking becomes essential. Nitroimidazole derivatives are highly active against most of the protozoal diseases. The survey of literature had revealed that very few amount of research work had been carried out on the synthesis of 5-nitroimidazole derivatives and its subsequent evaluation for antiprotozoal activity, and taste acceptance. It was thought worthwhile that to synthesized and characterized some derivatives of 5-nitroimidazole that was specific, potent and give better compliance with patients.

OBJECTIVE

To synthesized 5-nitroimidazole derivatives using procedures described in the literature.

To confirmed the structure of synthesized compounds using IR, Mass and ^{1}H-NMR spectroscopic methods and carried out the preliminary biological evaluation of the synthesized compounds for antimicrobial activity.

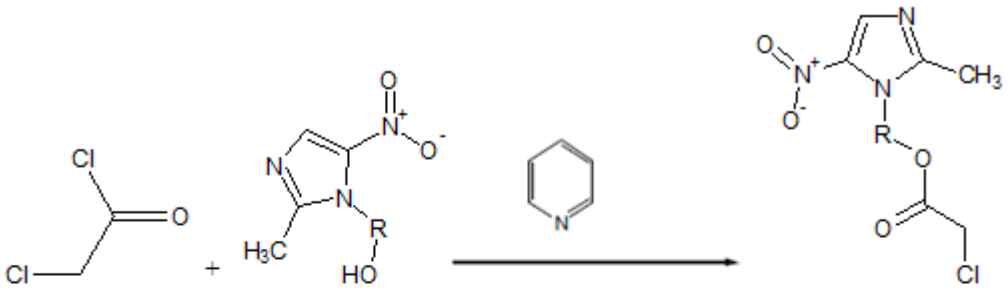


2-Methyl-5-nitroimidazole

SYNTHESIS OF 5-NITROIMIDAZOLE DERIVATIVES

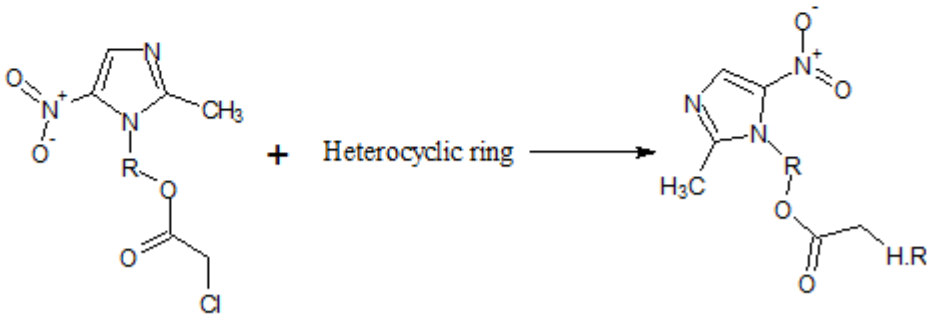
General Scheme I [9,10-16]

Step I:



Chloroacetyl Chloride | 5-nitroimidazole derivative | Chloroacetate ester of 5-nitroimidazole

Step II:



Chloroacetate ester of 5-Nitroimidazole | Ester derivative of 5-Nitroimidazole

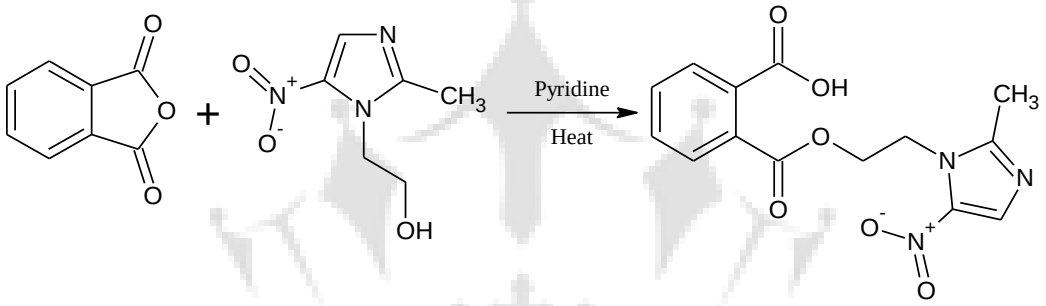
Table 1: Substituent for R used in the synthesis

Sr No.	Compounds	R
1	IIA, IIB, IIC	$CH_3CH_2CH_2OH$
2	IID & IIE	CH_2-CH_2 OH

Table 2: Substituents for heterocyclic rings used in the synthesis

Sr No.	Compounds	Heterocyclic Ring
1	IIA	Piperazine
2	IIB	Piperidine
3	IIC & IID	Pyrrol
4	IIE	Pyrrolidine

General Schem II[17,18-23]

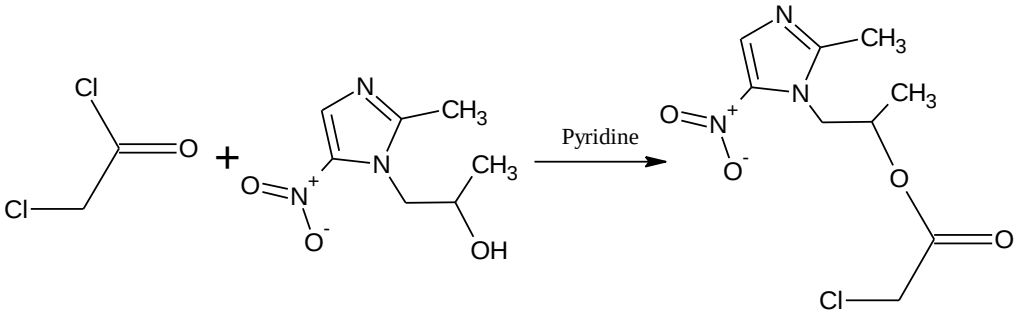


Pthalic anhydride Metronidazole Ester derivative of metronidazole (Compound F)

Preparation of various 5-nitroimidazole derivatives:

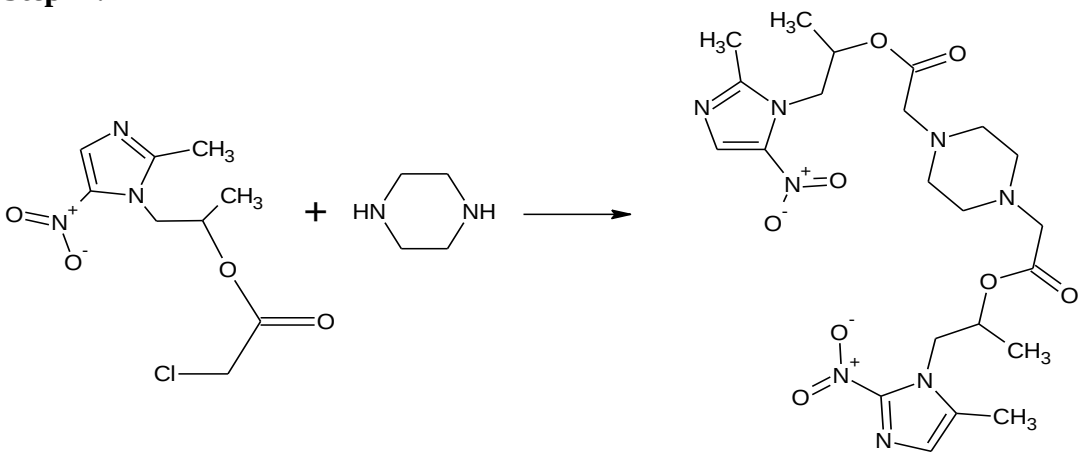
Synthesis of 1,4 bis{(2-methyl-5-nitro-1H-imidazole)2 ethyl propanoate} piperazine

Step I:



Chloroacetyl chloride Secnidazole 1-(2-methyl-5-nitro-1H-imidazole-1-yl)propan-2-ylchloroacetate **(IA)**

Step II:



1-(2-methyl-5-nitro-1H-imidazole-1-yl)propan-2-yl-chloroacetate

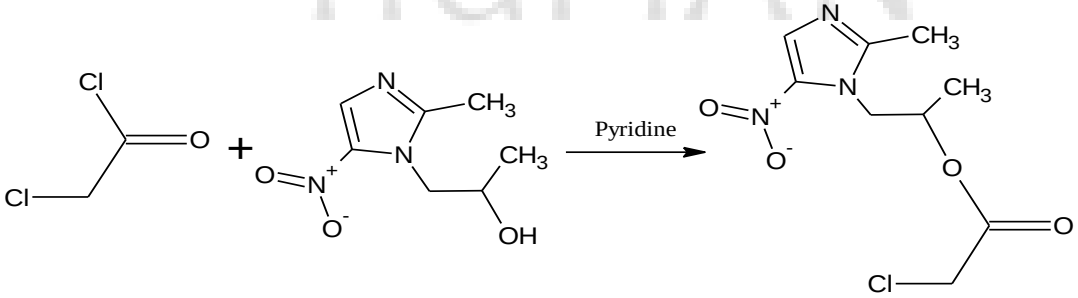
Piperazine

1,4 bis{(2-methyl-5-nitro-1H-imidazole)2-ethyl propanoate}piperazine **(IIA)**

The chloroacetyl chloride (0.8ml) which was highly fuming was reacted with secnidazole (1.5g) in the presence of pyridine (0.5ml). The reaction beaker was kept in an ice bath for 5-10 min. Then the intermediate product (IA) was mixed with the dry dioxin (5.5ml) and reacted with the heterocyclic ring like piperazine (0.5ml) dissolved in methanol to give the derivative IIA which was then purified by washing with saturated sodium chloride solution, dried over anhydrous sodium sulphate and recrystallized from chloroform - cyclohexane mixture.

Synthesis of 1-(2-methyl-5-nitro-1H-imidazol-1yl)propan-2-yl piperidin-1-ylacetate

Step I:

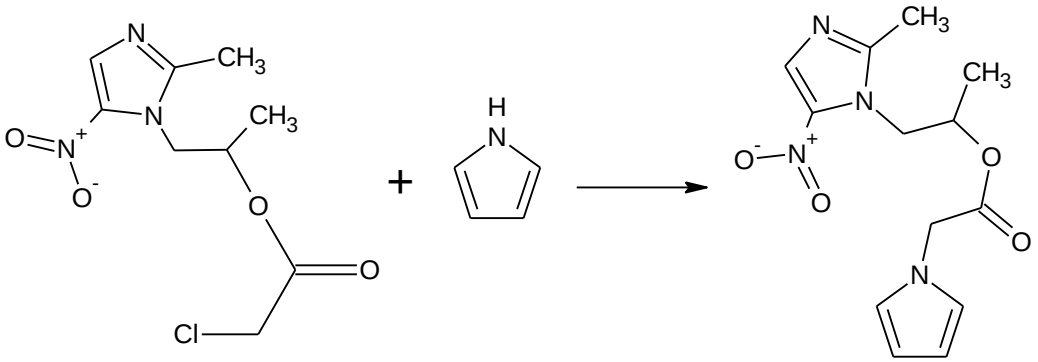


Chloroacetyl chloride

Secnidazole

1-(2-methyl-5-nitro-1H-imidazole -1-yl)propan-2-yl chloroacetate **(IA)**

Step II:



1-(2-methyl-5-nitro-1H-imidazole -1-yl)propan-2-yl chloroacetate (IA)

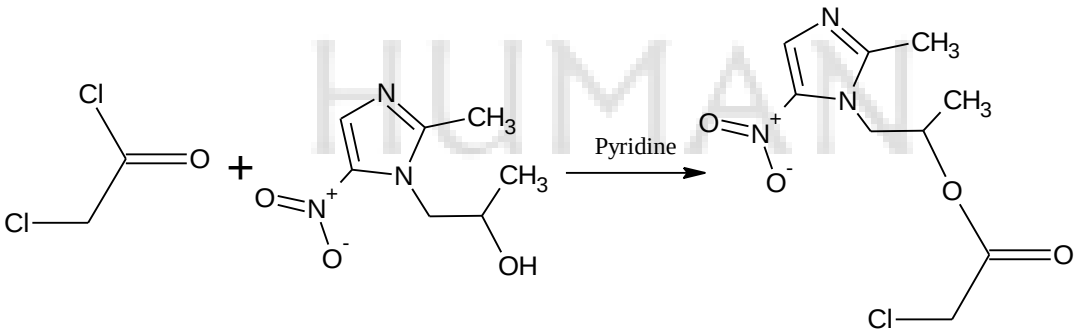
Piperidine

1-(2-methyl-5-nitro-1H-imidazole-1-yl) propan-2-yl piperidine-1-yl acetate **(IIB)**

Synthesis of compound IA was same as the previous step, then it was treated with dry dioxin (5.5ml) and reacted with piperidine (0.5ml) dissolved in methanol to give the derivative IIB which was then purified by washing with saturated sodium chloride solution, dried over anhydrous sodium sulphate and recrystallized from chloroform - cyclohexane mixture.

Synthesis of 1-(2-methyl-5nitro-1H-imidazol-1-yl)propan-2-yl-1H pyrrol-1-yl-acetate

Step I:

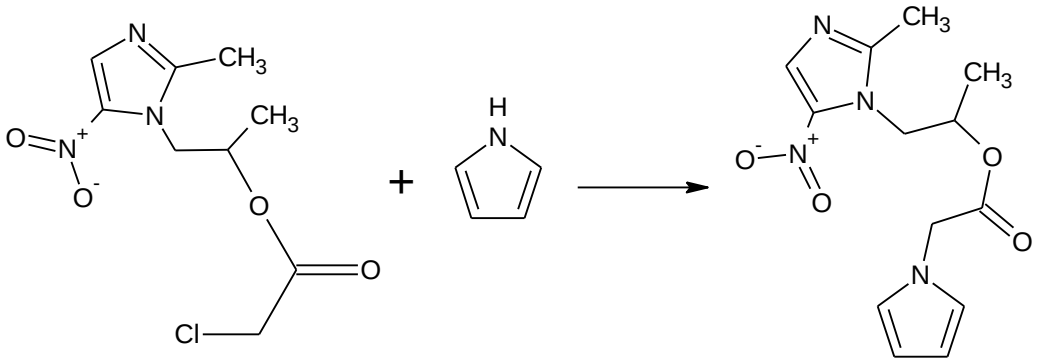


Chloroacetyl chloride

Secnidazole

1-(2-methyl-5-nitro-1H-imidazole -1-yl)propan-2-yl chloroacetate (IA)

Step II:



1-(2-methyl-5-nitro-1H-imidazole -1-yl)propan-2-yl chloroacetate **(IA)**

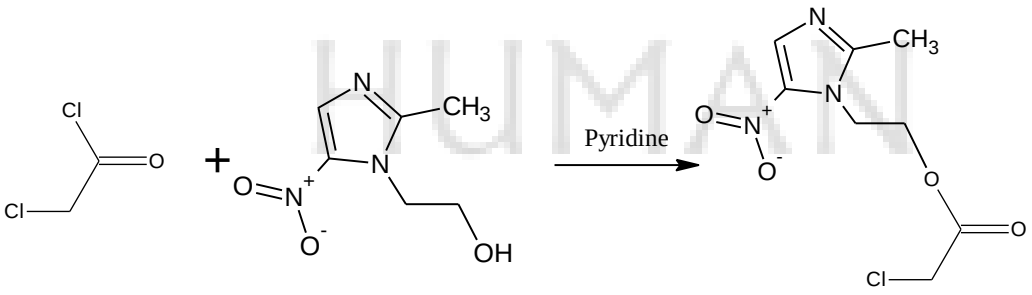
Pyrrol

1-(2-methyl-5nitro-1H imidazol -1-yl) propan-2-yl-1H pyrrol -1yl-acetate **(IIC)**

Synthesis of compound IIC was same as compound IIA, only the difference was in the heterocyclic ring. Here pyrrole (0.5ml) is used instead of piperazine ring. Then it was purified by washing with saturated sodium chloride solution, dried over anhydrous sodium sulphate and recrystallized from chloroform - cyclohexane mixture.

Synthesis of 2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethyl-1H-pyrrol-1yl acetate

Step I:

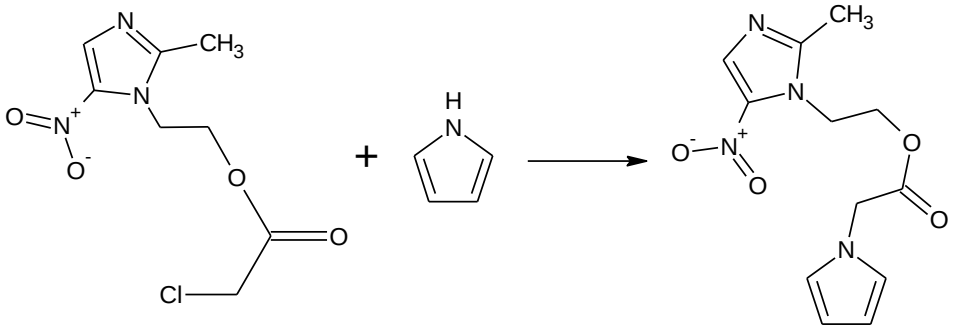


Chloroacetyl chloride

Metronidazole

2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethyl chloroacetate (ID)

Step II:



2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethyl chloroacetate

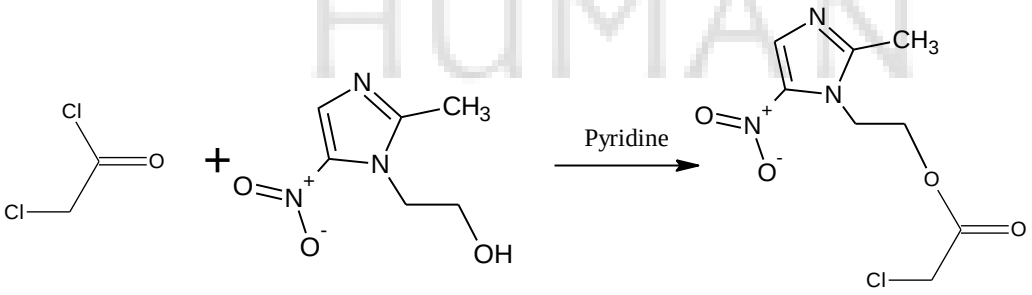
Pyrrol

2-(2-methyl-5-nitro-1H-imidazole -1-yl) ethyl-1H-pyrrol-1yl acetate **(IIID)**

The chloroacetyl chloride (0.8ml) which was highly fuming was reacted with metronidazole (1.5g) in the presence of pyridine (0.5ml). The reaction beaker was kept in an ice bath for 5-10 min. Then the intermediate product (ID) was mixed with the dry dioxin (5.5ml) and reacted with the heterocyclic ring like pyrrole (0.5ml) dissolved in methanol to give the derivative IID which was then purified by washing with saturated sodium chloride solution, dried over anhydrous sodium sulphate and recrystallized from the chloroform-cyclohexane mixture.

Synthesis of 2-(2-methyl-5 nitro-1H imidazole-1-yl)ethyl pyrrolidine-1-yl acetate

Step I:

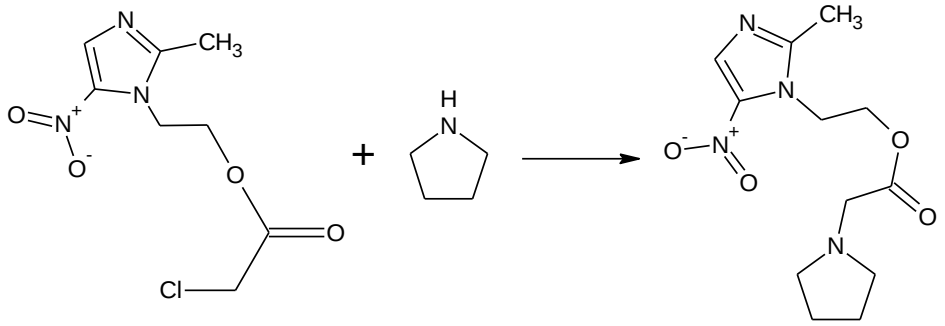


Chloroacetyl chloride

Metronidazole

2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethyl chloroacetate (ID)

Step II:



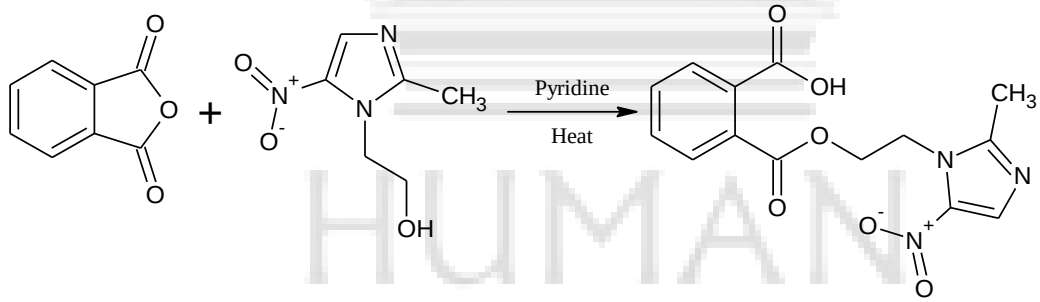
2-(2-methyl-5-nitro-1H-imidazole-1-yl) ethyl chloroacetate **(ID)**

Pyrrolidine

2-(2-methyl-5 nitro-1H imidazole-1-yl)ethyl pyrrolidine-1-yl acetate **(IIE)**

Synthesis of compound ID was same as the previous step, then it was treated with dry dioxin (5.5ml) and reacted with pyrrolidine (0.5ml) dissolved in methanol to give the derivative IIE which was then purified by washing with saturated sodium chloride solution, dried over anhydrous sodium sulphate and recrystallized from chloroform- cyclohexane mixture.

Synthesis of 2-{[2-(5-methyl-2-nitro-1H-imidazole-1-yl) ethoxy] carbonyl} benzoic acid



Phthalic anhydride Metronidazole Ester derivative of metronidazole **(F)**

A mixture of metronidazole (1g) and pyridine (1ml) was placed in a porcelain dish and stirred on the water bath to dissolved metronidazole. To it, phthalic anhydride (1g) was added slowly with constant stirring and heating on a water bath maintained at 100^{o}c. When phthalic anhydride dissolved completely, it was cooled and to it 5-10 ml hot water was added, stirred and allowed to cool. The crude product was washed with water, dried and recrystallized from hot water to get shining crystals.

RESULTS

OBSERVATIONS

Table 3: Physicochemical data of substituted 5-nitroimidazole derivatives (IIA-F)

Compound	Molecular formula	Molecular weight (g/mole)	Nature	Yield (% w/w)	M.P. °C
IIA	$C_{22}H_{32}N_8O_8$	536.53828	White crystals	71.46	282-285
IIB	$C_{14}H_{22}N_4O_4$	310.34888	Light brown crystals	59.13	274-278
IIC	$C_{13}H_{16}N_4O_4$	292.29054	Dark brown crystals	72.80	110-115
IID	$C_{12}H_{14}N_4O_4$	278.26396	Dark brown crystals	55.26	164-168
IIE	$C_{12}H_{18}N_4O_4$	282.29572	Light yellow crystals	89.73	154-158
F	$C_{14}H_{13}N_3O_6$	319.26952	White crystals	72.40	152-156
Secnidazole	$C_7H_{11}N_3O_3$	185.180	White Powder	---	70.6-72.6
Metronidazole	$C_6H_9N_3O_3$	171.15	White Powder	---	159-161

PHYSICOCHEMICAL STUDIES

Table 4: Solubility of derivatives (IIA-F) in different solvents

Compounds	H2O	Methanol	Ethanol	Acetone	Chloroform	DMSO	DMF
IIA	+	-	-	-	-	-	-
IIB	+	-	-	-	-	-	-
IIC	+	+	+	-	-	+	-
IID	+	+	+	+	-	+	+
IIE	-	+	+	+	-	+	+
F	+	+	+	+	-	+	+

Note: + means soluble and – means insoluble.

Chromatographic chamber , conditions of saturation and development of TLC:[24]

Developing solvent system :

A number of developing solvent system was tried, but the satisfactory resolution was obtained in the Chloroform : Methanol. TLC results obtained in these systems were enumerated in Table 5. The solutions of the derivatives IIA-F were prepared in methanol and spotted on TLC plate using glass capillaries. The mobile phase used was **Chloroform : methanol (6:4)**. And for derivative F **Chloroform : Hexane : Ethanol (8:1.5:0.5)** was used.

Detection of spots

Spots were detected using iodine chamber and UV light at 254nm (UV chamber) and with the help of different spraying reagents like iodine vapors , 50% H_2SO_4 , 2,4 Dinitrophenylhydrazine, 5% alcoholic $FeCl_3$ etc.

Table 5: Rf values of different derivatives of 5-nitroimidazole (IIA-F)

Compounds	Rf values
IIA	0.888*
IIB	0.836*
IIC	0.962*
IID	0.793*
IIE	0.863*
F	0.443**
Secnidazole	0.746*
Metronidazole	0.851*

Note: * means Chloroform : Methanol (6:4)

** means Chloroform : Hexane : Ethanol (8:1.5:0.5)

SPECTRAL STUDIES

IIA:1,4bis{(2-methyl-5-nitro-1H-imidazole)-2-ethylpropanoate}piperazine

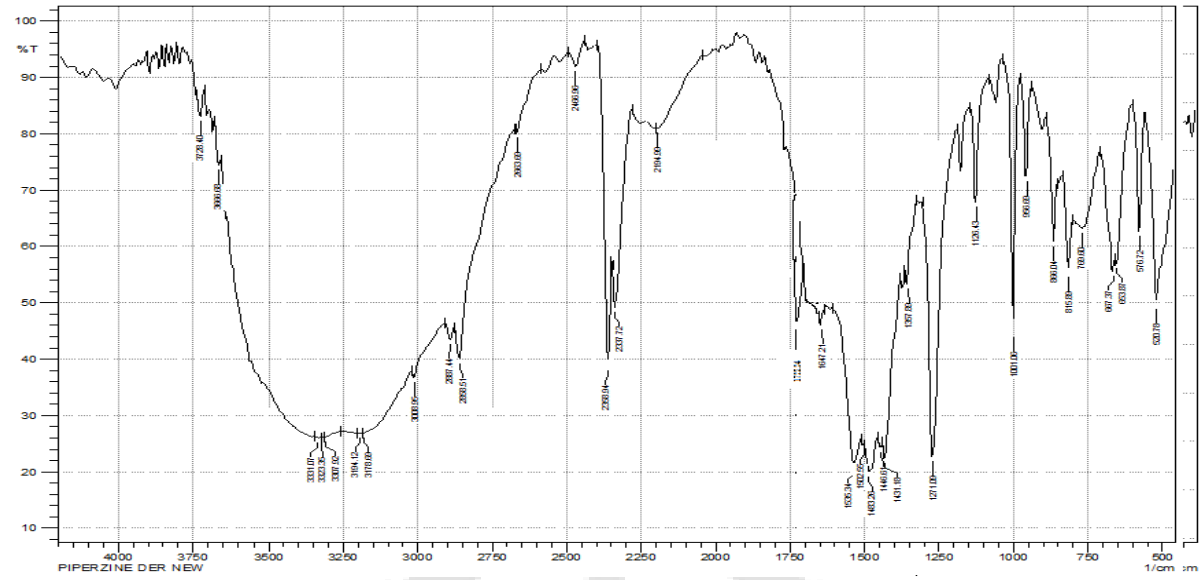


Figure 1: FT-IR spectrum of 1,4 bis{(2-methyl-5-nitro-1H-imidazole)- 2-ethyl propanoate}piperazine

IIB: 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-yl piperidin-1 ylacetate

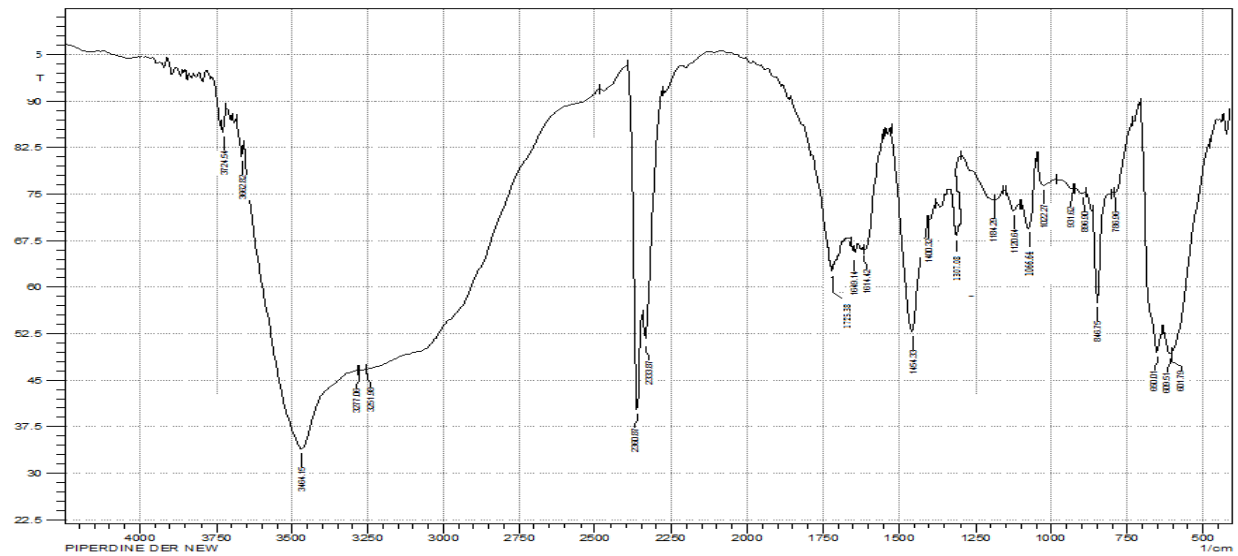


Figure 2 : FT-IR spectrum of 1-(2-methyl-5-nitro-1*H*-imidazol-1 yl)propan-2-yl piperidin-1-ylacetate

IIC: 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-yl 1*H*-pyrrol-1-ylacetate

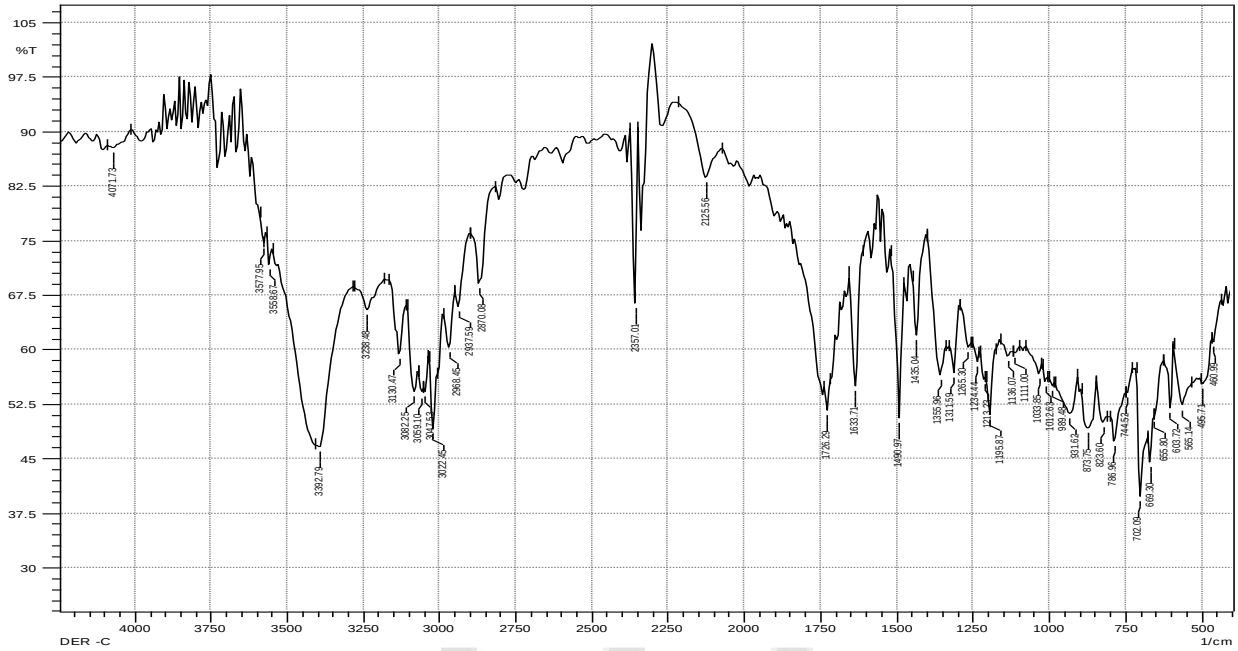


Figure 3 : FT-IR spectrum of 1-(2-methyl-5-nitro-1*H*-imidaz yl)propan-2-yl 1*H*- pyrrol-1-ylacetate

IID: 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl 1*H*-pyrrol-1-ylacetate

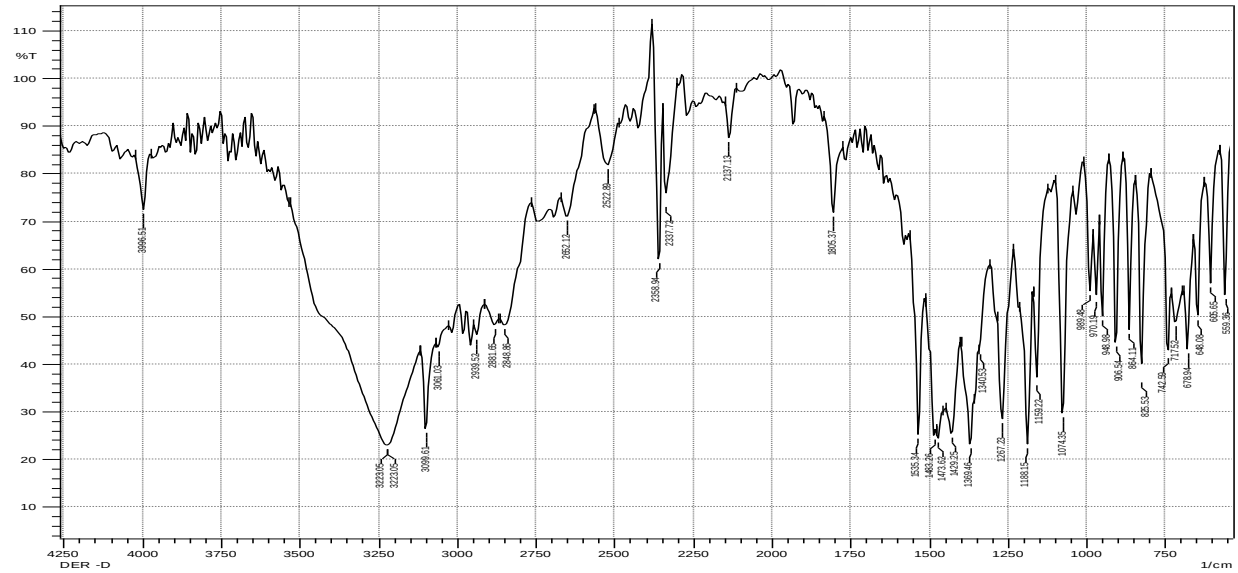


Figure 4 : FT-IR spectrum of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl 1*H*-pyrrol-1-ylacetate

IIE: 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl pyrrolidin-1-ylacetate

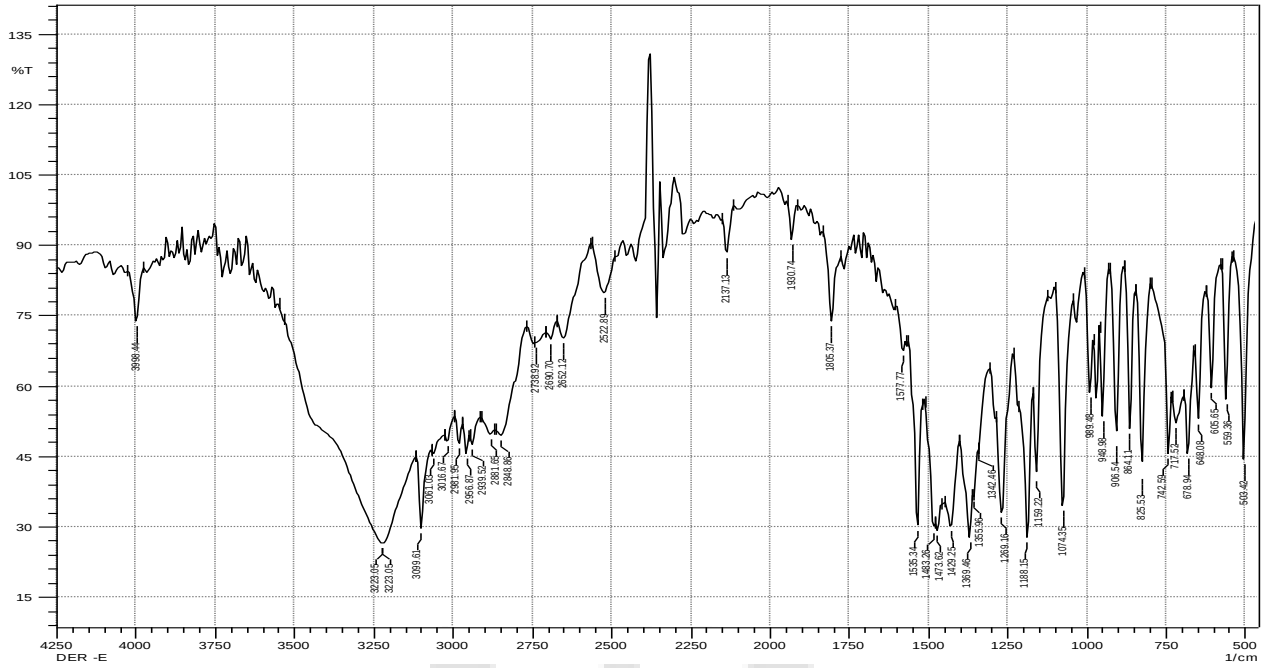


Figure 5 : FT-IR spectrum of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl pyrrolidin-1-yl acetate

F: 2-{[2-(5-methyl-2-nitro-1*H*-imidazol-1-yl)ethoxy]carbonyl}benzoic acid

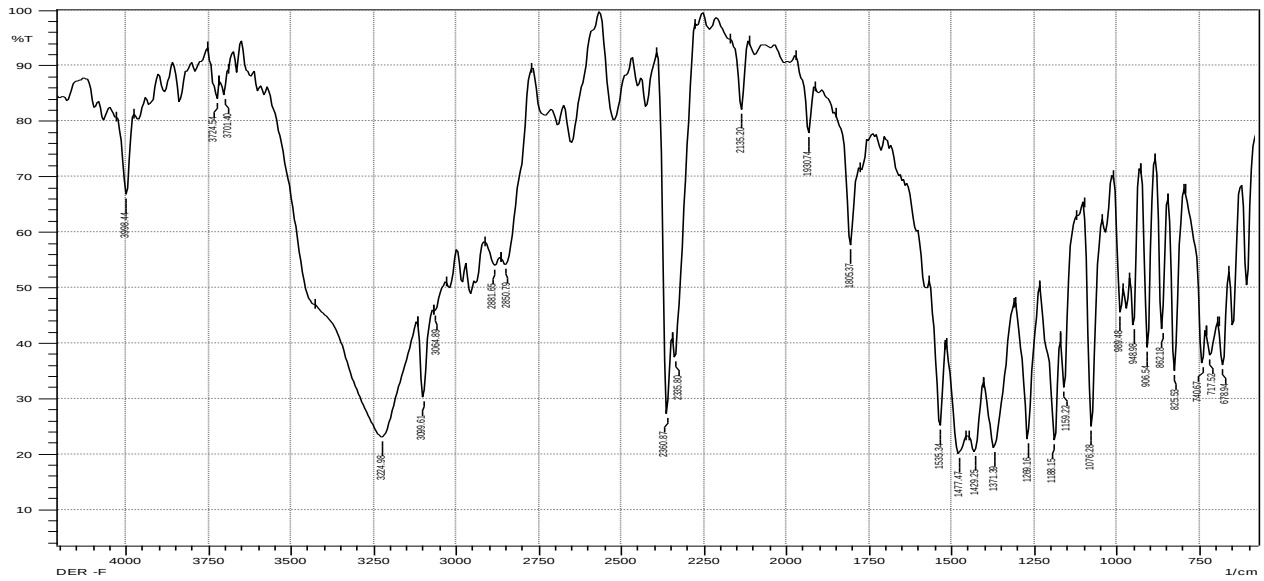


Figure 6: FT-IR spectrum of 2-{[2-(5-methyl-2-nitro-1*H*-imidazol-1-yl)ethoxy]carbonyl}benzoic acid

Mass Spectral studies[25,26]

The mass spectra were obtained by Micromass Quattro II triple quadrupole Mass Spectrometer for compounds **IIA, IIB, IID and F**. The spectra recorded in fig. no.**7-10** and spectral data shown in table no. **7.**

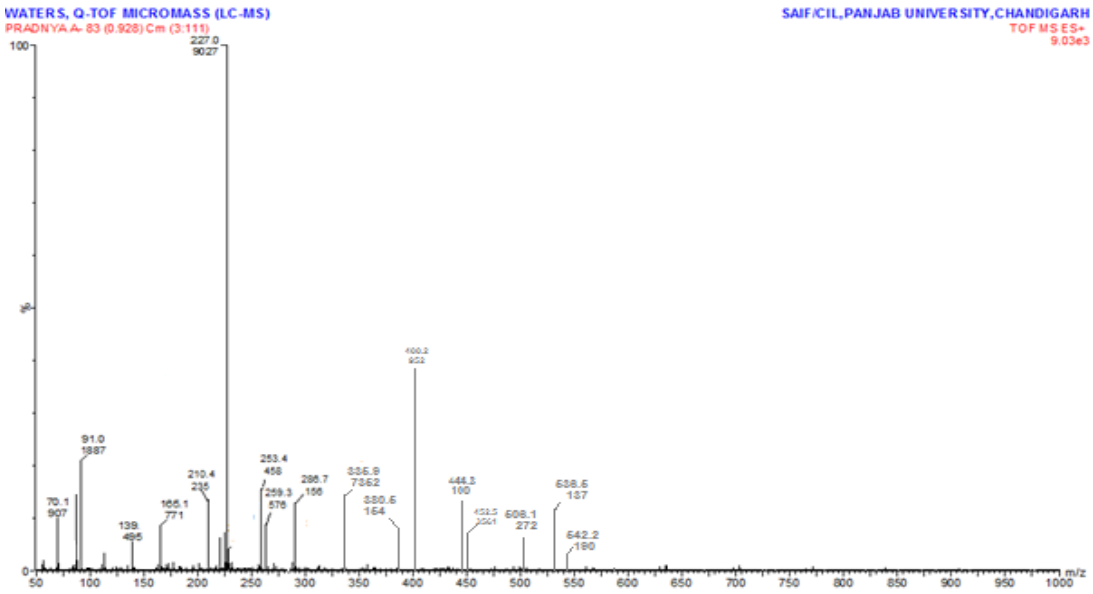


Figure No.7. Mass spectra of 1,4 bis{(2-methyl-5-nitro-1H-imidazole)-2-ethyl propanoate}piperazine

Mass spectroscopy showed molecular ion at m/e 536.51 for IIA compound .The other fragments were observed at various m/e 506.12, 444.31, 400.22, 452.51, 335.97. Mass spectrum indicated that the molecular weight of the compound IIA is 536.51 and the calculated molecular weight of the same compound is 536.53. Therefore, the molecular ion peak was found to be very much close to the calculated value.

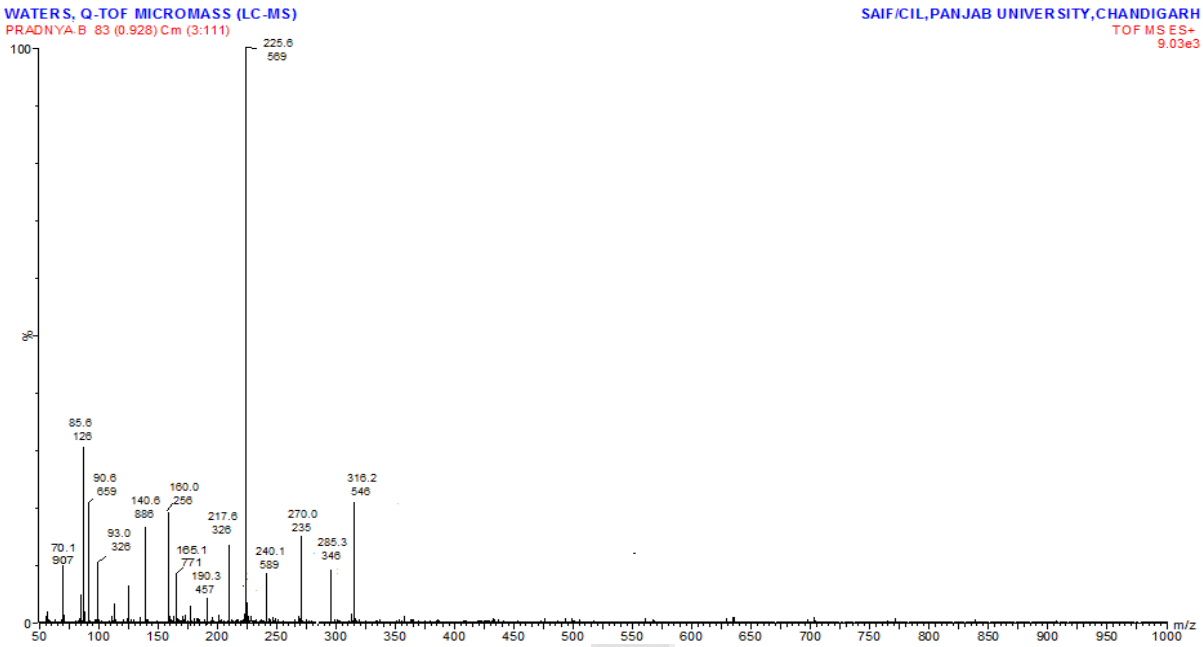


Figure No.8. Mass spectra of 1-(2-methyl-5-nitro-1*H*-imidazol-1 yl)propan-2-yl piperidin-1-yl acetate

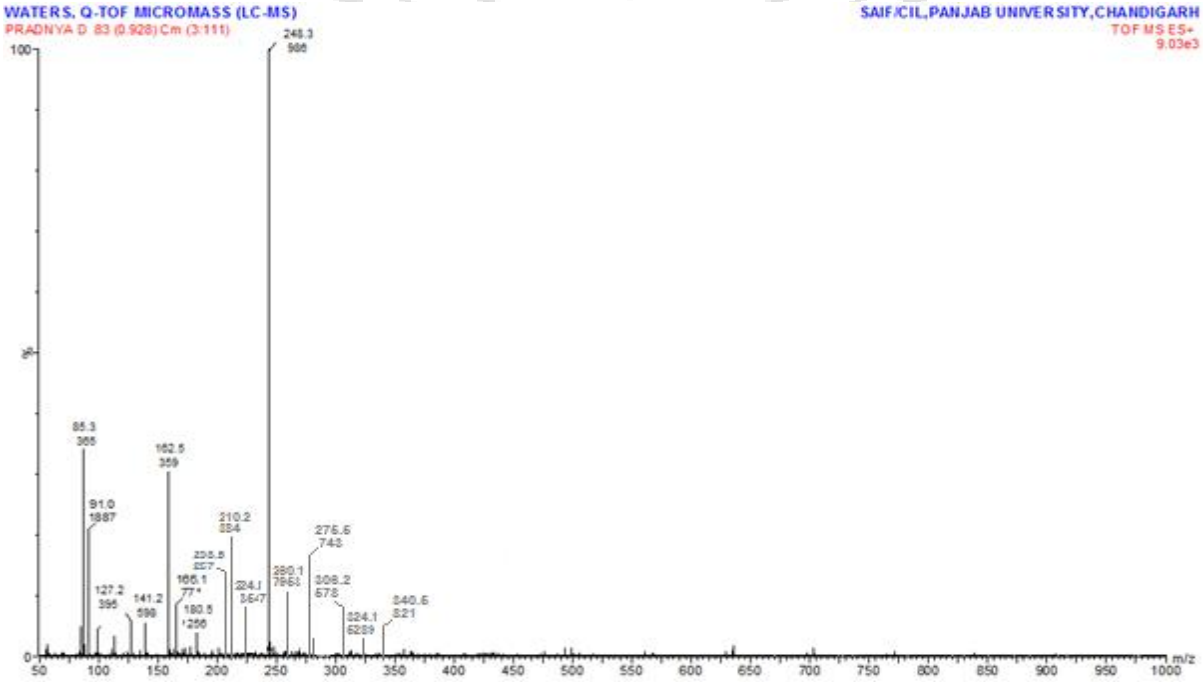


Figure No.9. Mass spectra of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl 1*H*-pyrrol-1-yl acetate

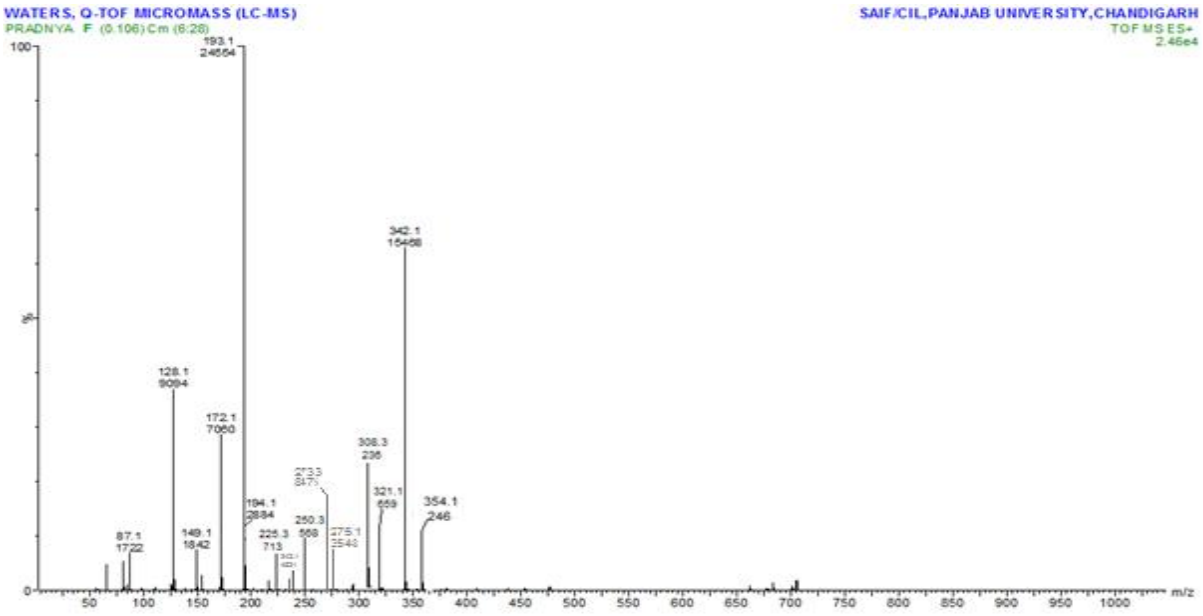


Figure No.10. Mass spectra of 2-{[2-(5-methyl-2-nitro-1*H*-imidazol-1-yl)ethoxy]carbonyl}benzoic acid

^{1}H-NMR spectral studies[25,26]

The NMR spectra were obtained by BRUKER AVANCE II 400 Spectrometer for compounds **IIA, IIB, IID and F**. The spectra recorded in fig. no.**11-14** and spectral data shown in table no.8

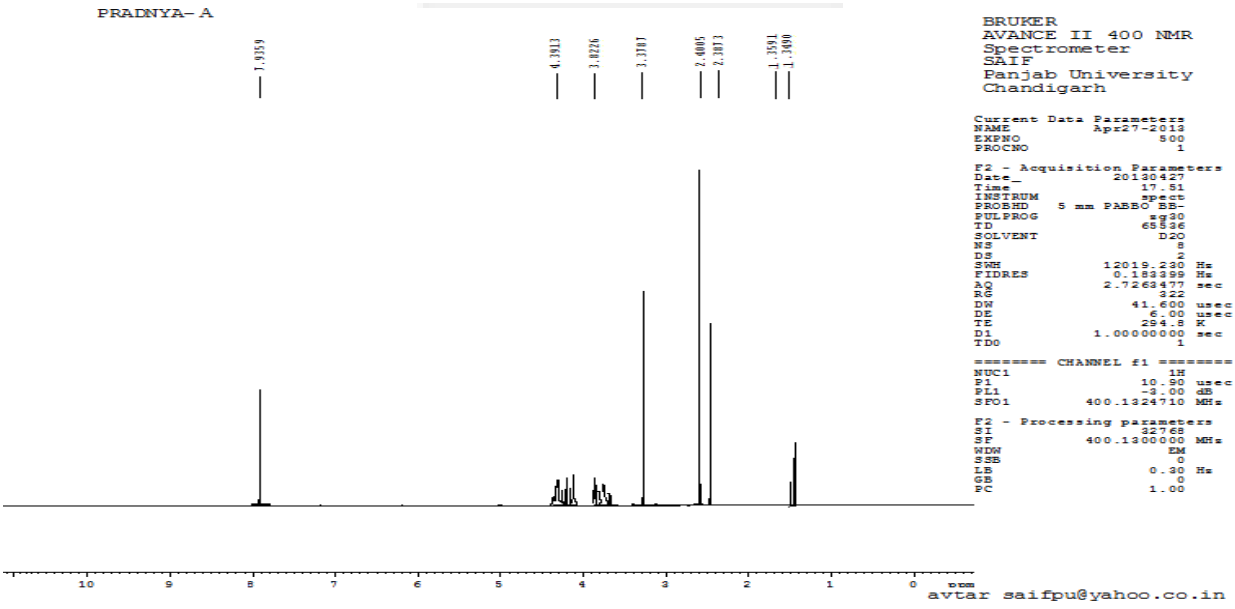


Figure No.11. ^{1}H-NMR spectra of 1,4 bis{(2-methyl-5-nitro-1H-imidazole)-2-ethyl propanoate}piperazine

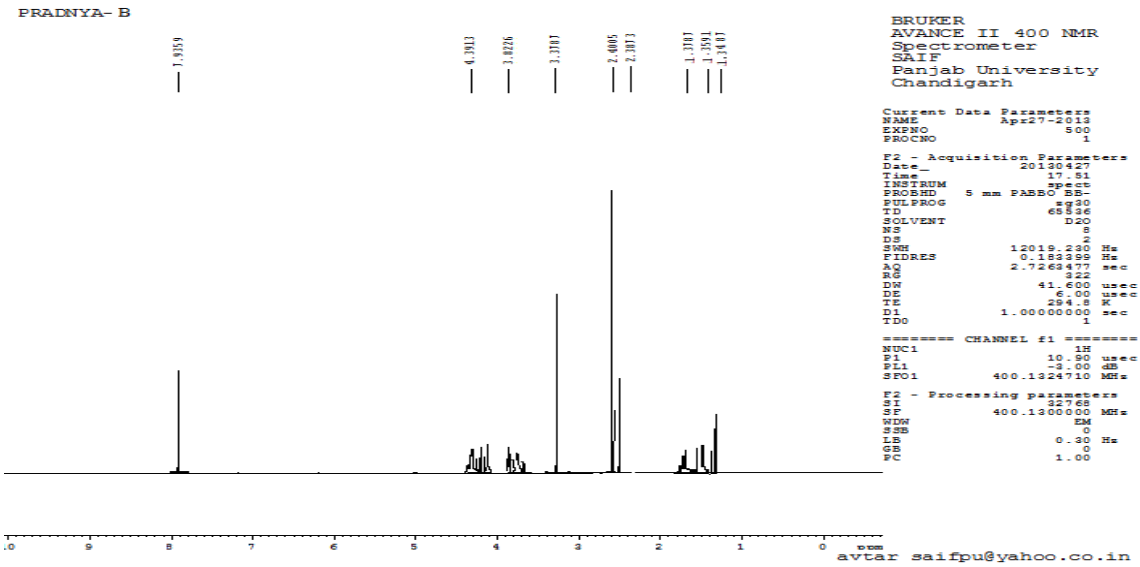


Figure No.12. [1]H-NMR spectra of 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-yl piperidin-1-yl acetate

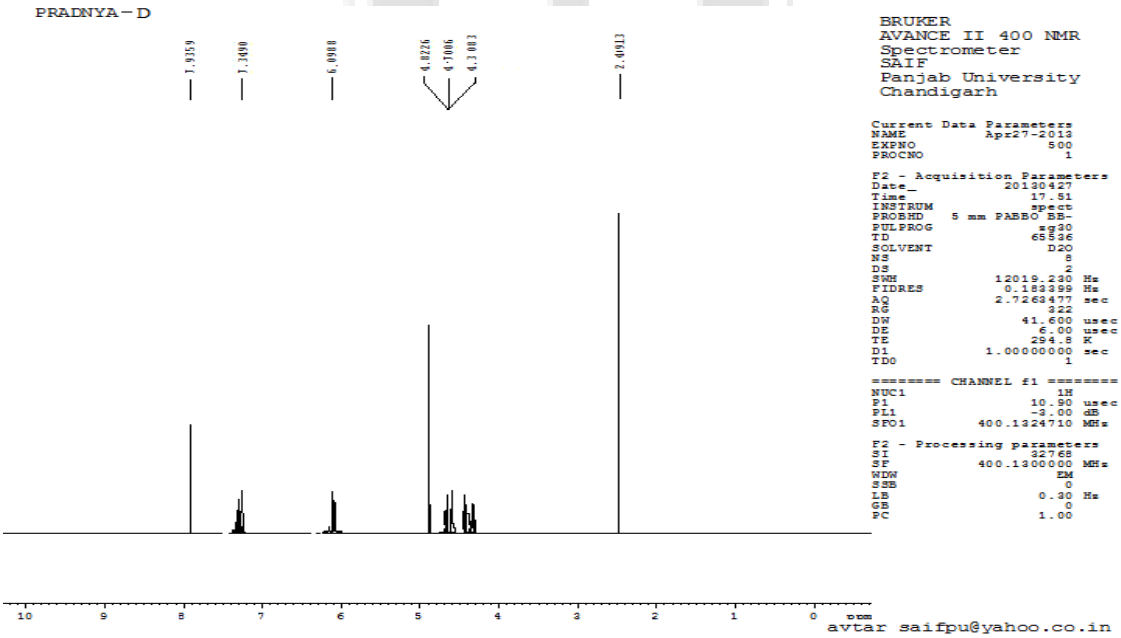


Figure No.13.[1]H-NMR spectra of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl 1*H*-pyrrol-1-yl acetate

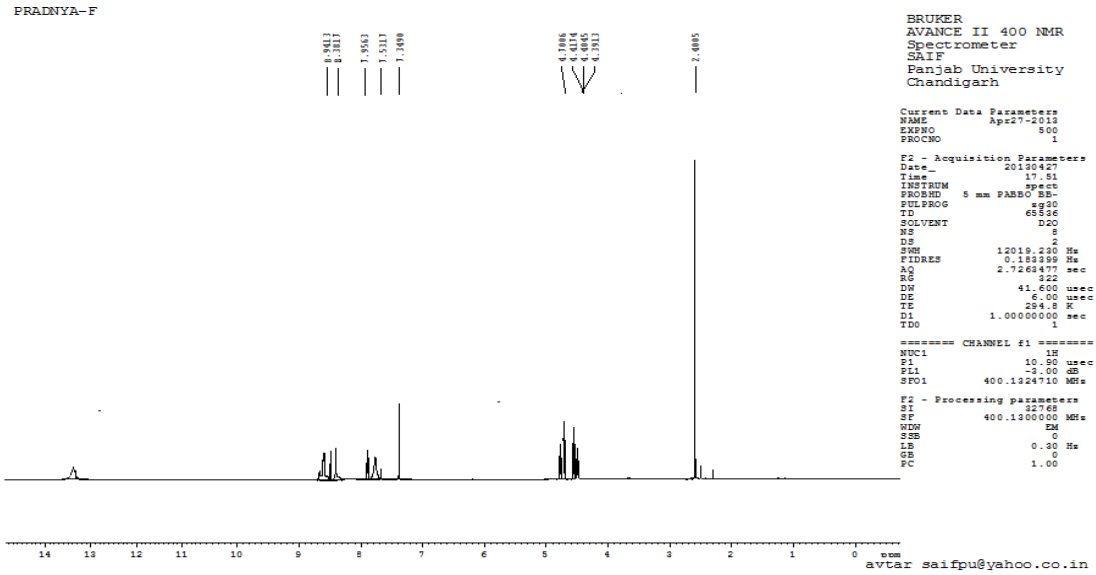


Figure No.14. ^{1}H-NMR spectra of 2-{[2-(5-methyl-2-nitro-1*H* imidazol-1-yl) ethoxy]carbonyl}benzoic acid

ANTIMICROBIAL STUDIES[27-32]

In the present investigation, cup-plate agar diffusion method was used to evaluate the antibacterial activity.

Cup-Plate Agar Diffusion Method

Preparation of solution of compound

Stock solutions of the synthesized compounds were prepared in dimethyl sulphoxide (DMSO) in the concentration of 50µg/ml, 100µg/ml, 300µg/ml, and 500µg/ml. Ofloxacin and Clotrimazole were used as a standard for antibacterial and antifungal activity respectively. For standard antibiotics the concentration ranges used were 50µg/ml, 100µg/ml, 300µg/ml, and 500µg/ml.

Antimicrobial activity data for compounds IIIA-F and Ofloxacin against *E. coli*.

Compound	Bacteria along with zone of inhibition (mm)			
	E. coli			
	50µg/ml	100µg/ml	300 µg/ml	500 µg/ml
IIA	2	7	10	14
IIB	2	4	9	13
IIC	-	-	4	7
IID	8	14	16	20
IIE	-	6	8	10
F	6	10	15	21
Std.- Ofloxacine	13	16	24	31

Antimicrobial activity data for compounds IIIA-F and Ofloxacin against *S. Aureus*.

Compound	Bacteria along with zone of inhibition (mm)			
	S. Aureus			
	50µg/ml	100µg/ml	300 µg/ml	500 µg/ml
IIA	-	5	12	14
IIB	2	4	9	13
IIC	-	-	5	6
IID	9	13	16	18
IIE	-	-	6	9
F	7	11	16	20
Std.- Ofloxacine	15	16	20	28

Antimicrobial activity data for compounds IIIA-F and Clotrimazole against *C. Albicans*.

Compound	Bacteria along with zone of inhibition (mm)			
	C. Albicans			
	50µg/ml	100µg/ml	300 µg/ml	500 µg/ml
IIA	-	-	9	11
IIB	3	8	10	12
IIC	2	3	6	8
IID	5	9	12	15
IIE	-	4	6	8
F	6	10	12	16
Std.- Clotrimazole	10	19	22	25

Antimicrobial activity data for compounds IIIA-F and Clotrimazole against *A. Niger*.

Compound	Bacteria along with zone of inhibition (mm)			
	A. Niger			
	50µg/ml	100µg/ml	300 µg/ml	500 µg/ml
IIA	2	4	10	12
IIB	6	8	10	13
IIC	-	-	2	4
IID	8	13	19	20
IIE	3	5	6	8
F	-	-	5	8
Std.- Clotrimazole	11	13	22	25

Among the entire synthesized compound **IIA, IIB, IID, and F** were found to show significant antibacterial activity against *S. aureus* and *E. coli* when compared with other compounds. Compound **IIC and IIE** are slightly less effective against *S. aureus* as compared to other four. Antibacterial activity of reference compound is highest among the entire synthesized compounds.

Also, all the synthesized compounds, **IIA, IIB, IID and F** showed the highest zone of inhibition against *C.Albicans* and *A. Niger* hence are more effective against fungi than the other synthesized compounds. Compound **IID and F** also showed remarkable activity when compared with **IIA and IIB.**

CONCLUSION

It can be concluded that all compound possess appreciable antibacterial and antifungal activities against gram-positive and gram-negative bacteria and fungi.So among six synthesized derivatives, compound **IIA, IIB, IID and F** are potent than compound **IIC and IIE.** And also more effective against bacterias (*S. aureus* and *E.* coli) and fungi (*C. Albicans* and *A. Niger*).

SUMMARY

The 5-nitroimidazole derivatives (A-F) have been synthesized. The compound 1,4 bis{(2-methyl-5-nitro-1H-imidazole)2ethyl propanoate} piperazine i.e. derivative IIA, 1-(2-methyl-5-nitro-1*H*-imidazol-1-yl)propan-2-yl piperidin-1 yl acetate i.e. derivative IIB, 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl 1*H*-pyrrol-1-ylacetate i.e. derivative IID and 2-{[2-(5-methyl-2-nitro-1*H*-imidazol-1-yl) ethoxy]carbonyl}benzoic acid i.e. derivative F showed good antimicrobial activity as compared to other synthesized compounds, which can be suggested a possible clinical significance of compound.

FUTURE SCOPE

The resistance to antimicrobial drugs is widespread, which has created a substantial medical need for new classes of antimicrobial agents. A potential approach to overcome the resistance problem is to design, innovative agents with different modes of action so that no cross-resistance with the present therapeutic agents can occur. In future, the derivatives showing potent antimicrobial activities can be developed into a suitable formulation for the treatment of microbial diseases.

The compounds can be synthesized by microwave assisted synthesis which will definitely increase the percentage yield of the product and also will reduce the total time taken for the syntheses. SAR studies can also be performed to get better derivatives having more potent activities. In future toxicity studies can also be done on the synthesized derivatives.

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