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Synthesis and Characterization of Novel Amide Derivatives of Nitro-Imidazole

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ABSTRACT

Synthesis of Amide derivatives of Nito-imidazole were investigated. various amide derivatives of 1-(2-chloroethyl)-5-nitro-1H-imidazole-2-carboxylic acid (III) (derived From Metronidazole) have been synthesized by condensing them with sulfanilamide, sulfamethoxazole, sulfadiazine, Sulfanilic acid, sulfacetamide and isoniazid. Phosphorus Oxychloride is used as condensing agent. Structures of all derivatives were established on the basis of elemental analysis IR, and 1H NMR spectral data.

Keywords: Nitro-imidazole, sulfonamides, isoniazid

INTRODUCTION

Heterocyclic compounds have constituted one of the largest areas of research in organic chemistry. Heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities with wide variety of heterocyclic systems known today. The nitrogen heterocyclics are of great importance as they are present in nucleic acids, vitamins, proteins and other biologically important molecular systems [1]. The amide functionality is a common feature in small or complex synthetic or natural molecules. For example, it is ubiquitous in life, as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). Amides also play a key role for medicinal chemists. An in-depth analysis of the Comprehensive Medicinal Chemistry database revealed that the carboxamide group appears in more than 25% of known drugs [2] .This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties [3]. The heterocyclic compound Imidazole and its derivatives are of great significance due to their important roles in biological system, particularly in enzymes, as proton donors and/or acceptors, coordination system ligands and the base of charge–transfer processes [4]. Imidazole derivatives possess a broad spectrum of pharmacological activities such as anticonvulsant[4,6], anti-Parkinson[5,7] and mono-aminooxidase (MAO) inhibitory[4,8] activity.

In the present study, different novel amide derivatives of carboxylic acid which is derived from nitroimidazole ring have been reported by employing direct Amidation process. It is very crucial to have such method when acid is very important and its synthesis have low yield. In the present study we bypassed the preparation of acid chloride form acid (one of the process for the activation of acid) and used direct condensation method to prepare amides by using $POCl_3$ as a condensing agent.

Scheme of Synthesis

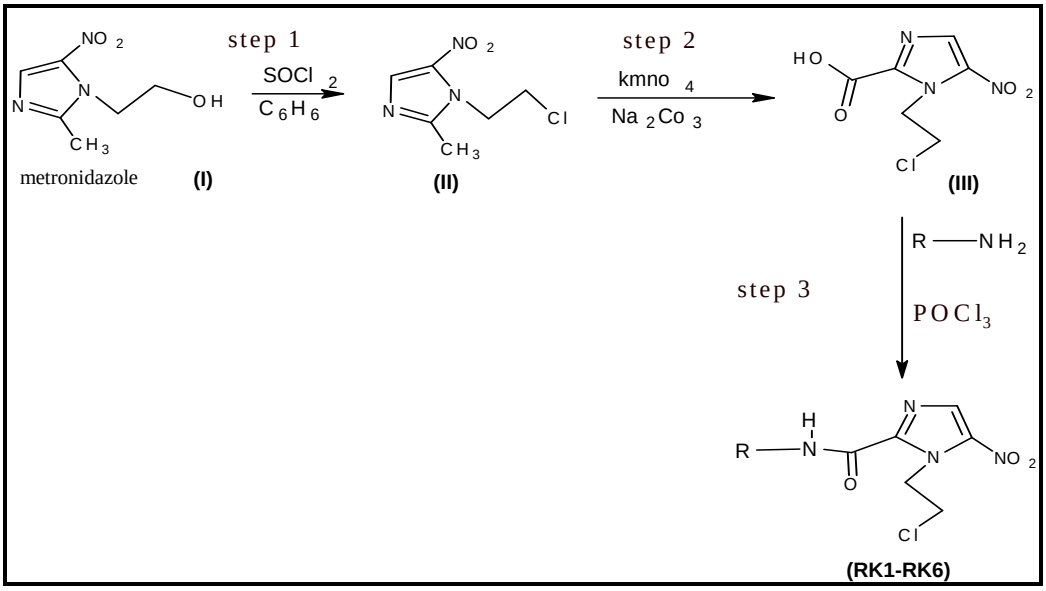
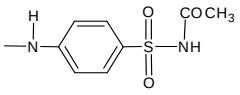
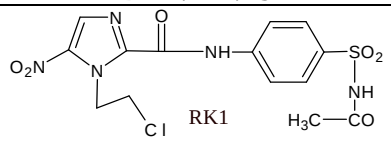
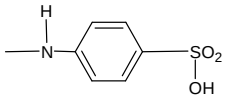
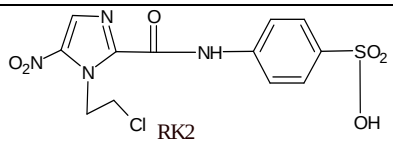
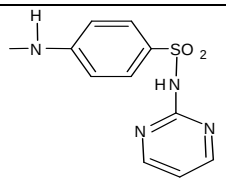
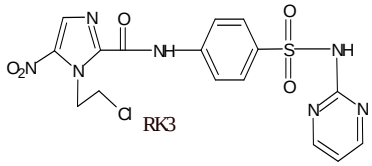
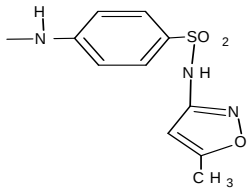
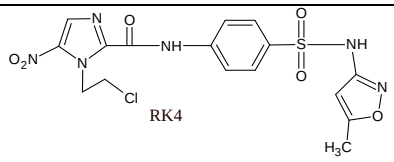
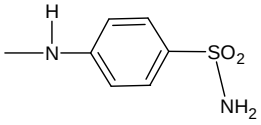
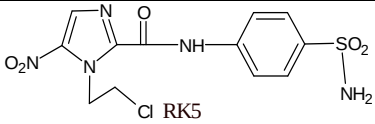
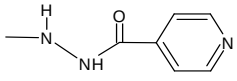
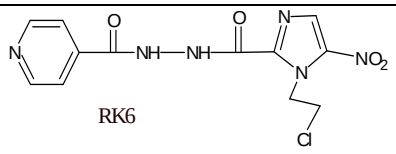


Table No. 1 List of Drugs with free amino groups and their amide derivatives (RK1-RK6)

DRUGS (with free NH_2 group)	R	DERIVATIVES
Sulfacetamide		 RK1
Sulfanilic acid		 RK2
Sulfadiazine		 RK3
Sulfamethox-azole		 RK4
Sulfanilamide		 RK5
Isoniazid		 RK6

MATERIALS AND METHODS

Melting points were determined by open capillary method using Veego "VMP-I" melting point apparatus and were uncorrected. FTIR spectra were taken on "Jasco FT/IR-410", using KBr pressed pellet technique. The 1H-NMR spectra were run on a Bruker spectrometer in DMSO (300 MHz) using tetramethylsilane as internal standard. Metronidazole (starting compound) was purchased from Aarti Drugs Ltd., Mumbai. Sulfa drugs and isoniazid purchased from research Lab Mumbai, Chemicals were purchased from Aldrich, Himedia and Fluka. All the reactants were identified by comparison of melting points with those reported in the literature

EXPERIMENTAL PROCEDURE:-

1. Synthesis of 1-(2-chloroethyl) -2-methyl-5-nitro-1H-imidazole (II) [5]

Initially Thionyl chloride (1.18 g, 0.01 mole) was added to a solution of Metronidazole **(I)** (1.71g, 0.01 mole) in dry benzene (20 mL), and then the reaction mixture was refluxed for 7 hrs.the course of reaction is monitered by TLC. After complition of reaction solvent used is subjected for the evaporation, the product was collected and recrystallized from ethanol-water.

IR (KBr, (ν cm^{-1}): 3127 (C-H_{aryl}), 2924, 2852 (C-H_{alkyl}), 1551 (C=$N_{imidazole}$), 1491 ($NO_{2\ sym}$), 1344($NO_{2\ asym}$), 1260 (C-N), 667 (C-Cl)

2 Synthesis of 1-(2-chloroethyl)-5-nitro-1*H*-imidazole-2-carboxylic acid(III) [5]

Compound **(II)** (1.89 g, 0.01 mole) was added to a solution of sodium bicarbonate (1.06 g, 0.01 mole) and potassium permanganate (1.57 g, 0.01 mole) in water (20 mL), then the reaction mixture was refluxed for 15 hrs. The reaction mixture was cooled and acidified with conc. HCl and the product was collected and recrystallized from ethanol.

IR (KBr, (ν cm^{-1}): 3422 (OH_{acid}), 2927, 2854 (C-H_{alkyl}), 1703 (C=O_{acid}),1536 (C=$N_{imidazole}$), 1492 (NO_{2sym}), 1334 ($NO_{2\ asym}$), 1267 (C-N), 666 (C-Cl)

3 General procedure for the synthesis of amides (RK1-RK6) [9] Amides were synthesized by dissolving 1-(2-chloroethyl)-5-nitro-1*H*-imidazole-carboxylic acid (0.001 mol) and sulfanilamide / sulfadiazine / sulfamethoxazole/ sulfacetamide /sulfanilic acid/ isoniazid(0.001 mol) in a minimum quantity of dry pyridine,separately.The two solutions were then mixed together and stirred magnetically followed by the addition of phosphorous oxychloride (0.9 ml) dropwise,while maintaining a temperature below 5^0C.Then The mixtures were stirred for another 1 hr and left overnight. The reaction mixture was then poured into ice cold water and a solid mass, which separated out, was filtered, washed, dried and crystallized from ethanol to give Amides (RK1-RK6)

The physico-chemical data of all intermediate compounds and six derivatives (RK1-RK6) is given in Table 2

SPECTRAL DATA OF SYNTHESIZED COMPOUNDS RK1-6

N-[4-(acetylsulfamoyl) phenyl]-1-(2-chloroethyl)-5-nitro-1H-imidazole-2-carboxamide **(RK1)**

IR (KBr,cm^{-1}): 3357 (N-H Str Amide),3080 (Aryl C-H),2923,2853 (Alkyl C-H),1691 (C=O str,Amide) 1637 (N-H def),1535 (C=N str),1494 (NO_2 Str sym.) 1334 (NO_2 Str Asym) ,679 (C-Cl Str) 1302 (C-N str amide,SO_2sulfonamide sym.)1153 (SO_2Asym.str.) ^{1}HNMR (δppm):11.841 (s,1H ,SO_2-NH),10.5 (s,1H, CO-NH),8.85 (s,1H,C-H Imidazole), 7.615-7.545 (d,2H Aryl C-H), 6.781-6.741(d,2H,Aryl C-H),1.85 (s,3H,CH_3), 2.563-2.224(t,2H,N-CH_2).

4-({[1-(2-chloroethyl)-5-nitro-1H-imidazol-2yl]carbonyl}amino)benzene sulfonic acid **(RK2)**

IR (KBr,cm^{-1}):3332(N-H Str Amide),3159(Aryl C-H),2924,2853(Alkyl C-H),1678 (C=O str,Amide) 1650 (N-H def),1546 (C=N str),1498 (NO_2 Str sym.)1330(NO_2 Str Asym), 678(C-Cl Str) 1310 (C-N str amide, SO_2 sulfonamide sym.), 1165(SO_2Asym.str.)^{1}HNMR (δppm):10.5 (s, 1H, CO- NH), 9.86 (s, 1H, OH), 8.74 (s, 1H, C-H Imidazole), 7.86-7.83 (d, 2H Aryl C-H), 6.84-6.79 (d, 2H, Aryl C-H), 2.27-2.40 (t, 2H, N-CH_2)

4-({[1-(2-chloroethyl)-5-nitro-1H-imidazol-2-yl] carbonyl} amino) benzene sulfonic acid **(RK3)**

IR (KBr,cm^{-1}): 3442 (N-H Str Amide),3082 (Aryl C-H),2924,2854 (Alkyl C-H),1666 (C=O str,Amide) 1629 (N-H def),1549 (C=N str),1499 (NO_2 Str sym.) 1337 (NO_2 Str Asym) ,679 (C-Cl Str) 1301 (C-N str amide,SO_2sulfonamide sym.)1151 (SO_2Asym.str.). ^{1}HNMR (δppm):11.731 (s,1H ,SO_2-NH),10.86 (s,1H, CO-NH),8.3 (m.2H-3,4,diazine ring)7.9 (t,1H,H-4 Diazine Ring) 8.3 (s,1H,C-H Imidazole), 7.71-7.61 (d,2H Aryl C-H), 6.68-6.65 (d,2H,Aryl C-H), 2.19-2.24(t,2H,N-CH_2).

1-(2-chloroethyl)-N-{4-[(5-methylisoxazol-3-yl) sulfamoyl]phenyl}-5-nitro-1H-imidazole-2-carboxamide **(RK4)**
IR (KBr,cm^{-1}): 3322 (N-H Str Amide),3073 (Aryl C-H),2924,2855 (Alkyl C-H),1640 (C=O str,Amide) 1594 (N-H def),1526 (C=N str),1495 (NO_2 Str sym.) 1354 (NO_2 Str Asym) ,679 (C-Cl Str) 1302 (C-N str amide,SO_2sulfonamide sym.)1164 (SO_2Asym.str.) ^{1}HNMR (δppm):11.74 (s,1H ,SO_2-NH),10.68 (s,1H, CO-NH),8.88 (s,1H,C-H Imidazole), 7.73-7.76 (d,2H Aryl C-H), 6.68-6.71 (d,2H,Aryl C-H), 5.8 (s,1H,isoxazole),1.874 (s,3H,CH_3 isoxazole ring), 2.28-2.30 (t,2H,N-CH_2).

1-(2-chloroethyl)-5-nitro-N-(4-sulfamoylphenyl)-1H-imidazole-2-carboxamide **(RK5)**
IR (KBr,cm^{-1}): 3466 (N-H Str Amide),3136 (Aryl C-H),2924,2854 (Alkyl C-H),1633 (C=O str,Amide) 1594 (N-H def),1512 (C=N str),1491 (NO_2 Str sym.) 1321 (NO_2 Str Asym) ,667 (C-Cl Str) 1301 (C-N str amide,SO_2sulfonamide sym.)1174 (SO_2Asym.str.) ^{1}HNMR (δppm):10.71 (s,1H, CO-NH), 8.75 (s,1H,C-H Imidazole), 7.55-7.58 (d,2H Aryl C-H), 6.66-6.69,(d,2H,Aryl C-H),6.846 (s,2H,SO_2NH_2), 2.29-3.33 (t,2H,N-CH_2).
N'-{[1-(2-chloroethyl)-5-nitro-1H-imidazol-2-yl]carbonyl}pyridine-4-carboh- ydrazide **(RK6)**

IR (KBr,cm^{-1}): 3411 (N-H Str Amide),3085 (Aryl C-H),2924,2853 (Alkyl C-H),1697 (C=O str,Amide) 1557 (N-H def),1532 (C=N str),1488 (NO_2 Str sym.) 1364 (NO_2 Str Asym) ,667 (C-Cl Str) 1298 (C-N str amide). ^{1}HNMR (δppm): 8.70 (s,1H,C-H Imidazole), 7.90-7.87 (d,2H Aryl C-H), 6.89-6.84,(d,2H,Aryl C-H), 2.29-3.33 (t,2H,N-CH_2),9.20-9.59 (s,2H, NH-NH-)

Table No2: Physicochemical data for the compound RK1-RK6

Compd. No.	M. P.	Molecular Formula (Weight)	% Yield	Mobile Phase	R_f value
RK1 Amide of Sulfacetamide	188-190 ^{0}C	$C_{14}H_{14}ClN_5O_6S$ 415.8	47	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.62
RK2 Sulfanilic acid amide	194-196^{0}C	$C_{12}H_{11}ClN_4O_6S$ 374.75	59	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.56
RK3 Sulfadiazine Amide	182-184 ^{0}C	$C_{16}H_{14}ClN_7O_5S$ 451.84	54	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.66
RK4 Sulfamethoxazole amide	196-198 ^{0}C	$C_{16}H_{15}ClN_6O_6S$ 454.1	42	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.53
RK5 Sulfanilamide amide	198-200 ^{0}C	$C_{12}H_{12}ClO_5N_5S$ 373.77	51	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.50
RK6 Isoniazid amide	178-180 ^{0}C	$C_{13}H_{12}ClN_5O_4S$ 337.4	45	Ethyl acetate: CCl_4:GAA (3:1:0.5)	0.58

RESULTS AND DISCUSSION

Different derivatives of Nitro-imidazole containing sulfonamide and Pyridine group were synthesized by reaction of aromatic carboxylic acid **(III)** i.e.*(1-(2-chloroethyl)-2-nitro-1H-imidazol-5-carboxylic acid)*synthesized from metronidazole with Sulfonamide moiety (Sulfacetamide /sulfanilic acid/sulfadiazine/ sulfamethoxazole/ sulfanilamide) and isoniazid. The designated compounds were synthesized according to proposed Scheme with three steps of reaction given in the experimental part. Reaction of 2-*(2-methyl-5-nitro-1H-imidazol-1-yl) ethanol* (metronidazole **(I)**) with thionyl chloride afforded 1-(2-chloroethyl)-2-methyl-5-nitro-1*H*-imidazole **(II).** The IR Spectrum of product shown that, the absence of absorption bands due to OH and the presence of a C-Cl absorption band at (667 cm-1). *1-(2-chloroethyl)-2-nitro-1H-imidazol-5-carboxylic acid* **(III)** which was readily prepared via oxidation of the CH3 group of compound **(II)**, The structures of compounds **(III)** were confirmed by IR spectral data and element analysis. In the IR spectrum compound **(III)** the presence of an OH absorption at 3,422-3,270 cm-1 besides the C=O absorption at 1,703 cm-1 was observed from which compound **(III)** was confirmed. The amides (**RK1-RK6**) were synthesized by reacting *1-(2-chloroethyl)-2-nitro-1H-imidazol-5-carboxylic acid* **(III)** with Sulfa drugs and isoniazid in dry pyridine in the presence of phosphorous oxychloride as condensing agent and obtained in appreciable yields (40-60%) **.**The purity of the compounds was controlled by TLC in solvent System, ethyl acetate : carbon tetrachloride : glacial acetic acid (3:1: few drops) Nuclear magnetic resonance spectra (1H NMR;δ ppm) showed two doublets at around 7.73 and 6.78 ppm (4H-Aryl CH) and signals in the region 10.65 ppm (1H, from CO-NH) which is characteristics to all Amide derivatives.

CONCLUSION

In summary, we have synthesized some of novel Amide derivatives of Nitro-imidazole.

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