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Synthesis and Characterization of Some Novel Hydrazone Derivatives Of 3-(5-Mehylisoxazolyl-3-Ylcarbamoyl) Propanoic Acid.

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ABSTRACT

Among wide variety of heterocycles,isoxozole unit,an important group due to wide variety of biological activity such as antitumor,CNS-active,analgesic ,antimicrobial, chemotherapy and found to possess vasodilating effect similar to that of nifedipine. Hydrazide-hydrazones display a wide variety of interesting pharmacological properties such as antimicrobial & anti-oxidant activity, anti-platelet and analgesic properties. Inaddition , hydrazide-hydrazones are reported to bring forth anti-HIV and anti-cancer properties and therefore they have gained a significant place in medicinal chemistry. In view of this here in reported the synthesis of a series of novel isoxazolyl hydrazide-hydrazone derivatives **5a-j** ,synthesized from 4-hydrazinyl-N-(5-methylisoxazol-3-yl)-4-oxobutanamide **4** and different Benzaldehydes in methanol under reflux conditions.The structures of all the synthesized compounds(**3,4and 5a-j**),have been established on the basis of IR,[1]HNMR and Mass spectral data.

Keywords: 3-Amino-5-methylisoxazole, 3-(5-methylisoxazol-3-ylcarbamoyl) propanoic acid, Benzaldehydes, isoxazolyl hydrazide-hydrazones.

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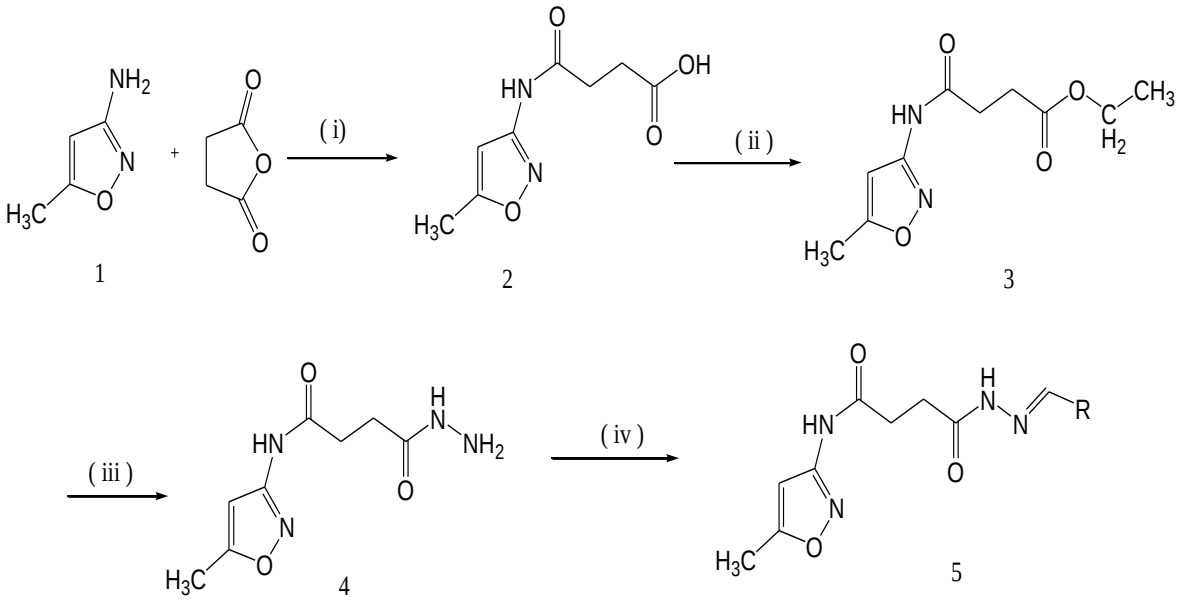
INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life; hence they have attracted considerable attention towards the design of biologically active molecules and advanced organic materials. Among wide variety of heterocycles that have been explored for developing pharmacologically important molecules , isoxozole unit, constitutes an important group due to wide variety of biologically activity such as antitumor[1],CNS-active[2],analgesic [3],antimicrobial[4] , chemotherapy[5] and found to possess vasodilating effect [5] similar to that of nifedipine. Hydrazide-hydrazones display a wide variety of interesting pharmacological properties such as antimicrobial & antioxidant activity [6], anti-platelet and analgesic properties[7-10]. Inaddition , hydrazide-hydrazones are reported to bring forth anti-HIV[11] and anti-cancer properties [12-16] and therefore they have gained a significant place in medicinal chemistry. Recently, hydrazide-hydrazones have gained great impotence due to their biological properties, including anti-inflammatory anti-malarial and anti tuberculostic anti-virus [17-21]. As sequel to our work on isoxazole[22-24] we herein reported the synthesis of a series of novel isoxazolyl hydrazide-hydrazones.

RESULTS AND DISCUSSION

The synthesis of new isoxazolyl hydrazone derivatives. **5a-j** is depicted in **Scheme I**. The 3-(5-methylisoxazol-3-ylcarbamoyl)propanoic acid **2** [22] was converted into corresponding ethylester **3** in presence of catalytic amount H_2SO_4 in ethanol. The compound **3** was treated with hydrazine hydrate in ethanol to afford key intermediate hydrazide derivative **4**. Condensation reaction between hydrazide **4** and various benzaldehydes, resulted in the formation of isoxazolyl hydrazide-hydrazone derivatives **5a-j**. They were characterized by ^{1}HNMR, Mass and IR Spectral data. As representative examples, the ^{1}HNMR of compound **5a** is as follow. The –NH-N and NH-CO Protons was observed as a two independent singlet at δ 11.25, 9.00 and the azomethine protan(-N=CH) was observed as singlet at δ 8.50 . All the other aromatic and aliphatic protons were observed at the expected regions. The ^{1}HNMR data for all the remaining hydrazone derivatives were also consistent with the assigned structures. The Mass spectra of the compound showed (M^++1) Peaks which were in agreement with the their molecular formula. In the IR Spectra, some significant stretching bands due to N-H, CO,and C=N were observed in the range 3405-3302,1655-1630 & 1575-1558 cm^{-1} respectively. The physicochemical data of compounds **3,4&5a-j** are given in **Table I.**



5a: R=C_6H_5 ; 5b:R=4-ClC_6H_4 ; 5c: R=4-$OCH_3C_6H_4$; 5d: R=4-$NO_2C_6H_4$; 5e: R=3-BrC_6H_4; 5f: R= 4-FC_6H_4; 5g: R=2,4-$Cl_2C_6H_3$; 5h: R=4-OHC_6H_4; 5i: R=3-$OCH_3C_6H_4$; 5j: R=2-OHC_6H_4

Scheme I: Synthesis of compounds 5a-j:Reagents and conditions:(i)Solide state; (ii)Ethanol,H_2SO_4,Reflux;(iii)NH_2-NH_2 ,Ethanol, Reflux;(iv)R-CHO,Methanol, Reflux

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Table I: The physicochemical characteristics of the newly synthesized compounds 3,4&5a-j.

Compound	R	Mol.Formula	Mol.Weight	Yield(%)	m.p(°C)
3	—	$C_{10}H_{14}N_2O_4$	226	91	209
4	—	$C_8H_{12}N_4O_3$	212	85	221
5a	C_6H_5	$C_{15}H_{16}N_4O_3$	300	82	175
5b	4-ClC_6H_4	$C_{15}H_{15}ClN_4O_3$	334	85	182
5c	4-$OCH_3C_6H_4$	$C_{16}H_{18}N_4O_4$	330	85	190
5d	4-$NO_2C_6H_4$	$C_{15}H_{15}N_5O_5$	345	82	200
5e	3-BrC_6H_4	$C_{15}H_{15}BrN_4O_3$	378	88	198
5f	4-FC_6H_4	$C_{15}H_{15}FN_4O_3$	318	83	195
5g	2,4-$Cl_2C_6H_4$	$C_{15}H_{14}Cl_2N_4O_3$	368	87	202
5h	4-OHC_6H_4	$C_{15}H_{16}N_4O_4$	316	85	192
5i	3-$OCH_3C_6H_4$	$C_{16}H_{18}N_4O_4$	330	98	194
5j	2-OHC_6H_4	$C_{15}H_{16}N_4O_4$	316	84	196

MATERIALS AND METHODS

All the chemical were purchased from Sigma Aldrich,all the reagents were analytically pure. Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds checked by TLC (Merck precoted) and visualized under U.V. Light. IR Spectra were recorded as a KBr pellet with a Perkin Elmer BX series FT-IR spectrophotometer, ^{1}HNMR spectra were recorded in DMSO-d_6 with a Verian Gemini of 300 MHz instrument. Chemical Shift values were reported in δ(ppm) using TMS as an internal standered Mass Spectra were recorded using Jeol JMC D-300 spectrometre at 70ev.

General procedure for synthesis of ethyl 3-(5-methylisoxazol-3-ylcarbamoyl)propanoate 3: To solution of 3-(5-mehylisoxazolyl-3-ylcarbamoyl) Propanoic acid **2** (5g 0.025mole) in ethanol(20ml), Sulphuric acid (0.1ml) were added and refluxed for 8hrs, after completion of the reaction (monitored with TLC) , excess ethanol was evaporated under reduced pressure and the obtained residue was dissolved in ethyl acetate (100ml) washed with aqueous 10% Sodium bicarbonate solution (2X20ml) followed by water and saturated brine. The separated organic layer was dried over Na_2SO_4 and evaporated to offered compound **3**:IR(KBr): 3398(NH), 1665(NHCO)1742 (ester-C=O)cm^{-1}; ^{1}HNMR(300MHz,DMSO-d_6): 1.20(t,3H,OCH_2CH_3), 2.24(s,3H, isoxazole-CH_3), 2.98(t,2H,CH_2-CH_2), 3.15(t,2H,CH_2-CH_2),4.21(q,2H, OCH_2CH_3), 5.98(s,1H, isoxazole-H),8.95(bs,1H,NH,D_2O exchangeable);MS: m/z(M^++1)227.

General procedure for Synthesis of 4-hydrazinyl-N-(5-methylisoxazol-3-yl)-4-oxobutanamide 4: To a solution of compound **3** (4grs, 0.018 mole) in ethanol(20ml) hydrazine hydrate (99%) (0.056 mole)was added the resulting reaction mixture was refluxed for 12hr., After completion of the reaction (monitored with TLC) ,reaction mixture was cooled to room temperature,solid separated out from reaction mixture filtered and washed with cold methanol to obtain the pure compound **4** : IR(KBr): 3420-3145(-NH-NH_2),1645(-C=O)cm^{-1}; ^{1}HNMR(300MHz,DMSO-d_6): δ2.20 (s,3H,isoxazole-CH_3), 3.02(m,4H,CH_2-CH_2), 4.12(bs,2H,NH,D_2O exchangeableleable), 6.05(s,1H, isoxazole-H), 9.20(bs,1H, NH),11.42(bs,1H,NH,D_2O exchangeable);MS: m/z(M^++1)213.

General procedure for Synthesis of (E)-4-(2-benzylidenehydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5a-j: To a solution of compound 4(1 equivalent) in methanol (10ml) was added corresponding benzaldehydes(1.2 equivalents) and contents were refluxed for 4-6 hours. After complete the reaction (monitored with TLC) it was cooled and separated solid was filtered and washed with cold methanol,to obtain the pure compound **5**.Spectral(IR,^{1}HNMR and Mass) data of the compounds **5a-j** are described below.

(E)-4-(2-benzylidenehydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5a:IR(KBr): 3390(NH), 1628(-C=O), 1562(C=N) cm^{-1}, ^{1}HNMR(DMSO-d_6), δ2.29 (s,3H,isoxazole-CH_3), 2.91(t,2H,CH_2-CH_2), 3.21(t,2H,CH_2-CH_2), 5.90(s,1H,isoxazole-H), 7.49(m,3H,Ar-H), 7.80(m,2H,Ar-H), 8.5(s,1H,-N=CH), 9.0(bs,1H,NH,D_2O exchangeableleable), 11.25(bs,1H,NH,D_2O exchangeable);MS: m/z(M^++1):301.

(E)-4-(2-(4-chlorobenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5b: IR(KBr):3318(NH), 1648(-C=O),1560(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.25(s,3H,isoxazole-CH_3), 3.01(t,2H,CH_2-CH_2), 3.32(t,2H,CH_2-

CH_2), 6.01(s,1H,isoxazole-H), 7.42(d,2H,Ar-H), 7.49(d,2H,Ar-H), 8.48(s,1H,-N=CH), 9.08(bs,1H,NH,D_2O exchangeable), 11.42(bs,1H,NH,D_2O exchangeable) ; MS: m/z(M^++1)235.

(E)-4-(2-(4-methoxybenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5c: IR(KBr):33145(NH), 1650(-C=O),1558(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.25(s,3H,isoxazole-CH_3), 2.89(t,2H,CH_2-CH_2), 3.21(t,2H,CH_2-CH_2), 3.95(s,3H,-OCH_3), 6.02(s,1H,isoxazole-H), 6.95(d,2H,Ar-H), 7.62(d,2H,Ar-H), 9.32(bs,1H,NH,D_2O exchangeable), 11.25(bs,1H,NH,D_2O exchangeable) ; MS: m/z(M^++1)331.

(E)-N-(5-methylisoxazol-3-yl)-4-(2-(4-nitrobenzylidene)hydrazinyl)-4-oxobutanamide,5d: IR(KBr):3320(NH), 1637(-C=O), 1560(C=N) cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.44(s,3H,isoxazole-CH_3), 2.99(t,2H,CH_2-CH_2), 3.21(t,2H,CH_2-CH_2), 6.00(s,1H,isoxazole-H), 7.45(d,2H,Ar-H), 8.18(d,2H,Ar-H), 8.65(s,1H,N=CH),9.20(bs,1H,NH,D_2O exchangeable), 11.20(bs,1H,NH,D_2O exchangeable); MS: m/z(M^++1)346.

(E)-4-(2-(3-bromobenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5e: IR(KBr): 3405(NH), 1638(-C=O), 1558(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.32(s,3H,isoxazole-CH_3), 2.92(t,2H,CH_2-CH_2), 3.11(t,2H,CH_2-CH_2), 5.98(s,1H,isoxazole-H), 7.25(m,1H,Ar-H), 7.59(d,1H,Ar-H), 7.75(d,1H,Ar-H), 8.00(s,1H,Ar-H), 8.42(s,1H,-N=CH), 9.25(bs,1H,NH,D_2O exchangeable), 11.45(bs,1H,NH,D_2O exchangeable); MS: m/z(M^++1)379.

(E)-4-(2-(4-fluorobenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5f: IR(KBr): 3392(NH), 1635(-C=O), 1567(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6):δ2.28(s,3H,isoxazole-CH_3), 3.01(t,2H,CH_2-CH_2), 3.32(t,2H,CH_2-CH_2), 6.05(s,1H,isoxazole-H), 7.14(m,2H,Ar-H), 7.80(m,2H,Ar-H), 8.48(s,1H,-N=CH), 9.18(bs,1H,NH,D_2O exchangeable), 11.38(bs,1H,NH,D_2O exchangeable); MS: m/z(M^++1)319.

(E)-4-(2-(2,4-dichlorobenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5g: IR(KBr): 3392(NH), 1630(-C=O), 1562(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.26(s,3H,isoxazole-CH_3), 2.95(t,2H,CH_2-CH_2), 3.22(t,2H,CH_2-CH_2), 6.15(s,1H,isoxazole-H), 7.30(d,1H,Ar-H), 7.45(d,1H,Ar-H), 8.15(s,1H,Ar-H), 8.90(s,1H,-N=CH), 9.18(bs,1H,NH,D_2O exchangeable), 11.55(bs,1H,NH,D_2O exchangeable); MS: m/z(M^++1)369.

(E)-4-(2-(4-hydroxybenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5h: IR(KBr): 3302(NH), 1638(-C=O), 1568(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.22(s,3H,isoxazole-CH_3), 2.90(t,2H,CH_2-CH_2), 3.25(t,2H,CH_2-CH_2), 6.10(s,1H,isoxazole-H), 6.90(d,2H,Ar-H), 7.79(d,2H,Ar-H), 8.65(s,1H,-N=CH), 9.05(bs,1H,NH,D_2O exchangeable), 10.55(bs,1H,OH,D_2O exchangeable),11.25(bs,1H,NH,D_2O exchangeable); MS: m/z(M^++1)317.

(E)-4-(2-(3-methoxybenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5i: IR(KBr):3321(NH),1632(-C=O), 1565(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.65(s,3H,isoxazole-CH_3), 2.85(t,2H,CH_2-CH_2), 3.15(t,2H,CH_2-CH_2), 4.05(s,3H,-OCH_3), 6.02(s,1H,isoxazole-H), 6.95-7.05(m,4H,Ar-H), 9.32(bs,1H,NH,D_2O exchangeable), 11.25(bs,1H,NH,D_2O exchangeable) ; MS: m/z(M^++1)331.

(E)-4-(2-(2-hydroxybenzylidene)hydrazinyl)-N-(5-methylisoxazol-3-yl)-4-oxobutanamide,5j: IR(KBr): 3315(NH), 1638(-C=O), 1575(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6): δ2.38(s,3H,isoxazole-CH_3), 3.03(t,2H,CH_2-CH_2), 3.30(t,2H,CH_2-CH_2), 6.10(s,1H,isoxazole-H), 6.95-7.40(m,4H,Ar-H),8.65(s,1H,-N=CH), 9.05(bs,1H,NH,D_2O exchangeable), 11.25(bs,1H,NH,D_2O exchangeable) 12.05(bs,1H,OH,D_2O exchangeable), ; ms: m/z(M+1):317.

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