Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(7):445-448

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and characterization of novel isoxazolyl benzimidazoles

Ramu Kakkerla

Department of Chemistry, Satavahana University, Karimnagar, Telangana, India

---

ABSTRACT

A series of novel isoxazolyl benzimidazole (4,6,8,10,12&14), have been synthesized from β-(5-methyl-3-isoxazolylamido)-benzoic acid (3), β-(5-methyl-3-isoxazolylamide)-acrylic acid(5), β-(5-methyl 3-isoxazolylamide)-propionic acid(7), β-(3-methyl-4-isoxazolyl amido-5-styryl)-benzoic acid (9), β-(3-methyl-4-isoxazolyl amido-5-styryl)- acrylic acid (11) and β-(3-methyl-4-isoxazolyl amido-5-styryl)- propionic acid (13) was separately subjected to cyclo condensation with N-methyl o-phenylene diamine in Polyphosphoric acid give corresponding isoxazolyl benzimidazoles. Structure of all the synthesized compounds have been elucidated by means of IR, ^{1}HNMR and Mass spectral data.

Keywords: Amino isoxazole, N-methyl *o*-Phenylene diamine, Polyphosphoric acid, cyclo condensation, isoxazolyl benzimidazoles.

INTRODUCTION

Benzimidazole is an important nucleus that has been essentially used is medicinal chemistry, notable examples being the antihistaminic and the antiulcer omeprazole[1]. Benzimodazoles are also known of their anti-inflammatory [2], anti biotic [3], antihelmintic [4].anti cancer [5]. Besides this benzimidazole derivatives exhibit significant activity against several viruses such as HIV[6-7].Herpes(HSV-1)[8], RNA[9], influenza[10,11], human cytomegalovirus(HCMV)[6] and in diverse area of chemistry [12], isoxazoles have been found posses marked biological effects as CAN stimulants [13], anti inflammatory and analgesic [14], anti microbial[15], anti tumor [16], in chemo therapy[17] and found to posses vasodilating effect[18] similar to that of nifedipine.

Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity was produced [19-20]. The chemistry of these linked biheterocyclies has been a fascinating field of investigation in medicinal chemistry as they have been found to exhibit enhanced biological profile [21]. In view of this, we under took the synthesis of isoxazolyl benzimidazoles.

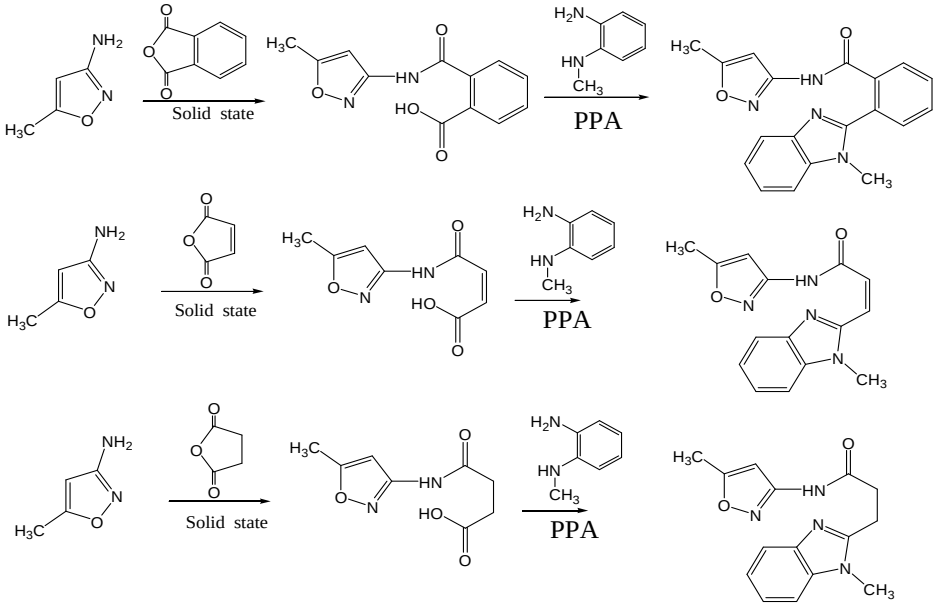
As a sequel to our work on isoxazole[22-24] the present investigation reports synthesis and antimicrobial activity of isoxazolyl benzimidazoles.

EXPERIMENTAL SECTION

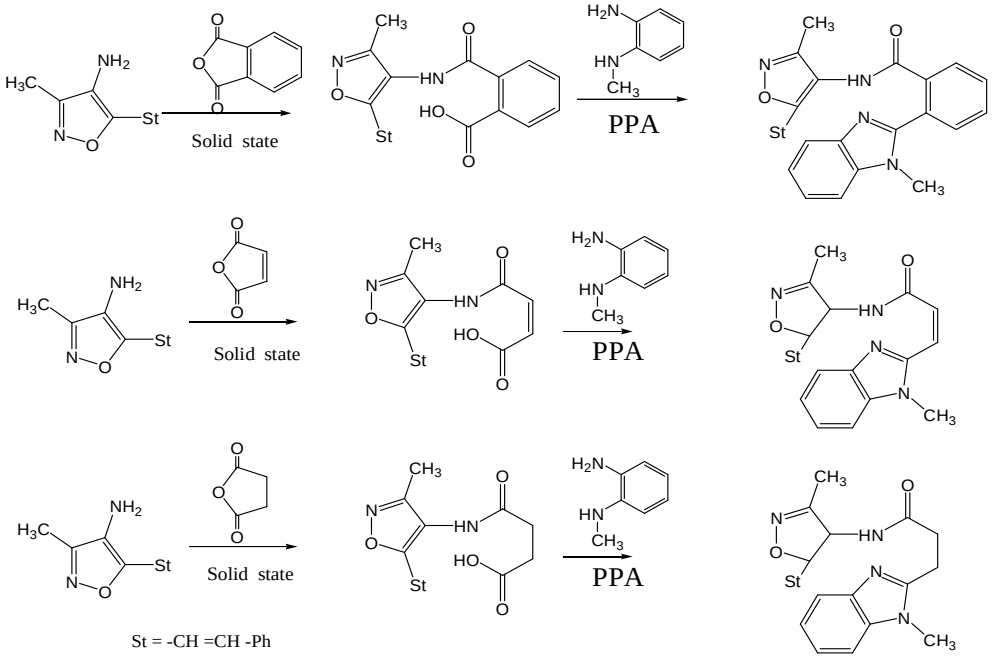
Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a spectra Perkin Elmer spectrum Bx series FT-IR spectrometer,^{1}HNMR spectra on a varies Gemini 300 MHz. Spectrometer using Tetramethyl Silane as internal standard and Mass spectra on Jeol JMC D-300 spectrometer. Elemental analysis (C, H & N) were carried out on Carlo Erbo 106 & Elmer mode l240 analysis.

General procedure for the synthesis of (E)-3-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(5-methylisoxazol-3-yl)acrylamide(6): Take a Poly Phosphoric acid(0.0153 moles) and heat 75^{0}C at this temperature slowly add the β-

(5-methyl-3-isoxazolylamide)-acrylic acid(5)(0.0051 moles) and N-methyl *o*-phenylene diamine(0.0051 moles) simultaneously , then raise the temperature up to 125^0C slowly after this stirring was continued for another 10 hours at 125^0C. after complete the reaction (monitored with TLC), Reaction mixture cool to 90^0C then ice cold water slowly added to the reaction mixture with stirring, adjust the p^H 6-6.2 using with saturated NaOH solution , stirr another 20 minutes formed solid was Filtered & washed with water.



Scheme-I



Scheme-II

2-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(5-methylisoxazol-3-yl)benzamide(4):IR (KBr): cm^{-1} 3280 (NHCO), 1708 (CO); ^{1}H NMR (300MHz $CDCl_3$) : δ2.30 (s, 3H, CH_3), 3.25 (Benzimidazole-N-CH_3), 6.60(s, 1H, isoxazole-H) 6.80-7.64(m, 8H, ArH), 9.72(bs, NH, 1H, D_2O exchangeable); MS: m/z 332[M+].

E)-3-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(5-methylisoxazol-3-yl)acrylamide(6): IR (KBr): cm^{-1} 3200 (NHCO), 1685 (CO); ^{1}H NMR (300MHz $CDCl_3$): δ 2.30 (s, 3H, CH_3) 3.20 (Benzimidazole-N-CH_3), 6.00(s, 1H, isoxazole-H) 6.60-6.80(m, 6H, ArH & CH=CH),10.12(bs, NH, 1H, D_2O exchangeable); MS: m/z 282[M+].

(3-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(5-methylisoxazol-3-yl)propanamide(8):IR (KBr): cm^{-1} 3265 (NHCO), 1678 (CO); ^1H NMR (300MHz $CDCl_3$) : δ2.32 (s, 3H, CH3), 2.92(t, 2H, CH_2-CH_2), 3.12(t, 2H, CH_2-CH_2), 3.30 (Benzimidazole-N-CH_3), 6.50(s, 1H, isoxazole-H) 7.00(m, 2H, ArH), 7.30(m, 2H, ArH), 8.02(bs, NH, 1H, D_2O exchangeable); MS: m/z 284[M+].

2-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(3-methyl-5-styrylisoxazol-4-yl)benzamide(10):IR (KBr): cm^{-1} 3380 (NHCO), 1700 (CO); ^1H NMR (300MHz $CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.29 (Benzimidazole-N-CH_3), 6.65(d, J= 12Hz, CH=CH), 6.82 (d, J=12Hz, CH=CH), 7.05-7.86(m, 13H, ArH), 9.72(bs, NH, 1H, D_2O exchangeable); MS: M/Z 434[M+].

(2E)-3-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(3-methyl-5-styrylisoxazol-4-yl)acrylamide(12): IR (KBr): cm^{-1} 3200 (NHCO), 1685 (CO); ^1H NMR (300MHz $CDCl_3$) : δ2.40 (s, 3H, CH3), 3.22 (Benzimidazole-N-CH_3), 6.65(d, J=12Hz, 1H, CH=CH), 6.80 (d, J=12Hz, 1H, CH=CH), 7.02-8.06(m, 11H, ArH, CH=CH), 9.92(bs, NH, 1H, D_2O exchangeable); MS: m/z 384[M+].

3-(1-methyl-1H-benzo[d]imidazol-2-yl)-N-(3-methyl-5-styrylisoxazol-4-yl)propanamide(14): IR (KBr): cm^{-1} 3260 (NHCO), 1675 (CO); ^1H NMR (300MHz $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 3.02(t, 2H, CH_2-CH_2), 3.35(t, 2H, CH_2-CH_2), 3.25 (Benzimidazole-N-CH_3), 6.62(d, J=12Hz, 1H, CH=CH), 6.82 (d, J=12Hz, 1H, CH=CH), 7.05-7.64(m, 9H, ArH), 7.82(bs, NH, 1H, D_2O exchangeable); MS: m/z 386[M+].

Table I : Physical and Analytical data of compounds 4,6,8,10,12 and 14

Compound	M.P (^0C)	Yild (%)	Mol.Formula (Mol.Wt.)	Found(%)(Calcd)		
				C	H	N
4	258	88	$C_{19}H_{16}N_4O_2$ (332)	68.66 (68.73)	4.85 (4.90)	16.86 (16.83)
6	240	86	$C_{15}H_{14}N_4O_2$ (282)	63.82 (63.88)	5.00 (5.02)	19.85 (19.91)
8	232	83	$C_{15}H_{16}N_4O_2$ (284)	63.37 (63.42)	5.67 (5.70)	19.71 (19.75)
10	181	82	$C_{27}H_{22}N_4O_2$ (434)	74.64 (74.65)	5.10 (5.14)	12.89 (12.92)
12	170	80	$C_{23}H_{20}N_4O_2$ (384)	71.86 (71.83)	5.24 (5.28)	14.57 (14.52)
14	150	85	$C_{23}H_{22}N_4O_2$ (386)	71.48 (71.55)	5.74 (5.79)	14.50 (14.56)

RESULTS AND DISCUSSION

The required starting materials.*viz* β-(5-methyl-3-isoxazolylamido)-benzoic acid (3), β-(5-methyl-3-isoxazolylamide)-acrylic acid(5), β-(5-methyl 3-isoxazolylamide)-propionic acid(7) and β-(3-methyl-4-isoxazolyl amido-5-styryl)-benzoic acid (9), β-(3-methyl-4-isoxazolyl amido-5-styryl)- acrylic acid (11) and β-(3-methyl-4-isoxazolyl amido-5-styryl)- propionic acid (13) have been prepared by grinding the 3-amino-5-methyl isoxazole and 4-amino-3-methyl-5-styryl isoxazole (25) with pthalic anhydride, malic anhydride and succinic anhydride separates in a mortar for 2 hours, the reaction was monitored with TLC. After complete the reaction extracted with $NaHCO_3$ solution. The clear filtrate on neutralization gave the corresponding products [26-27].

The foregoing β-(5-methyl-3-isoxazolylamido)-benzoic acid (3), β-(5-methyl-3-isoxazolylamide)-acrylic acid(5), β-(5-methyl 3-isoxazolylamide)-propionic acid(7) , β-(3-methyl-4-isoxazolyl amido-5-styryl)-benzoic acid (9), β-(3-methyl-4-isoxazolyl amido-5-styryl)- acrylic acid (11) and β-(3-methyl-4-isoxazolyl amido-5-styryl)- propionic acid (13) was separately subjected to cyclo condensation with N-methyl *o*-phenylene diamine in Polyphosphoric acid give corresponding isoxazolyl benzimidazoles. (**Scheme-I and Scheme-II**).

The structure of the title compound, *viz.* 4,6,8 &10,12 &14 were established by IR, ^{1}HNMR and Mass spectral data. IR spectra of 4,6&8&10,12&14 shows around 1685,3200 cm^{-1}(compound-6) due to amide Carbonyl & amide NH respectively. ^{1}HNMR spectra of 4,6,8&10,12,14 shows two sharp singlet around δ3.20 and10.12(compound-6) due newly formed benzimidazloe N-CH_3 protons & amide NH protons respectively . The Products were further confirmed by their mass spectra.

Acknowledgement
The authors are thankful to Head Department of Chemistry and Principal University College of Science,Satavahana University, Karimnagar for providing facilities and for her constant encouragement . The authors are also grateful to the Director, Indian Institute of Chemical Technology, Hyderabad for ^{1}H NMR and Mass spectra.

REFERENCES

[1] (a) JE Ritcher. *A.M.J Gastroenterol*., **1997**, 340. (b)Al.Muhaimeed,*H.J.J.Int.Med.Res*.**,1997**,175.
[2] D Evans,TA Hicks, WRN Williamson, W Dawson,SCR Cocok. EA Kitchen.*Eur.J.Med.Chem.*,**1996**,31,635
[3] P Asobo,H Wahe,JT Mbafor , AE Nkengfack , ZT Fomum ,EF Sopbue ,J Doppo, *J. Chem.Soc,Perkin Trans*,**2001**,457.
[4] (a) NP Shetgiri,SV Kokitar. *Indian J.Chem.*,**2001,** 40B, 163.(b) NS Habib,R Soliman, FA Ashour,El Taiebi,M.Pharmazie. **1997**,52844.(c) S Salcuja ,R Zou,JC Drach,LB Townsend . *J.Med.Chem.,* **1996**,39,881(d) LB Townsend,DS Wise. *Parasitol Today*,**1990**,60,106.
[5] D Kumar,MR Jacob,MB Reynolds, SM Kerwin.*Bioorg.Med.Chem.*,**2002**,10,3997.
[6] AR Porcari,RV Devivar,LS Kucera,JC Drach,LB Townsend,*J Med.Chem*., **1998**, 41,1252.
[7] T Roth.ML Morningstar,PL Boyer,SH Hughes,RW Bnckheitir,CJ Michejda ,*J Med.Chem*.40,**1997**,4199.
[8] MT Migawa ,JL Girard ,JA Walker,G Koszalka,SD Chamberlain,JC Drach, LB Townsend, *J Med Chem.*,41 **1998** 1242.
[9] I Tamm,PB Sehgal , *Adv.Virus Res*.,22,**1978**,87
[10] I Tomm , Science,126,**1957**,1253.
[11] T Hisano,M Ichikawa.Tsumotok,M Tasaki, *Chem..Pharm.Bull.*,30 ,**1982,** 2996.
[12] C Stevenson ,R Davies,H Jeremy.*Chem..Res.Taxical.*,**1999,** 10(3)411.
[13] Eugster, *Prog.Chem.org.nat.prod.*,**1969**,27,261.
[14] H Kano,I Adachi,R Kido , K Hirase, *J.Med.Chem.,* **1967,** 10(3),411.
[15] PB Reddy,SM Reddy,E Rajanarendar,.AK Murthy . *Indian Phyto Pathology*. **1984**,37,370.
[16] Gesal.*J.Antibiot.*,**1975**,28(1),91.
[17] A Sadanandam,MV Rajam , K Subhash, E Rajanarendar. *J.Indian Bot,Report*. **1984**,37,370.
[18] M John,S Ludwing,RN Nicholas,DW Roger,EM Bruce,FF Stephen. *J.Med.Chem.*,**1988**, 31,473.
[19] C Boschail ,A Cana,R Disftilo,A Frutlero,Garco. *Bioorg.Med.Chem.Lett.*, **2000**,7,1727.
[20] Moloney Gerard P,Martin Graemer Mathew.*J.Chem.Soc.Perkin Trans* **1999**,19,2725.
[21] RD Clark,JH Carron, AFKloge,DB Repke ,AP Roszhowski,AM Strosberg,SB Earker, SM Bitter, MD OKando. *J.Med.Chem.***,1983**,26(15),657.
[22] E Rajanarender,K Ramu,D Karunakar ,P Ramesh ,*J Heterocyclic Chemistry*.,**2005**,42,711.
[23] E Rajanarender ,M Srinivas,D Karunkar,K Ramu ,*J Heterocyclic Chemstry***,2005**,5,411.
[24] E Rajanarender ,P Ramesh ,M Srinivas,K Ramu ,G Mohan.Syn. Common.,**2006**,36, 665.
[25] (a) GT Morgan,HB Burgers. *J.Chem Soc*.**1921**,699.(b) AK Murthy, KSRKM Rao, NVS Rao *J.Indian Chem. Soc*. **1976**,53,1047.
[26] E Rajanarender,K Ramu ,A Shivarami Reddy ,Firoz Pasha Shaik,*Indian J.Chem.,* **2008** ,47B,1284.
[27] E Rajanarendar ,Md Afzal .*Indian J.Chem*. **2003**,42B,674.