Octa Journal of Environmental Research ***Jan.-March, 2014***
International Peer-Reviewed Journal ISSN 2321 3655
Oct. Jour. Env. Res. Vol. 2(1): 48-53
Available online http://www.sciencebeingjournal.com

Research Article

Octa Journal of Environmental Research
(Oct. Jour. Env. Res.) ISSN: 2321-3655
Journal Homepage: http://www.sciencebeingjournal.com

STUDIES OF NOVEL THIAZOLE-IMIDAZOLE COMBINED MOLECULE

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Received: 22th Jan., 2014 Revised: 23rd Feb., 2014 Accepted: 25th March 2014

Abstract: The condensation reaction of 4-benzylidene-2-p-tolyloxazol-5(4H)-one(2) with 2-amino substituted benzothiazole3(I-VI) was yielded a series of 4-benzylidene-1-(substitued-2-benzo thiazolyl)-2-(4-methoxyphenyl)-1H-imidazol-5(4H)-one 4(I-VI).The 4-benzylidene-2-p-tolyloxazol-5(4H)-one(2) has been prepared from cyclo condensation reaction between hippuric acid (1) with p-methyl benzaldehyde. The novel prepared compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. All the prepared compounds were screened for their antibacterial activities and antifungal activities.

Keywords: 2-amino benzthiazole; Antibacterial activities; Antifungal activities; Imidazole.

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INTRODUCTION

In recent years, antimicrobials are one of a very significant class of drug. Because these classes of drugs are prescribed exact from an uncomplicated disease to the serious diseases like cancer. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Majority of the drugs being introduced in pharmacopeias every year are heterocyclic compounds. Sulphar and nitrogen containing heterocyclic compounds represent an important class of drugs in the therapeutic chemistry and also contributed to the society from biological and industrial point which helps to understand life processes (Patel and Shaikh, 2010; Shah, 2012) The synthesis of novel imidazolo quinoline analogs and investigation of their chemical and pharmacological behavior have gained more importance in recent decades for medicinal reasons (Raghavendra *et al.,* 2011). Imidazole derivatives including saturated imidazoles are important heterocycles due to their antibacterial, antitubercular, antifungal, antiHIV, antiinflammatory, analgesic,anticancer and anticonvulsant activities (Shalini *et al*., 2010; Husain *et al*., 2009; Robert *et al*.,2010; Neves *et al*.,2010; Sharma and Khan,2001; Khan and Chawla,2002; Khan and Gupta,2003). They have also been utilized as a versatile template for the synthesis of compounds with potential enzyme inhibition activities (Patel *et al*., 2004). Benzothiazole is one of the most important heterocycle that has received overwhelming response owing to its diversified molecular design and remarkable optical, liquid and electronic properties (Ha *et al*., 2009). Benzothiazole shows various biological activities such as antimicrobial (Gupta *et al*., 2009; Kumbhare and Ingle, 2009; Murthi anf Pathak, 2008; Rajeeva *et al*., 2009; Maharan *et al*., 2007), anticancer (Stanton *et al*., 2008), anthelmintic (Sreenivasa *et al*.,2009), anti-diabetic (Pattan *et al*., 2005) activities. Hence, it was thought of interest to merge both of thiazole and imidazole moieties which may enhance the drug activity of compounds to some extent or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of Imidazole- benzothiazole containing moiety. Hence the current communication contains the study on novel 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-tolyl)-1H-imidazol-5(4H)-one 4(I-VI) (Figure 1).

EXPERIMENTAL

All the chemicals used were of analytical grade. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples was taken on LC-MSD-Trap-SL_01046. Melting points were determined in open capillary tubes and were uncorrected.

Synthesis of 4-benzylidene-2-p-tolyloxazol-5(4H)-one (2): The mixture of hippuric acid(1) (0.1mole), p-methyl benzaldehyde (0.1mole), anhydrous sodium acetate (0.1mole) and acetic anhydride (0.2mole) warm on water bath with occasional stirring until solution is complete. Boil the resulting solution for 2 hrs, cool to 0-5^{o}C. Stir the yellowish brown solid product with water. The solid separated was collected by filtration, washed with ether, dried and recrystallized from ethyl acetate The yield of the product was 76 % and the product melts at 172-173^{o}C. For $C_{17}H_{13}NO_2$(263) Calcd.: %C,77.55;%H,4.98;%N,5.32,Found: % C, 77.5; %H, 4.9;%N, 5.3.IR (KBr); (cm^{-1}): 3080 (Aromatic C-H stretch), 2848(CH_3),760(Aromatic C-H bending),1620-1580(Aromatic C-C stretch), 1790 (C=O lacton), 1650(C=N),1260(C-N). ^{1}H NMR: 8.08–7.12(9H,m) (Ar-H), 7.98 (1H,s) (C=CH), 2.35(3H,s) (CH_3). ^{13}C NMR: 166.4 (CO lacton), 163.3-114.6 (Ar-12C), 161.3 (C=N), 131.9, 112.7 (C=C), 21.7(CH_3).

Synthesis of 2-amino-4-substitued benzothiazoles 3(I-VI): The solution of substituted aniline (0.2 mole) and potassium thiocyanate (0.8 mole) in glacial acetic acid was added drop wise to 20% bromine glacial acetic acid (0.2 mole) with stirring, while the temperature was kept below 35^{o}C. After all the bromine solution had been added. The mixture was stirred for 9-11 hrs, then filtered and the residue washed with water. The combined filtrate and washings were neutralized with ammonium hydroxide. The precipitate was collected on a filter and dried. The yields, melting points and other characterization data of these compounds are given in Table 1.

Synthesis of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-tolyl)-1H-imidazol-5(4H)-one 4(I-VI): A mixture 4-benzylidene-2-p-tolyloxazol-5(4H)-one (2)(0.01mole) and 2-amino-4-substituted benzothiazoles 3(I-VI) (0.01mole) was refluxed in presence of pyridine for 6-8 hours. Excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralized with acid, filtered and crystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-2.

BIOLOGICAL SCREENING

Antibacterial activity: The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 3(III), 3(V), 4(III) and 4(V) were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Table -3 and represented in figure 1.

Antifungal activity: The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum*, *Fusarium oxyporium*. The antifungal activity of all the compounds (3(I-VI)) and (4(I-VI)) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1cc. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds 3(I-VI) and 4(I-VI) are shown in Tables-4 and represented in figure 2.

RESULTS AND DISCUSSION

In present communication the condensation reaction between hippuric acid (1) with p-methyl benzaldehyde gives 4-benzylidene-2-p-tolyloxazol-5(4H)-one (2). The structures of (2) were confirmed by elemental analysis and IR spectra showing an absorption band at 3080(Aromatic C-H stretch), 2848(CH_3),760(Aromatic C-H bending),1620-1580(Aromatic C-C stretch), 1790(C=O lacton), 1650 (C=N),1260(C-N); ^{1}H NMR: 8.08–7.12(9H,m) (Ar-H), 7.98 (1H,s) (C=CH), 2.35(3H,s) (CH_3). ^{13}C NMR: 166.4 (CO lacton), 163.3-114.6 (Ar-12C), 161.3 (C=N), 131.9,112.7 (C=C),21.7(CH_3). For $C_{17}H_{13}NO_2$(263) Calcd.: %C,77.55;% H,4.98; %N,5.32,Found: % C, 77.5; %H, 4.9;%N, 5.3. The structures assigned to 2-amino substituted benzothiazole 3(I-VI) were supported by the elemental analysis and IR spectra showing absorption bands at 3475cm^{-1}(NH_2), 3030-3080cm^{-1}(Aromatic C-H stretch),1542cm^{-1}(Aromatic C=C),1560 cm^{-1}(C=N),615cm^{-1}(C-S),1120cm^{-1}(OCH_3),1452cm^{-1}(NO_2), 686 cm^{-1}(Aromatic C-Cl),1076cm^{-1}(Aromatic C-Br);^{1}H NMR:7.06 (2H,s) (-NH_2), 3I:8.20-7.65(4H,m)(Ar-H), 3II: 8.02-7.40(3H,m)(Ar-H),2.46(3H,s) (-CH_3),3III:8.22-7.60(3H, m) (Ar-H), 3IV: 8.80-7.70(3H,m) (Ar-H),3V:7.60 -7.10(3H,m) (Ar-H),3VI:8.70-8.20(3H,m)(Ar-H);^{13}CNMR: 166.8 (C=N),3I:153.6,131.4, 125.6,124.8, 122, 118.8 (Ar-C),3II:150.4,134.3,131.2,126.8, 121.5 (Ar-C),21.2(CH_3),3III:151.6,132.8,130.2, 126, 121.4,118.5 (Ar-C), 3IV: 152.4, 133.2,129,124.3,119.2,117.4(Ar-C), 3V: 157.2, 145.8, 132.4, 118.6, 114.8,105.6(Ar-C), 3VI: 159.6, 144.8, 131.5, 121.6,119.5,117.8 (Ar-C). The C, H, N, S analysis data of all compounds are presented in Table-1.

IR spectra of 3(I-VI) are almost resemble those of the corresponding 4(I-VI) only discernable variation observed that the bend at 3475cm^{-1}(NH_2) is absent and the new bands at 3080(Aromatic C-H stretch), 2848(CH_3),760(Aromatic C-H bending),1620-1580(Aromatic C-C stretch), 1790(C=O lacton), 1650 (C=N),1260(C-N) are observed in all the spectra of 4(I-VI), which might be responsible for formation of imidazole ring systems.^{1}H NMR: 7.63-7.09 (9H,s)(Ar-H),7.45(1H,s)(CH=C),2.35-2(3H,s) (CH_3).4I: 8.25-7.59 (4H,m) (Ar-H),4II:7.932-7.35(3H,m)(Ar-H),2.42(3H,s)(-CH_3),4III:7.57-7.03(3H,m)(Ar-H),1.32(CH_3), 4IV:8.67-8.06(3H,m)(Ar-H),4V:8.18-7.57(3H,m)(Ar-H),4VI:8.76-7.69(3H,m)(Ar-H);^{13}CNMR:139.7,135.4,130.2,129.3 , 129.3,128.9,128.9,128.9,128.8,128.7,128.5,128.3(Ar-C),130.6,114.7(C=C),170.4(C=Oimidazole ring),158.1 (C=N),160.3(C=Nbenzothiazole ring),21.7 (CH_3), 4I:139.7,135.5, 125.4,124.8,122.2,118.6(Ar-C),4II: 147.3, 131.4,126.8,126.2,124.7, 119.2 (Ar-C), 16.5 (CH_3),4III: 150.3,142.6,132.3, 122.1,114.4,105.5 (Ar-C), 56.1 (OCH_3),4IV:145.2,142.2,128.3,125.9,125.5,122.7(Ar-C),4V:149.4,132.6,126.1,122.2,121.8,120.3(Ar-C),4VI: 151.7,128.8,128.5,126.8,121.2,116.7(Ar-C).The C,H,N,S analysis data of all compounds are presented in Table 2.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in Tables 1 and 2.

Table 1. Analytical Data and Elemental Analysis of Compounds 3(I-VI)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	M.P.* ^{0}C	Yield	Elemental Analysis							
					%C		%H		%N		%S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3I	$C_7H_6N_2S$ (150)	169	159-161	72	55.97	55.9	4.03	4.0	18.65	18.6	21.35	21.3
3II	$C_8H_8N_2S$ (164)	178	162-164	67	58.51	58.4	4.91	4.8	17.06	17.0	19.52	19.5
3III	$C_8H_8N_2OS$ (180)	196	153-156	64	53.31	53.2	4.47	4.4	15.54	15.5	17.79	17.7
3IV	$C_7H_5N_3O_2S$ (195)	212	156-158	68	43.07	43.0	2.58	2.5	21.53	21.5	16.43	16.4

3V	$C_7H_5N_2OSCl$ (183)	199	153-155	70	45.53	45.5	2.73	2.7	15.17	15.1	17.37	17.3
3VI	$C_7H_5N_2OSBr$ (229)	238	161-163	67	36.70	36.6	2.20	2.1	12.23	12.2	14.00	13.9

*Uncorrected

Table 2. Analytical Data and Elemental Analysis of Compounds 4(I-VI)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	M.P.* ^0C	Yield	Elemental Analysis							
					%C		%H		%N		%S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4I	$C_{24}H_{17}N_3O_2S$ (411)	426	192-194	70	70.05	70.0	4.16	4.1	10.21	10.1	7.79	7.7
4II	$C_{25}H_{19}N_3O_2S$ (425)	438	194-196	64	70.57	70.5	4.50	4.4	9.88	9.8	7.54	7.5
4III	$C_{25}H_{19}N_3O_3S$ (441)	460	203-205	65	68.01	68.0	4.34	4.3	9.52	9.5	7.26	7.2
4IV	$C_{24}H_{16}N_4O_4S$ (456)	477	198-199	58	63.15	63.1	3.53	3.53	12.27	12.2	7.02	7.0
4V	$C_{24}H_{16}N_3O_2SCl$ (445)	462	194-195	56	64.64	64.6	3.62	3.6	9.42	9.4	7.19	7.1
4VI	$C_{24}H_{16}N_3O_2SBr$ (489)	497	207-209	59	58.78	58.7	3.29	3.2	8.57	8.5	6.54	6.5

*Uncorrected

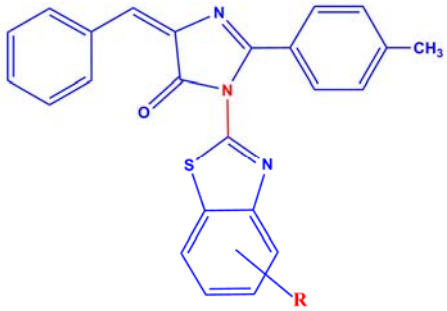
Table 3. Antibacterial Activity of Compounds

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3I	52	51	59	61
3II	51	57	54	64
3III	62	68	71	73
3IV	50	57	69	65
3V	55	65	70	78
3VI	53	59	67	70
4I	52	56	67	67
4II	55	57	58	61
4III	76	77	81	80
4IV	68	73	77	75
4V	54	74	69	73
4VI	64	67	62	61
Tetracycline	55	79	74	84

Table 4. Antifungal Activity of Compounds

Zone of Inhibition at 1000 ppm (%)					
Compounds	*Nigrospora Sp.*	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Rhizopus Nigricum*	*Fusarium oxyporium*
3I	65	62	62	56	68
3II	57	51	59	64	61
3III	72	69	71	72	75
3IV	65	65	62	61	60
3V	67	65	63	76	72
3VI	61	59	61	65	70
4I	65	63	64	61	60
4II	64	61	56	62	55
4III	75	69	74	65	66
4IV	60	65	66	62	61

4V	66	68	68	65	67
4VI	61	65	62	58	62



4(I-VI)
4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(4-*p*-tolyl)-1*H*-imidazol-5(4*H*)-one

Where R= (I) -H **(II) 4-Me** **(III) 4-OMe**

(IV) 4-NO_2 **(V) 4-Cl** **(VI) 4-Br**

Figure 1. Structure of 4-benzylidene-1-(substitued-2-benzothiazolyl) -2-(p-tolyl)-1H-imidazol-5(4H)-one

CONCLUSION

In conclusion, novel 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-tolyl)-1H-imidazol-5(4H)-ones has been synthesized by an extremely efficient process. All the novel synthesized compounds show moderate to excellent antibacterial and antifungal activities.

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CONFLICT OF INTEREST : Nothing