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Preparation, Characterization and Biological Screening of Novel Imidazoles

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Abstract

The 4-benzylidene-2-(4-methoxyphenyl)oxazol-5(4H)-one (**B**) has been prepared from cyclo condensation reaction between hippuric acid (**A**) with p-anisaldehyde. A series of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(4-methoxyphenyl)-1H-imidazol-5(4H)-one (**D1-6**) have been synthesized from 2-amino substituted benzothiazole (**C1-6**) by condensation reaction with 4-benzylidene-2-(4-methoxyphenyl) oxazol-5(4H)-one (**B**). The synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. All the compounds were screened for their antibacterial and antifungal activities.

Keywords: Imidazole; Benzothiazole and Antibacterial and Antifungal activities.

1. Introduction

In medicinal chemistry the study of heterocyclic compounds has been an interesting field because of their various biological properties. A number of heterocyclic derivatives containing nitrogen and sulphur atom provide as a exclusive and multipurpose gallows for experimental drug design [1]. 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 [2]. Benzothiazole shows various biological activities such as antimicrobial [3-5], anticancer[6,7], anthelmintic[8], anti-diabetic activities[9]. The consequential compounds, Imidazole also reveal a number of significant biological activities such as antiparasitic,fungicidal,anithelemintic,anti-inflammatory, antiprotozoal and herbicidal activity[10-14]. 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 present communication comprises the synthesis 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(4-methoxyphenyl)-1H-imidazol-5(4H)-one (**D1-6**). The synthetic approach is shown in scheme-1.

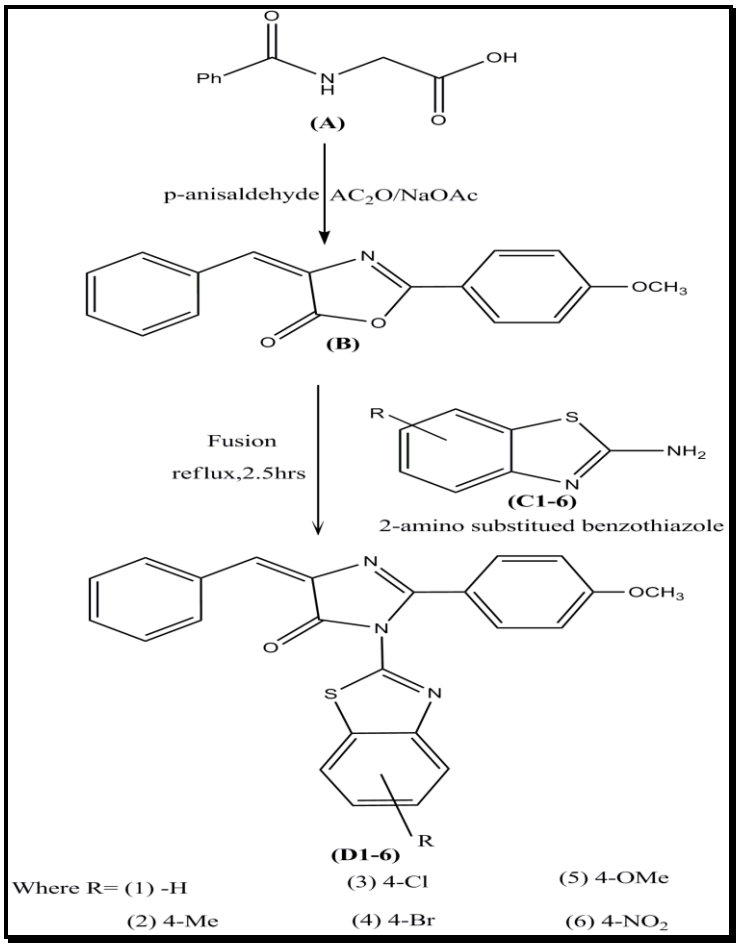
2. Experimental

Melting points were determined in open capillary tubes and were uncorrected. 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 taken on LC-MSD-Trap-SL_01046.

2.1 Preparation of 4-benzylidene-2-(4-methoxyphenyl)oxazol-5(4H)-one(B):

The mixture of hippuric acid **(A)** (0.25mole), p-anisaldehyde (0.25mole), anhydrous sodium acetate (0.25mole) and acetic anhydride (0.50mole) 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 176-77^{o}C. For $C_{17}H_{13}NO_3$ (279)Found: % C,73.1; %H, 4.6;%N, 5.0,Calcd.: %C,73.11;%H, 4.69;% N,5.02.IR(KBr);(cm^{-1}):3080(Aromatic C-H stretch),2850(OCH_3),760(AromaticC-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), 3.86(3H,s)(OCH_3).^{13}CNMR:166.4(CO lacton), 163.3-114.6 (Ar-12C),161.3(C=N),131.9,112.7 (C=C),56.4 (OCH_3).



Scheme-1: Synthetic Approach

2.2 Preparation of 4-benzylidene-2-(4-methoxyphenyl)oxazol-5(4H)-one(B):

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2.3 Preparation of 2-amino-4-substitued benzothiazoles(C1-6):

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.

Table 1. Analytical Data and Elemental Analysis of Compounds (C1-6)

Compd.	Molecular Formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis			
					%C	%H	%N	%S
					Found (Calcd.)	Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
C1	$C_7H_6N_2S$ (150)	153	72	159-161	55.9 (55.97)	4.0 (4.03)	18.6 (18.65)	**21.3 (21.35)**
C2	$C_8H_8N_2S$ (164)	168	67	162-164	58.4 (58.51)	4.8 (4.91)	17.0 (17.06)	**19.5 (19.52)**
C3	$C_7H_5N_2OSCl$ (183)	189	70	153-155	45.5 (45.53)	2.7 (2.73)	15.1 (15.17)	**17.3 (17.37)**
C4	$C_7H_5N_2OSBr$ (229)	226	67	161-163	36.6 (36.70)	2.1 (2.20)	12.2 (12.23)	**13.9 (14.00)**
C5	$C_8H_8N_2OS$ (180)	183	64	153-156	53.2 (53.31)	4.4 (4.47)	15.5 (15.54)	**17.7 (17.79)**
C6	**$C_7H_5N_3O_2S$ (195)**	**197**	**68**	**156-158**	**43.0 (43.07)**	**2.5 (2.58)**	**21.5 (21.53)**	**16.4 (16.43)**

2.4 Preparation of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(4-methoxyphenyl)-1H- imidazol-5(4H)-one (D1-6):

A mixture 2-amino-4-substituted benzothiazoles **(C1-6)** (0.01mole) and 4-benzylidene-2-(4-methoxy phenyl) oxazol-5(4H)-one (B) (0.01mole) was refluxed in presence of pyridine for 7-8 hours. Excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralized with dil HCl, filtered and crude product was purified by recrystallization from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-2.

Table 2. Analytical Data and Elemental Analysis of Compounds (D1-6)

Compd.	Molecular Formula (Mol.wt.)	LC- MS Data	Yield	M.P. ^{0}C	Elemental Analysis			
					%C	% H	%N	%S
					Found (Calcd.)	Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
D1	$C_{24}H_{17}N_3O_2S$ (411)	415	70	192-194	70.0 (70.05)	4.1 (4.16)	10.1 (10.21)	**7.7 (7.79)**
D2	$C_{25}H_{19}N_3O_2S$ (425)	428	64	194-196	70.5 (70.57)	4.4 (4.50)	9.8 (9.88)	**7.5 (7.54)**
D3	$C_{24}H_{16}N_3O_2SCl$ (445)	442	56	194-195	64.6 (64.64)	3.6 (3.62)	9.4 (9.42)	**7.1 (7.19)**
D4	$C_{24}H_{16}N_3O_2SBr$ (489)	492	59	207-209	58.7 (58.78)	3.2 (3.29)	8.5 (8.57)	**6.5 (6.54)**
D5	$C_{25}H_{19}N_3O_3S$ (441)	450	65	203-205	68.0 (68.01)	4.3 (4.34)	9.5 (9.52)	**7.2 (7.26)**
D6	**$C_{24}H_{16}N_4O_4S$ (456)**	**457**	**58**	**198-199**	**63.1 (63.15)**	**3.53 (3.53)**	**12.2 (12.27)**	**7.0 (7.02)**

3. Biological Screening

3.1 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 **C5, C3, D5** and **D3** were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Table -3 and represented in Figure 1.

Table 3. Antibacterial Activities of Compounds

Compd.	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Klebsiella promioe***
C1	55	54	62	**64**
C2	54	60	57	**67**
C3	58	68	73	**81**
C4	56	62	70	**73**
C5	65	71	74	**76**
C6	53	60	72	**68**
D1	55	59	70	**70**
D2	58	60	61	**64**
D3	57	77	72	**76**
D4	67	70	65	**64**
D5	79	80	84	**83**
D6	72	76	80	**78**
Tetracycline	**55**	**79**	**74**	**84**

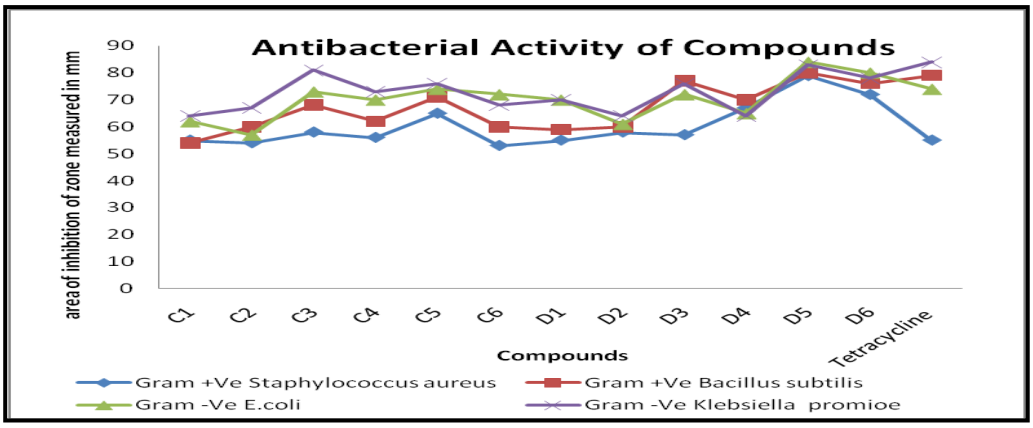

Figure 1: Antibacterial Activity of Compounds

3.2 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 **(C1-6)** and **(D1-6)** 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:

Percentage of inhibition = 100(1-Y/ X)

Where, X = Area of colony in control plate; Y = Area of colony in test plate

The fungicidal activity displayed by various compounds **(C1-6)** and **(D1-6)** are shown in Tables-4 and represented in figure 2.

Table 4: Antifungal Activity of Compounds

Compd.	Zone of Inhibition at 1000 ppm (%)				
	Nigrospora Sp.	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
C1	**68**	**65**	**65**	**59**	**70**
C2	**60**	**54**	**62**	**67**	**64**
C3	**70**	**68**	**66**	**79**	**75**
C4	**64**	**62**	**64**	**68**	**73**
C5	**75**	**72**	**74**	**75**	**78**
C6	**68**	**68**	**64**	**64**	**63**
D1	**68**	**66**	**67**	**64**	**63**
D2	**67**	**64**	**59**	**65**	**58**
D3	**69**	**71**	**72**	**68**	**70**
D4	**64**	**68**	**65**	**60**	**65**
D5	**78**	**72**	**77**	**68**	**69**
D6	**63**	**68**	**69**	**65**	**64**

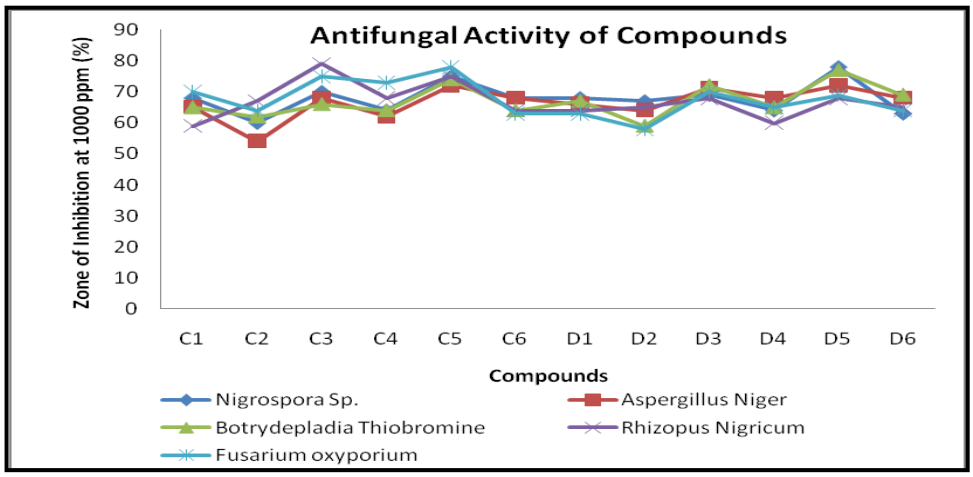

Figure 2: Antifungal Activity of Compounds

4. Results and Discussion

In present communication the condensation reaction between hippuric acid **(A)** with p-anisaldehyde gives 4-benzylidene-2-(4-methoxyphenyl)oxazol-5(4H)-one**(B)**.The structures of **(B)** were confirmed by elemental analysis and IR spectra showing an absorption band at 3080(Aromatic C-H stretch), 2850(OCH_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), 3.86(3H,s) (OCH_3). ^{13}C NMR: 166.4 (CO lacton), 163.3-114.6 (Ar-12C), 161.3 (C=N), 131.9, 112.7 (C=C),56.4(OCH_3). For $C_{17}H_{13}NO_3$ (279)Found: % C, 73.1; %H, 4.6;%N, 5.0,Calcd.: %C,73.11;%H,4.69;%N,5.02.

The structures assigned to 2-amino substituted benzothiazole **(C1-6)** 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),1560cm^{-1}(C=N),615cm^{-1}(C-S),1120cm^{-1}(OCH_3),1452cm^{-1}(NO_2),686cm^{-1}(AromaticC-Cl),1076cm^{-1}(Aromatic C-Br); ^{1}H NMR:7.06 (2H,s) (-NH_2), 3a:8.20-7.65(4H,m)(Ar-H),3b:8.02-7.40(3H,m)(Ar-H),2.46(3H,s)(-CH_3), 3c: 7.60 -7.10 (3H, m) (Ar-H),3d:8.70-8.20(3H,m)(Ar-H),3e:8.22-7.60(3H,m)(Ar-H),3f:8.80-7.70(3H,m) (Ar-H);^{13}C N-MR:166.8(C=N), 3a:153.6, 131.4,125.6, 124.8,122, 118.8 (Ar-C),3b:150.4,134.3, 131.2, 126.8, 121.5 (Ar-C), 21.2(CH_3), 3c:157.2, 145.8, 132.4, 118.6, 114.8, 105.6 (Ar-C),3d: 159.6, 144.8, 131.5, 121.6,119.5,117.8 (Ar-C), 3e:151.6, 132.8, 130.2, 126,121.4,118.5 (Ar-C), 3f: 152.4, 133.2,129,124.3,119.2,117.4(Ar-C). The C, H, N, S analysis data of all compounds are presented in Table-1.

IR spectra of **(C1-6)** are almost resemble those of the corresponding **(D1-6)** only discernable variation observed that the bend at 3475cm^{-1}(NH_2) is absent and the new bands at 3080(Aromatic C-H stretch), 2850(OCH_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 **(D1-6)**, 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),D1:8.25-7.59(4H,m)(Ar-H),D2:7.932-7.35(3H, m) (Ar-H),2.42(3H,s)(-CH_3),D3:8.18-7.57(3H,m)(Ar-H),D4:8.76-7.69(3H,m)(Ar-H)D5:7.57-7.03(3H,m)(Ar-H), 3.93 (O-CH_3), D6:8.67-8.06(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=O imidazole ring),158.1 (C=N), 160.3(C=N benzothiazole ring), 56.3(OCH_3), D1:139.7, 135.5,125.4,124.8,122.2,118.6(Ar-C), D2: 147.3, 131.4, 126.8,126.2,124.7, 119.2 (Ar-C), 16.5 (CH_3), D3:149.4,132.6,126.1,122.2,121.8,120.3(Ar-C), D4: 151.7, 128.8, 128.5, 126.8, 121.2, 116.7(Ar-C),D5: 150.3,142.6,132.3,122.1,114.4,105.5 (Ar-C), 56.1 (OCH_3),D6: 145.2, 142.2, 128.3, 125.9, 125.5, 122.7(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 are confirmed by LC-MS. LC-MS data of all compounds are presented in Table-1 and Table-2.

5. Conclusion

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

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