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SYNTHESIS OF NOVEL FUSED HETEROCYCLIC COMPOUNDS 4-BENZYLIDENE-1-(SUBSTITUED-2-BENZOTHIAZOLYL)-2-(P-NITRO)-1H-IMIDAZOL-5(4H)-ONE

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ABSTRACT
A novel heterocyclic compounds series of (E)-1-(subsituted benzo[d]thiazol-2-yl)-4-benzylidene-2-(4-nitrophenyl)-1H-imidazol-5(4H)-one **(9-14)** was synthesized by condensation reaction of 4-benzylidene-2-p-nitrooxazol-5(4H)-one **(2)** with various substituted benzothiazole **(3-8)**.The reaction between hippuric acid **(1)** with p-nitro benzaldehyde yielded previous compound 4-benzylidene-2-p-nitrooxazol-5(4H)-one **(2)**. The novel prepared compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral data. All the prepared compounds were screened for their antibacterial activities and antifungal activities.

KEYWORDS: Various substituted Benzothiazole, Imidazole, spectral studies, Antibacterial activities and Antifungal activities.

INTRODUCTION
Benzothiazole is a heterocyclic compound having which contains Sulphar and nitrogen varied biological activities like, antimicrobial[I,II], anthelmintic[III], anti-inflammatory activity[IV], anti-diabetic activity[V] and anticancer[VI], etc.

The another most important heterocyclic compounds says, Imidazole also exhibit various antibacterial, antitubercular, antifungal, anti HIV, anti inflammatory, analgesic, anticancer and anticonvulsant activities[VII-XIV].

Nowadays, the researches in fused heterocyclic compounds are done due to their good biological as well as their Therapeutic activities. Hence, in continuous of our previous work[XIII] present article contains the study on novel 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-nitro)-1H-imidazol-5(4H)-one **(9-14)**. (Figure-1).

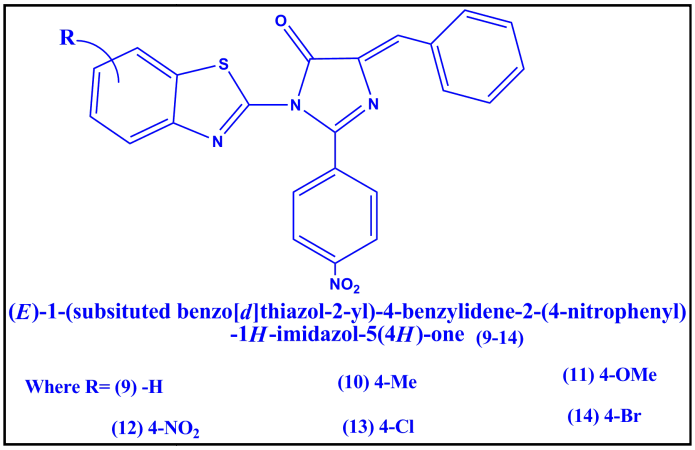
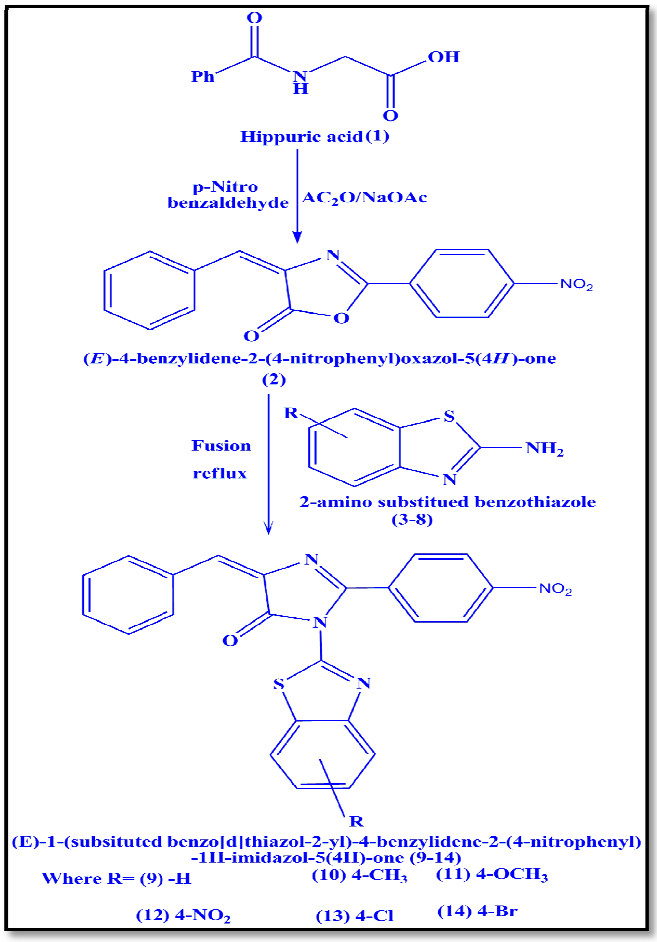


Figure 1. Structure of 4-benzylidene-1-(substitued-2-benzothiazolyl) -2-(p-nitro)-1H-imidazol-5(4H)-one

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. Melting points were determined in open capillary tubes and were uncorrected.

Reaction Scheme



Synthesis of 4-benzylidene-2-p-nitrooxazol-5(4H)-one (2):

The mixture of hippuric acid(1) (0.1mole), p-nitro 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 1.5 hrs, cool to 0-5^{o}C. Stir the yellow 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 72 % and the product melts at 148-149^{o}C.For $C_{16}H_{12}N_2O_4$(294) Calcd.: %C,65.31;H,3.43; N, 9.52,Found: % C, 65.29; H, 3.41; N, 9.51. IR(KBr,cm^{-1}):3075-3020(Aromatic C-H stretch), 2880 (C-H),790-745 (Aromatic C-H bending),1640-1590(Aromatic C-C stretch),1780(C=O lacton),1650(C=N),1585, 1370(NO_2,)1260(C-N).^{1}HNMR:8.48–7.23(9H,m,Ar-H),8.01 (1H,s, C=CH). ^{13}CNMR:166.6(CO), 151.3-124.9 (Ar-12C), 161.2 (C=N), 132, 112.5 (C=C).

Synthesis of various substituted benzothiazoles(3-8):

The solution of substituted aniline (0.2 mole) and KSCN (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 -I.

Table I. Elemental Analysis of Compounds (3-8)

Compd.	Molecular formula	M.P* °C	Yield	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3	$C_7H_6N_2S$	159-161	72	55.9	55.97	4.0	4.03	18.6	18.65	21.3	21.35
4	$C_8H_8N_2S$	162-164	67	58.4	58.51	4.8	4.91	17.0	17.06	19.5	19.52
5	$C_8H_8N_2OS$	153-156	64	53.2	53.31	4.4	4.47	15.5	15.54	17.7	17.79
6	$C_7H_5N_3O_2S$	156-158	68	43.0	43.07	2.5	2.58	21.5	21.53	16.4	16.43
7	$C_7H_5N_2OSCl$	153-155	70	45.5	45.53	2.7	2.73	15.1	15.17	17.3	17.37
8	$C_7H_5N_2OSBr$	161-163	67	36.6	36.70	2.1	2.20	12.2	12.23	13.9	14.00

*****Uncorrected

Synthesis of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-nitro)-1H-imidazol-5(4H)-one (9-14):

A mixture 4-benzylidene-2-p-nitrooxazol-5(4H)-one**(2)**(0.01mole) and various substituted benzothiazoles **(3-8)** (0.01mole) was refluxed in presence of pyridine for 5-7 hours. Excess of pyridine was distilled off and resulting mass was poured on to crushed ice and neutralized with HCl, filtered and crystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-II.

Table II. Elemental Analysis of Compounds (9-14)

Compd.	Molecular formula	M.P *. ^{0}C	Yield	Elemental Analysis							
				%C		%H		%N		%S	
				Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
9	$C_{23}H_{14}N_4O_3S$	178-179	69	64.76	64.78	3.30	3.31	13.13	13.14	7.51	7.52
10	$C_{24}H_{16}N_4O_3S$	165-166	62	65.43	65.44	3.64	3.66	12.70	12.72	7.27	7.28
11	$C_{24}H_{16}N_4O_4S$	183-184	66	63.14	63.15	3.51	3.53	12.25	12.27	7.01	7.02
12	$C_{23}H_{13}N_5O_5S$	176-177	64	58.58	58.60	2.76	2.78	14.84	14.86	6.79	6.80
13	$C_{23}H_{13}N_4OSCl$	172-173	63	59.93	59.94	2.83	2.84	12.15	12.16	6.95	6.96
14	$C_{23}H_{13}N_4OSBr$	179-180	62	54.65	54.67	2.57	2.59	11.07	11.09	6.34	6.35

*Uncorrected

BIOLOGICAL SCREENING

ANTIBACTERIAL ACTIVITY:

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and gram-negative bacteria (*E.coli and Salmonella typhi*) 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 and compare with standard. Compounds 5,7,11 and 13 were found more toxic for microbes. (Table –III).

Table III. Antibacterial Activity of Compounds

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	***Bacillus subtilis***	***E.coli***	***Salmonella typhi***
3	08	09	07	09
4	11	12	10	10
5	**13**	**14**	**15**	**13**
6	11	12	14	12
7	**15**	**16**	**14**	**13**
8	12	11	12	11
9	14	15	11	14
10	12	16	12	13
11	**18**	**19**	**18**	**16**
12	14	13	13	12
13	**16**	**18**	**15**	**14**
14	14	16	16	13
Tetracycline	19	21	20	18

ANTIFUNGAL ACTIVITY:

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Aspergillus niger, Botrydepladia thiobromine and Nigrospora Sp.*. The antifungal activity of all the compounds **(3-8)** and **(9-14)** 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 = (1-Y/X)100

Where,X = Area of colony in control plate,Y = Area of colony in test plate.The fungicidal activity displayed by various compounds **(3-8)** and **(9-14)** are shown in Tables-IV.

Table IV. Antifungal Activity of Compounds

Compounds	*Aspergillus Niger*	*Botrydepladia Thiobromine*	*Nigrospora Sp.*
3	62	68	56
4	51	61	64
5	69	75	72
6	65	60	61
7	65	72	76
8	59	70	65
9	65	54	60
10	63	49	61
11	71	60	64
12	67	55	61
13	70	61	64
14	67	56	57

RESULTS AND DISCUSSION

In present communication the condensation reaction between hippuric acid **(1)** with p-methyl benzaldehyde gives 4-benzylidene-2-p-nitro oxazol-5(4H)-one **(2)**. The structures of **(2)** were confirmed by elemental analysis and IR spectra showing an absorption band at 3075-3020(Aromatic C-H stretch),2880(C-H),790-745(Aromatic C-H bending),1640-1590 (Aromatic C-Cstretch),1780(C=Olacton),1650(C=N),1585,1370(NO_2,)1260(C-N).^{1}HNMR: 8.48–7.23(9H, m,Ar-H),8.01(1H,s,C=CH).^{13}CNMR:166.6(CO),151.3-124.9(Ar-12C),161.2 (C=N),132,112.5 (C=C). For $C_{16}H_{12}N_2O_4$ (294)Calcd.: %C,65.31; H,3.43; N,9.52, Found: %C,65.29;H,3.41;N, 9.51. The structures assigned to various substituted benzothiazole (**3-8)** were supported by the elemental analysis and IR spectra showing absorption bands(cm^{-1}) at 3475(NH_2),3030-3080 (Aromatic C-H stretch),1542(Aromatic C=C),1560(C=N),615(C-S), 1120(OCH_3),1452(NO_2),686(AromaticC-Cl),1076(AromaticC-Br);^{1}HNMR: 7.06(2H,s, NH_2), **3**:8.20-7.65(4H,m,Ar-H),**4**:8.02-7.40(3H,m,Ar-H),2.46(3H,s,CH_3),**5**:8.22-7.60(3H,m,Ar-H), **6**: 8.80-7.70 (3H,m,Ar-H),**7**:7.60-7.10 (3H,m,Ar-H),8:8.70-8.20(3H,m,Ar-H);^{13}CNMR:166.8 (C=N), 3:153.6,131.4,125.6,124.8,122, 118.8(Ar-C),4:150.4,134.3,131.2,126.8,121.5(Ar-C), 21.2 (CH_3),**5:**151.6,132.8,130.2,126,121.4, 118.5 (Ar-C),**6**:152.4, 133.2,129, 124.3, 119.2, 117.4(Ar-C),**7**:157.2,145.8,132.4,118.6,114.8, 105.6 (Ar-C),**8**: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-I.

IR spectra of **(3-8)** are almost resemble those of the corresponding **(9-14)** only discernable variation observed that the bend at 3475(NH_2) is absent and the new bands 3075-3020(Aromatic C-H stretch),2880(C-H),790-745(Aromatic C-H bending),1640-1590 (Aromatic C-C stretch),1780(C=Olacton),1650(C=N),1585,1370(NO_2,)1260(C-N) are observed in all the spectra of **(9-14)**,which might be responsible for formation of imidazole ring systems.^{1}H NMR: 8.47-7.39(9H,s,Ar-H),7.88(1H,s,CH=C).**9**:8.22-8.07(5H,m,Ar-H),**10**: 8.01-7.48(3H,m,Ar-H),2.47(3H,s,CH_3),**11**:7.55-7.04(3H,m,Ar-H),3.86(OCH_3),**12**:8.67-8.03 (3H,m,Ar-H),**13**:8.17-7.52(3H,m,Ar-H),**14**:8.75-7.72(3H,m,Ar-H);^{13}CNMR:158.1,149.6, 141.5,135.7,130.2,128.9,128.7,128.3(Ar-C),130.6,114.7(C=C),170.3(C=Oimidazole ring), 158.2(C=N),160.3(C=N benzothiazole ring), **9**: 139.6,135.5,125.6,124.5,122.4,118.3(Ar-C), **10**:147.5,131.2,126.7,126.4,124.5,119.1(Ar-C),16.8(CH_3),**11**:150.5,142.8,132.6,122.3, 114.1, 105.6(Ar-C),56.3(OCH_3),**12**:145.4,142.1,128.4,125.7,125.6,122.4(Ar-C),**13**:149.5,132.7, 126.3, 122.4,121.6,120.5(Ar-C),**14**:151.5,128.6, 128.7,126.4, 121.3, 116.5(Ar-C).The C,H,N, S analysis data of all compounds are presented in Table-II.

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.

CONCLUSION

In conclusion, novel fused heterocyclic compounds 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-(p-nitro)-1H-imidazol-5(4H)-ones has been synthesized by an enormously competent method. All the novel synthesized compounds show reasonable to exceptional antibacterial and antifungal activities.

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