ISSN 2249-4073

Received : March 01, 2012; Accepted : May 15, 2012

Synthesis And Bological Activity Of Novel Imidazoles

Purvesh J. Shah

Department of Chemistry, Shri A.N. Patel P.G. Institute, Anand-388001

Abstract

N-phenylglycine (1) undergoes facile cyclocondensation with benzaldehydes to gives the corresponding 4-benzylidene-2-phenyloxazol-5-one (2) in good yields. The 4-benzylidene-2-phenyloxazol-5-one (2) condensed with 2-amino substitued benzothiazole (3a-f) afforded 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-phenyl-1H-imidazol-5(4H)-one (4a-f). The structures of these compounds were recognized on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: 2-aminobenzthiazole, imidazole, spectral studies, antibacterial activity

Introduction

Heterocyclic containing nitrogen(s) and an oxygen or sulfur atom constitute an essential class of compounds in the field of medicinal chemistry. Oxazoline derivatives exhibit several pharmaceutical activities such as antibiotics [1], anti proliferative [2], anti-inflammatory [3], analgesic [4], antibacterial, antifungal [5], hypoglycemic [6]. Another heterocyclic compounds says, benzothiazole shows various biological activities such as antimicrobial [7-11] anticancer [12-15], anthelmintic [16], anti-diabetic [17] activities. The resultant compounds, Imidazole also reveal a number of significant biological activities such as antiparasitic, fungicidal, anithelemintic, anti-inflammatory, antiprotozoal and herbicidal activity [18-24]. 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 of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-phenyl-1H-imidazol-5(4H)-ones (4a-f). The synthetic approach is shown in Fig. 1.

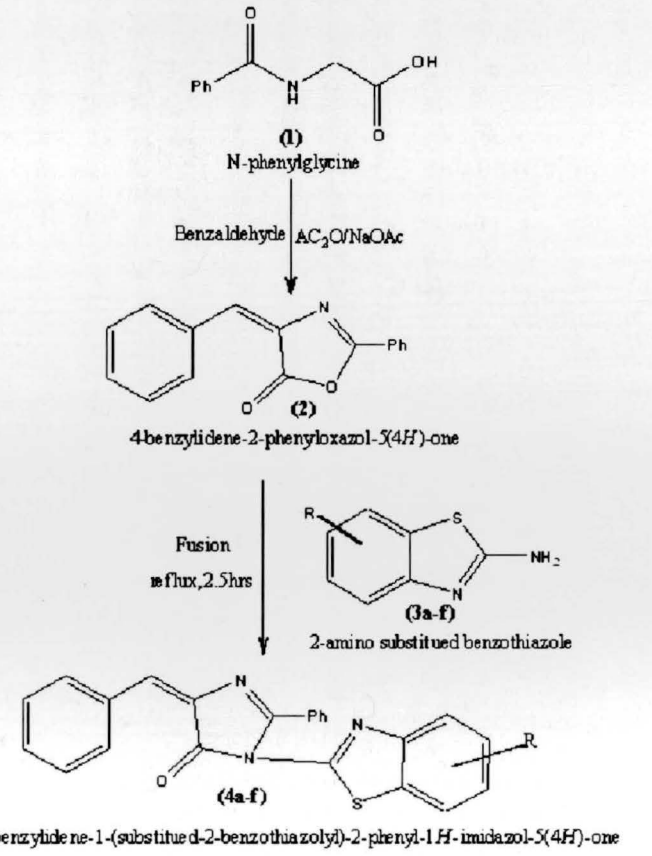

Figure 1.

Materials and Methods

Melting points were determined in open capillary tubes and were uncorrected. The spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and 1H NMR and 13C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz

*Corresponding author:
Dr. Purvesh J. Shah
Assistant Professor, Department of Chemistry,
Shri A.N. Patel P.G. Institute,Anand-388001(India).
E-mail:purvesh23184@gmail.com

and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Preparation of 4-benzylidene-2-phenyloxazol-5-one (2)

The mixture of N-phenylglycine (0.25mole), distilled benzaldehyde (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 1.5 hrs, cool to 0-5oC. 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 76 % and the product melts at 162-63 °C. For $C_{16}H_{11}NO_2$ (249)Found: % C, 77.0; %H, 4.4;%N,5.6,Calcd.: %C,77.10;%H,4.45;%N,5.62.IR (KBr); (cm-1): 3080(Aromatic C-H stretch),760(Aromatic C-H bending),1620-1580(Aromatic C-C stretch), 1790(C=O lacton), 1650(C=N),1260(C-N). 1H NMR: 8.06-7.32(10H,m) (Ar-H), 7.98 (1H,s) (C=CH). 13CNMR: 166.4 (CO lacton), 135.6-128.1(Ar-12C), 161.3 (C=N), 131.9, 112.7 (C=C).

Preparation of 2-amino-4-substitued benzothiazoles (3a-f):

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 °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.

Preparation of 4-benzylidene-1-(substitued-2-benzothiazolyl)-2-phenyl-1H-imidazol-5(4H)-one (4a-f)

A mixture 2-amino-4-substituted benzothiazoles (3a-f) (0.01mole) and 4-benzylidene-2-phenyloxazol-5-one (2) (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 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.

Biological Screening

Antibacterial activities

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 3c, 3e, 4c and 4e were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Table 3 and represented in Fig.2.

Table 1. Analytical Data and Elemental Analysis of Compounds (3a-f)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* °C	Elemental Analysis %C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_7H_6N_2S$ (150)	169	72	159-161	55.9	55.97	4.0	4.03	18.6	18.65	21.3	21.35
3b	$C_8H_8N_2S$ (164)	178	67	162-164	58.4	58.51	4.8	4.91	17.0	17.06	19.5	19.52
3c	$C_8H_8N_2OS$ (180)	196	64	153-156	53.2	53.31	4.4	4.47	15.5	15.54	17.7	17.79
3d	$C_7H_5N_3O_2S$(195)	212	68	156-158	43.0	43.07	2.5	2.58	21.5	21.53	16.4	16.43
3e	$C_7H_5N_2OSCl$(183)	199	70	153-155	45.5	45.53	2.7	2.73	15.1	15.17	17.3	17.37
3f	$C_7H_5N_2OSBr$(229)	238	67	161-163	36.6	36.70	2.1	2.20	12.2	12.23	13.9	14.00

Table 2. Analytical Data and Elemental Analysis of Compounds (4a-f)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* °C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{23}H_{15}N_3OS$ (381)	403	73	189-190	72.4	72.42	3.9	3.96	11.0	11.02	8.4	8.41
4b	$C_{24}H_{17}N_3OS$ (395)	416	66	193-194	72.8	72.89	4.3	4.33	10.6	10.63	8.1	8.11
4c	$C_{24}H_{17}N_3O_2S$ (411)	428	68	206-207	70.0	70.05	4.1	4.16	10.2	10.21	7.7	7.79
4d	$C_{23}H_{14}N_4O_3S$ (426)	437	61	197-198	64.7	64.78	3.2	3.31	13.1	13.14	7.5	7.52
4e	$C_{23}H_{14}N_3OSC_1$ (415)	428	58	195-196	66.4	66.42	3.3	3.39	10.1	10.10	7.7	7.71
4f	$C_{23}H_{14}N_3OSBr$ (459)	472	60	208-209	59.9	60.01	3.0	3.07	9.1	9.13	6.9	6.97

Table 3. Antibacterial Activities of Compounds

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiella promioe*
3a	55	54	62	64
3b	54	60	57	67
3c	65	71	74	76
3d	53	60	72	68
3e	58	68	73	81
3f	56	62	70	73
4a	55	59	70	70
4b	58	60	61	64
4c	79	80	84	83
4d	72	76	80	78
4e	57	77	72	76
4f	67	70	65	64
Tetracycline	55	79	74	84

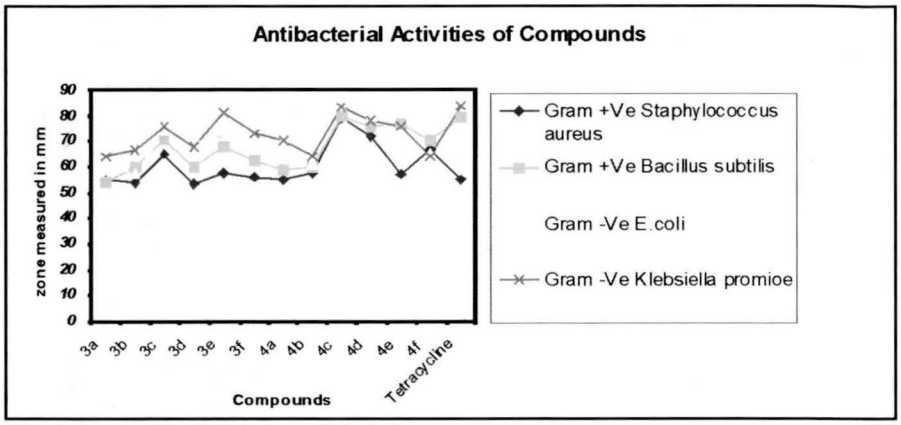

Figure 2. Antibacterial Activities of Compounds

Antifungal Activities

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 (3a-f) and (4a-f) 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 (1000 ppm) in a PDA medium and autoclaved at 120 °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(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 (3a-f) and (4a-f) are shown in Table 4 and represented in Fig. 3.

Table 4. Antifungal Activity of Compounds

Zone of Inhibition at 1000 ppm (%)					
Compounds	***Nigrospora* sp.**	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Rhizopus Nigricum***	***Fusarium oxyporium***
3a	68	65	65	59	70
3b	60	54	62	67	64
3c	75	72	74	75	78
3d	68	68	64	64	63
3e	70	68	66	79	75
3f	64	62	64	68	73
4a	68	66	67	64	63
4b	67	64	59	65	58
4c	78	72	77	68	69
4d	63	68	69	65	64
4e	69	71	72	68	70
4f	64	68	65	60	65

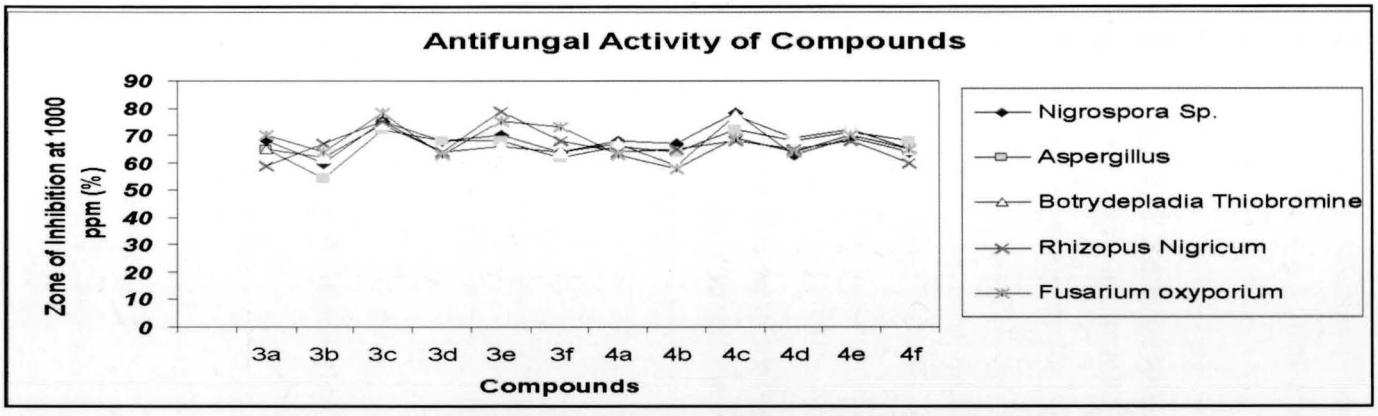

Figure 3. Antifungal Activity of Compounds

Results and Discussion

It was observed that N-phenylglycine (1) on condensation with distilled benzaldehyde yields 4-benzylidene-2-phenyloxazol-5-one (2). The structures of (2) were confirmed by elemental analysis and IR spectra showing an absorption band at 3080(Aromatic C-H stretch), 760(Aromatic C-H bending),1620-1580(Aromatic C-C stretch), 1790(C=O lacton), 1650 (C=N),1260(C-N);1H NMR: 8.06-7.32(10H,m) (Ar-H), 7.98 (1H,s) (C=CH); 13CNMR: 166.4 (CO lactone), 135.6-128.1(Ar-12C), 161.3 (C=N), 131.9, 112.7 (C=C). For $C_{16}H_{11}NO_2$ (249) Found: % C, 77.0; %H, 4.4;%N, 5.6,Calcd.: %C, 77.10; %H, 4.45; %N, 5.62. The structures assigned to 2-amino substituted benzothiazole (3a-f) were supported by the elemental analysis and IR spectra showing absorption bands at 3475cm-1(NH2), 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(NO2),686cm-1(Aromatic C-Cl),1076cm-1(Aromatic C-Br);1H 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);13CN-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.The IR spectra of (3a-f) are almost resemble those of the corresponding (4a-f) only discernable difference observed that the bend at 3475cm-1(NH_2) is absent and the new bands at 3080(Aromatic C-H stretch),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 (4a-f), which might be responsible for formation of imidazole ring systems.1H NMR: 7.64-7.34 (10H,s)(Ar-H),7.42(1H,s)(CH=C),4a: 8.24-7.58(4H, m) (Ar-H), 4b: 7.92-7.36(3H, m) (Ar-H), 2.41 (3H,s) (-CH_3), 4c:7.56-7.02(3H, m) (Ar-H),3.92(O-CH_3), 4d: 8.68-8.05(3H,m)(Ar-H),4e:8.16-7.58(3H,m)(Ar-H),4f:8.75-7.68(3H,m)(Ar-H);13C NMR: 135.4, 135.4,130.2, 129.3, 129.3, 128.9, 128.9, 128.7, 128.7, 128.4, 128.4,128.2(Ar-C), 130.5, 114.8 (C=C),170.2(C=O imidazole ring),130.5(=C-N),158.2(C=N),160.2(C=N benzothiazole ring), 4a: 139.6,135.4, 125.5,124.7,122,118.5(Ar-C),4b:147.4, 131.5, 126.8,126.1,124.6,119(Ar-C), 16.3(CH_3), 4c: 150.4,142.5,132.1,122,114.3,105.4 (Ar-C), 56.1(OCH_3) 4d: 145.1,142.4, 128.1, 125.8, 125.6, 122.6 (Ar-C), 4e:149.3,132.4,126,122.1,121.7,120.2 (Ar-C), 4f:151.6, 128.9, 128.4, 126.9, 121, 116.9 (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 2.

Conclusion

In conclusion, a highly efficient method for the synthesis of novel benzylidene-1-(substitued-2-benzothiazolyl)-2-phenyl-1H-imidazol-5(4H)-ones has been developed. All the novel synthesized compounds show moderate to good antibacterial and antifungal activities.

References

1. Ranabir S R, Neil L K, Jill C M and Christopher T W (1999) In vivo processing and antibiotic activity of microcin B17 analogs with varying ring content and altered bisheterocyclic sites. Chemistry & Biology 6(5):305-318.

2. Xin H, Liu P Ch L, Jia-Yu X, Bao-An S and ai-Liang Z (2009) Novel 2, 4, 5-trisubstituted Oxazole derivatives: Synthesis and antiproliferative activity.Eur J Med Chem 44(10): 3930-3935.

3. Singh N, Bhati K and Kumar A (2008) Thiazolyl/oxazolyl formazanyl indoles as potent anti-inflammatory agents. Eur J Med Chem 43(11): 2597-2609.

4. Perner R J, Koenig J R, Didomineco S, Gomtsyan A (2010) Synthesis and biological evaluation of 5-substituted and 4,5-disubstituted-2-arylamino oxazole TRPV1 antagonist. Bio Org Med Chem 18(13): 4821-4829.

5. Kaspady M, Narayanswamy V K, Raju M, Rao G K. (2009) Synthesis, Antibacterial Activity of 2,4-Disubstituted Oxazoles and Thiazoles as Bioisosteres, Lett. Drug Disc 6(1):21-28.

6. Conti P, Dallanoce C, Amici M D, Micheli C D (1998) Synthesis and evaluation of Hexa hydropyrrolo[3,4-d]isoxazole-4,6-diones. Bioorg Med Chem 6(4):401-408.

7. Gupta S, Ajmera N, Gautam N, Sharma R, Gauatam D (2009) Novel synthesis and biological activity study of pyrimido [2,1-b] benzothiazoles. Ind J Chem 48B:853-858.

8. Kumbhare R M, Ingle V N (2009) Synthesis of novel benzothiozole and benzisoxazolen functionalized unsymmetrical alkanes and study of their antimicrobial activity. Ind J Chem. 48B:996-1000.

9. Murthi Y and Pathak D (2008) Synthesis and Antimicrobial screening of Substituted 2-Mercaptobenzothiazoles. J Pharm Res.7(3);153-155.

10. Rajeeva B, Srinivasulu N, Shantakumar S (2009) Synthesis and Antimicrobial activity of some new 2-substituted benzothiazole derivatives. E-Journal of Chemistry 6(3):775-779.

11. Maharan M, William S, Ramzy F and Sembel A (2007) Synthesis and in vitro Evaluation of new benzothiazolederivaties as schistosomicidal agents. Molecules 12: 622-633.

12. Kini S, Swain S and Gandhi A (2007) Synthesis and Evaluation of novel Benzothiazole Derivates against Human Cervical Cancer cell lines. Ind J Pharm Sci : 46-50.

13. Stanton H L K, Gambari R, Chung H C, Johny C O T, Filly C and Albert S C C (2008) Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. Bioorg Med Chem 16:3626-3631.

14. Wang M, Gao M, Mock B, Miller K, Sledge G, Hutchins G, Zheng Q (2006) Synthesis of C-11 labelled fluorinated 2-arylbenzothiazoles as novel potential PET cancer imaging agent. Bioorg Med Chem. (14):8599-8607.

15. Hutchinson I, Chua MS, Browne H L, Trapani V, Bradshaw T D and Westwell A D (2001) Synthesis and Pharmaceutical Properties of Antitumor 2-(4-Aminophenyl) benzothiazole Amino Acid Prodrugs. J Med Chem. 44:1446-1449.

16. Sreenivasa M, Jaychand E, Shivakumar B, Jayrajkumar K, Vijaykumar J (2009) Synthesis of bioactive molecule flurobenzothiazole comprising potent heterocylic moieties for anthelmintic activity. Arch Pharm Sci and Res.1(2):150-157.

17. Pattan S, Suresh C, Pujar V, Reddy V, Rasal V and Koti B (2005) Synthesis and antidiabetic activity of 2-amino[5"(4-sulphonylbenzylidine)- 2,4 thiazolidinenone]-7-chloro-6-fluro benzothiazole. Ind J Chem. 44B:2404-2408.

18. Habib, N S, Soliman, R, Ashour F A and el-Taiebi M (1997) Synthesis and antimicrobial testing of novel oxadiazolylben- zimidazole derivatives. Pharmazie 52:746-749.

19. Tuncbilek, M, Goker, H, Ertan R, Eryigit R, Kendi E and Altanlar E (1997) Synthesis and antimicrobial activity of some new aniline benzimidazoles. Arch Pharm 330: 372-376.

20. Pedini, M, Alunni Bistochi G, Ricci A,Bastianini L & Lepri E (1994) New heterocyclic derivatives of benzimidazole with germicidal activity - XII. Synthesis of N1-glycosyl-2-furyl benzimidazoles. Farmaco 49: 823-827.

21. Lackner, T E and Clissold S P (1989) Bifonazole: A review of its antimicrobial activity and therapeutic use in superficial mycoses.Drugs 38: 204-225.

22. Devivar R V, Kawashima E, Revankar G R, Breitenbach J, Kreske E, Drach J and Townsend L (1994) Benzimidazole ribonucleosides:

Design, synthesis, and antiviral activity of certain 2-(alkylthio)- and 2-(benzylthio)-5,6-dichloro-1-(D-bofuranosyl) benzimidazoles. J Med Chem 37: 2942-2949.

23. Navarette-Vazquez G, Cedillo R, Hernandez-Campos A, Yepez L, Hernandez-Luis F, Valdez J, Morales R, Cortes R, Hernandez M and Castillo R (2001) Synthesis and antiparasitic activity of 2-(trifluoromethyl) benzimidazole derivatives. Bioorg Med Chem Lett 11:187-190.

24. Burton D E, Lambie A J, Ludgate J C, Newbold G T, Percival A and Saggers D T (1965) 2-Trifluoromethylbenzimidazoles; a new class of herbicidal compounds. Nature 208:1166-1170.