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Synthesis and Evaluation of New Pyrazolesof Benzimidazolesas Potent Antimicrobial Agents.

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ABSTRACT:A series of 7-chloro-2-[3-(1h-benzimidazol-2-yl)-5-aryl-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole (VII) was synthesized by the action of 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole (V) on chalcones in the presence of catalytic amount of glacial acetic acid and ethanol. Thus prepared pyrazolines were subjected to facile oxidation to give corresponding pyrazoles(VII) using iodobenzenediacetate (IBD). The structures of the synthesized compounds have been established on the basis of their elemental analysis and spectral (IR,^{1}HNMR) studies. Further they have been screened for their antimicrobial activity. Compounds FB4,FB7,FB8 and FB10 showed significant antimicrobial activity.

KEYWORDS:Benzimidazoles, Antibacterial, Antifungal, Pyrazoles

I. INTRODUCTION:

Benzimidaole is bicyclic in nature which consists of the fusion of benzene and imidazole.Benzimidazole have broad spectrum ofbiological activities, antibacterial[1],antiparasitic[2], antihypertensive[3], analgesic and anti-inflammatory activity[4]. Pyrazoles are one of the most active classes of compounds possessing wide spectrum of biological activities.[5-7]Many of these are therapeutically useful compound such as phenylbutazone[8],oxiphenabutazone[9],celecoxib[10].Se veral pyrazole derivatives have emerged as group of compound possessing broad spectrum of useful medicinal propertities.[11,12]Benzothiazole derivatives have been studied extensively and found to have diverse chemical activity and broad spectrum of biological activities like antimicrobial[13],antitumor[14,],anthelmintic [15]antileishmanial[16,17],anticonvulsant[18] and antiinflammatoryactivity.Hence in continuation[19-21] work on benzothiazoles,it is thought worthwhile to synthesize some new pyrazolobenzimidazole by incorporating 2-hydrazinobenzothiazole moieties in a single molecular frame work.

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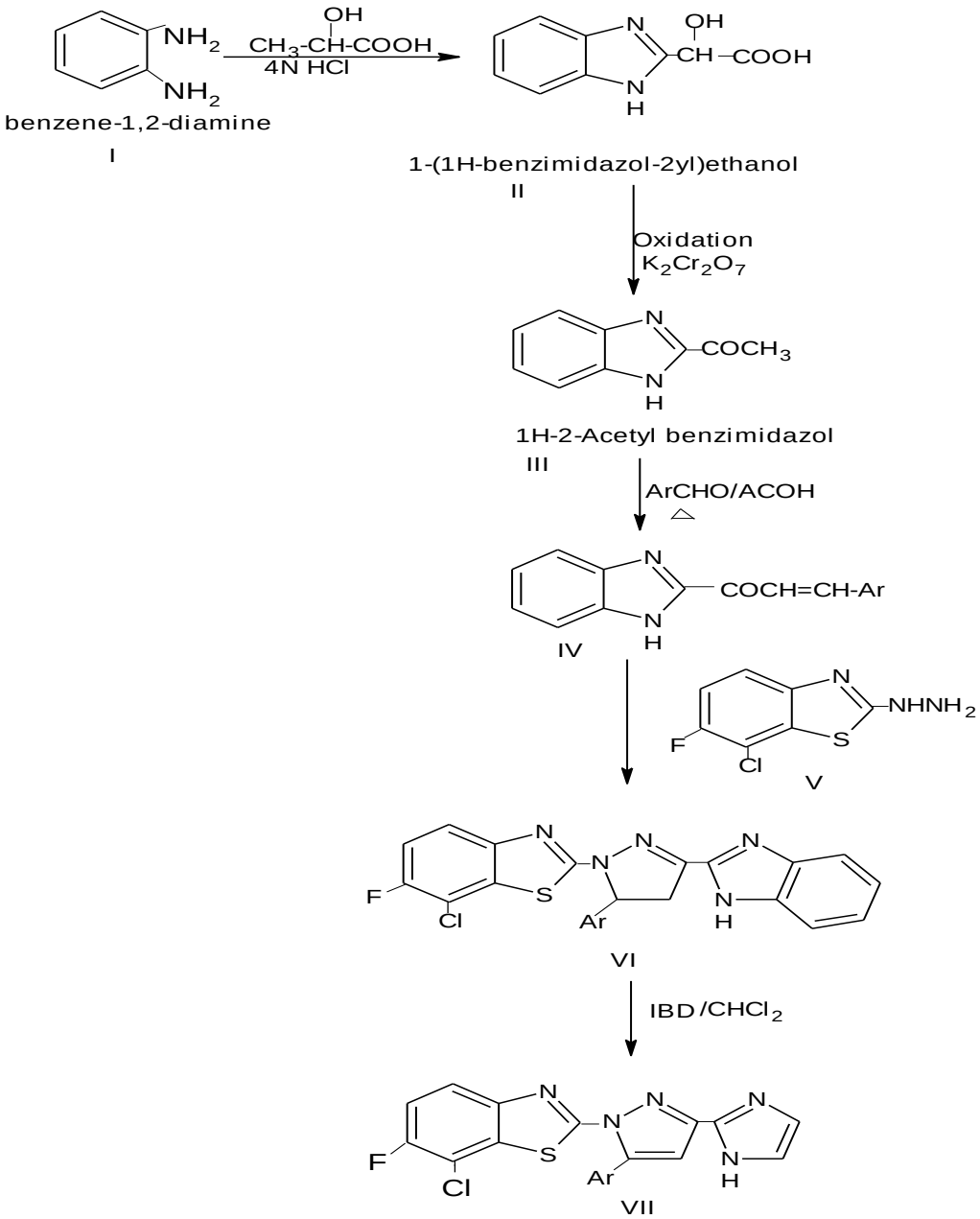

II. MATERIALS AND METHODS:

The identification and characterization of prepared compounds were carried out by thin layer chromatography, melting point,infrared spectroscopy and nuclear magnetic resonance spectroscopy.The melting point of organic compounds were determined by open capillary tube method which are uncorrected.The compounds were recorded on SHIMADZU FTIR- 8400S spectrophotometer by using KBr pallet technique.

EXPERIMENTAL SECTION:

Synthesis of 7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl] -6-fluoro-1,3-benzothiazole (VI):

General procedure:

A mixture of 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole (2.02gm,0.01 mol) and 1H-2- Acetyl benzimidazolechalcone (0.01mol) was refluxed for two hrs in ethanol (20 ml) containing few drops of acetic acid, kept at room temperature for 4-5 hrs. Separated solid was filtered washed with water, dried and crystallized from ethanol. Physical and analytical particulars of

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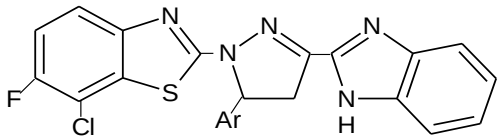
7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole are given.(m.p.-185^0 C,% Yeild-65.79%).It's IR spectrum (VI) PD5 in KBr showed peak at (absorbtion frequency in cm^{-1}) 3050(-NH),(-CH_2),1623(C=N),1180(C-F) and (C-Cl) at743.It's ^{1}HNMR spectrum (VI) PD5 in $CDCl_3$ showed characteristic proton signal (in δ ppm) at 3.101(S,6H,-N(CH_3)$_2$,6.91(d,3H,CH_2 and 1H of H_5 of pyrazolines),7.0125-8.419(m,10H,Ar-H) and 8.432(S,1H,-N-H).

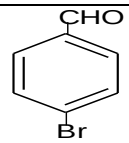
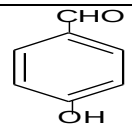
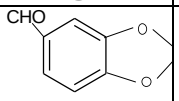
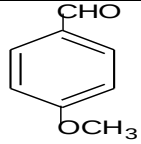
Synthesis of 7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole (VII):

General procedure:

A solution of pyrazolines(0.001mole) in dichloromethane(20ml)was added iodobenzenediacetate(0.0012mole) was stirred at room temperature for 4 hrs.Dichloromethane was distilled off on steam bath to give a gummy product which was triturate with petroleum ether to remove iodobenzenediacetate(IBD) and then was purified by recrystallisation from ethanol to afford the product. It's IR spectrum VII (FB9) in KBrshowed peak at(absorption frequency in cm^{-1}) at 3050(-NH),923(-CH_2),1623(C=N),1180(C-F)and (C-Cl)at 743. It's^{1}HNMR spectrum VII (FB9) in $CDCl_3$ showed characterstic proton signal(in d, ppm) at 2.112(S,3H,-OCH_3) , 3.905(d,1H,H_4),7.082-7.741(m,9H,Ar-H)and 8.975(S,1H,-NH)Table No.1 gives information of physical and analytical data of 7-chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazoles.
(m.p-182^{0}C, % Yield- 62.35%)



Physical and analytical data of 7-Chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-4,5-dihydro-1H-pyrazole-1-yl]-6-fluoro-1,3-benzothiazole. Table No. 1

Sr.No.	Compound code	Ar	Melting point	Yield %	Molecular formula	Molecular weight	C%	H%	O %
1	PB8		190^{0}C	62	$C_{23}H_{13}N_5$ SFClBr	522	52.8	2.49	13.40
2	PH10		191^{0}C	60.50	$C_{23}H_{15}ON_5$SClF	384	71.8	3.9	18.22
3	PP9		199^{0}C	69.32	$C_{23}H_{12}O_2N_5$SClF	486	56.7	2.46	14.40
4	PA3		180^{0}C	61.20	$C_{24}H_{16}ON_5$SFCl	473	60.8	3.38	14.79

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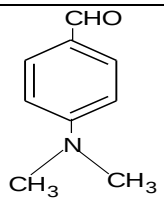
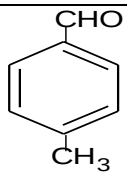
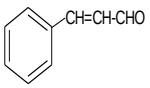
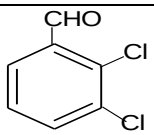
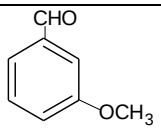
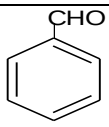
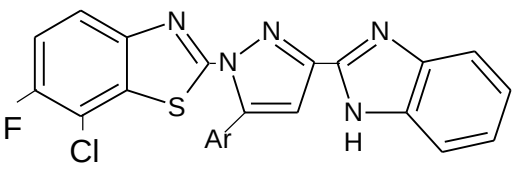
5	PD5		185^{0}C	65.79	$C_{25}H_{19}N_6$ SClF	486	61.7	3.90	14.81
6	PT7		195^{0}C	68.28	$C_{24}H_{13}SC$ lFN_5	458	62.8	2.83	15.28
7	PC4		192^{0}C	66.82	$C_{25}H_{16}N_5$ SClF	470	63.8	2.97	14.89
8	PD6		200^{0}C	67.23	$C_{23}H_{12}N_5$ Cl_3FS	513	53.8	2.33	13.64
9	PM1		192^{0}C	66.14	$C_{24}H_{16}OS$ $FClN_5$	474	60.7	3.37	14.76
10	PB2		195^{0}C	62.23	$C_{23}H_{12}N_5$ SClF	444	62.1	2.70	15.76



Physical and analytical data of 7-Chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-1H-pyrazole-1-yl]-6-fluoro-1,3-benzothiazole.

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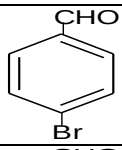
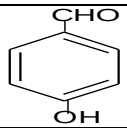
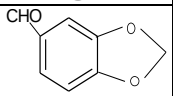
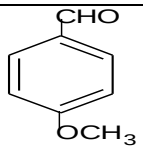
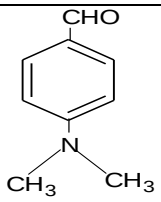
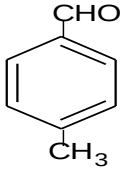
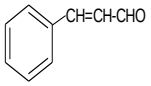
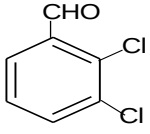
Table No. 2

Sr.No.	Compound code	Ar	Melting point	Yield %	Molecular formula	Molecular weight	C%	H%	O %
1	FB1		192^{0}C	64.20	$C_{23}H_{12}N_5SFClBr$	521	52.90	2.30	13.43
2	FB3		190^{0}C	63.53	$C_{23}H_{14}ON_5SClF$	383	72.40	3.6	18.27
3	FB4		200^{0}C	68.66	$C_{23}H_{11}O_2N_5SClF$	485	56.9	2.26	14.43
4	FB9		182^{0}C	62.35	$C_{24}H_{15}ON_5SFCl$	472	61.08	3.17	14.83
5	FB2		181^{0}C	65.83	$C_{25}H_{18}N_6SClF$	485	61.8	3.71	14.84
6	FB7		192^{0}C	68.30	$C_{24}H_{12}SClFN_5$	457	63.00	2.62	15.31
7	FB5		195^{0}C	64.82	$C_{25}H_{15}N_5SClF$	469	62.9	2.77	14.92
8	FB8		187^{0}C	69.30	$C_{23}H_{11}N_5Cl_3FS$	512	53.9	2.14	13.67

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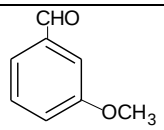
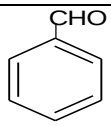
9	FB6		194^{0}C	68.35	$C_{24}H_{15}OSF ClN_5$	473	60.8	3.17	14.79
10	FB10		194^{0}C	63.67	$C_{23}H_{11}N_5SC lF$	443	62.3	2.48	15.80

Antibacterial activity of synthesized compounds.Table No.3

Sr.No.	Compound	Concentration µg/ml	E.coli	S.Aureus	p.mirabilis	k.pneumonia
1	FB1	50	8	11	12	10
		100	10	14	9	7
2	FB2	50	7	10	8	10
		100	14	12	10	12
3	FB3	50	8	14	8	12
		100	11	13	14	10
4	FB4	50	13	14	9	10
		100	15	13	11	8
5	FB5	50	12	9	10	8
		100	15	14	10	11
6	FB6	50	11	9	12	10
		100	9	11	9	14
7	FB7	50	13	12	16	14
		100	15	14	15	10
8	FB8	50	8	12	13	14
		100	13	13	7	10
9	FB9	50	12	14	14	16
		100	11	13	15	15
10	FB10	50	13	12	10	12
		100	16	16	15	10

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11	Ciprofloxacin	50	24	26	28	22

Antifungal activity of synthesized compounds. Table No.4

Sr.No.	Compound	Concentration µg/ml	Candida albicans	Aspergius Niger
1	FB1	250	-	-
		500	-	+
2	FB2	250	+	-
		500	+	-
3	FB3	250	-	-
		500	-	+
4	FB4	250	+	-
		500	-	-
5	FB5	250	-	+
		500	+	-
6	FB6	250	-	-
		500	+	+
7	FB7	250	-	-
		500	-	+
8	FB8	250	-	-
		500	+	+
9	FB9	250	-	-
		500	-	+
10	FB10	250	-	-
		500	+	-
11	Fluconazole	250	-	-
		500	-	-

Antimicrobial Activity: The antimicrobial activity of all synthesized compounds weredetermined by using Cup-plate method[22]. The in vitro antibacterial activity was carried out by using bacterial strains of E.Coli,Klessiella pneumonia (G – ve),Staphyloccoccusaureus,Protens Mirabilis (G +ve).The fungi used were Aspergilusniger,Candidaalbicans.Ciprofloxacin (2mg/ml) and Fluconazole (2mg/ml) were used as standard for antibacterial and antifungal activity respectively.The result presented in Table NO.3,4.

III. RESULT AND DISCUSSION:

The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in scheme. Treatment of o-phenylenediamine (I) with lactic acid in the presence of 4N HCl gave 2-hydroxyethyl-benzimidazole(II). Later on oxidation with acidic dichromate gave 2-acetylbenz-imidazole(III).Treatment of 2-acetylbenzimidazole on aromatic aldehydes in the presence of NaOH gave chalcones (IV). Condensation of chalcone with 7-chloro-6-fluoro-2-hydrazino-1,3-benzothiazole in presence of catalytic amount of ethanol and glacial acetic acid gave7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole(VI). Later on facile oxidation with iodobenzenediacetate in the presence of dichloromethane gave 7-chloro-2-[3-(1H-benzimidazol-2yl)-5-aryl-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazole.(VII)The structures of the synthesized compounds have been established on the basis of their elemental analysis and spectral (IR , ^{1}HNMR Spectroscopy) studies. Amongst the compounds tested for antimicrobial activity some compound exhibited promising activity and some exhibited significant activity.

IV. CONCLUSION:

Ten new compounds of 7-chloro-2-[3-(1H-benzimidazol-2-yl)-5-aryl-1H-pyrazol-1-yl]-6-fluoro-1,3-benzothiazoless(VII) were synthesized. All the synthesized compounds were characterized by IR,^{1}HNMR spectral properties.The synthesized compounds were screened forantimicrobialactivity. The results presented on above tables reveals that

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compounds show moderate to significant antimicrobial activity.

REFERENCES.

[1]. TuncbilekM,KiperTandAltanlarN,Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivative having potent activity against MRSA,Eur J Med chem.,200,44,1024-1033.

[2]. Hernandez-luisF,Hernandez-camposA,CastilloR,Navarret-Vazquez G,Soria-ArtecheO,Hernandez-M and Yepez-Mulia L, Eur J Med chem,2010,45 (7),3135.

[3]. Jat R K,Jat J K and Pathak D P,Synthesis of benzimidazolederivatives:As antihypertensive agents,E-Journal of chem,200,3,(27848).

[4]. RamanpreetWalia,MdHedaitullah,SyedaFarhaNaaz,KhalidIqbal and Hs.Lambar,Benzimidazole derivatives-An overview, International Journal of research in pharmacy and chemistry,2011:565-574.

[5]. Sharma S,SrivastvaV,KandkumarA,Synthesis and anti-inflammatory,analgesic,ulcerogenic and lipid peroxidation activities of 3,5-dimethylpyrazoles,3-methylpyrazol-5-ones and 3,5-disubstituted pyrazolines,Indian Journal of chemistry,41B(2002),2647.

[6]. SawhneyS.N,BhutaniandVirD.Synthesis and anti-inflammatory,ulcerogenic and lipid peroxidation ctivities of 3,5-dimethyl pyrazoles,3-methylpyrazol-5-ones and 3,5-disubstituted pyrazolines.Indian J.Chem.28B(1989),667.

[7]. DandiaA,SehgalV,and Singh P, Indian J chem..32B(1993).1288

[8]. Gennro A R, Remington: Synthesis of fluorinated ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one 1 thione-5-carboxylates under the microwave irradiation.Thescience and practice of pharmacy vol.II.20th edition(Lippncott Williams and Wilkins)(2001),1459.

[9]. Clemette D and Goa,Celecoxib: A review of its use in osteoarthritis,Rheumatoid Arthritis and acute pain. Drugs 59(2000),957

[10]. [a] Sector H V and BardelabehJ.F.Structure and confirmation of cis-benzoyl-2-chloracetyl-4,5-hexamethylenepyrazolidineian X-ray study J.med.chem.14(1971).
[b]BanerV.J.Fanshawe,W.J.dalalianH.P,Safir,S.R.TocusE.C.andBoshart C.R,J.med.chem..11(1968)981.
[c]DurhumN.N,Chestnut R W,Hashed M.M and BarlinK.D.Heterocyclicmonoazodyes derived from 3-cyano-2(H)-pyridinethione part 2:2-[(4(Arylazo)-3,5-disubstituted pyrazol-1-yl)carbonyl]-thieno[2,3-b]pyridine derivatives.J.med chem19(1976)229.

[11]. RajendraAgrawal,VinodKumar,Shiv P Singh.Synthesis of some new 1-(6-fluorobe-Nzothiazole-2yl)-3-(4-fluoro-phenyl-5-aryl pyrazolines and their Iodine(III) mediated Oxidation to corresponding pyrazoles.Indian J.Chem,46B,2007,1332-36.

[12]. Sreenivasa,M V, Nargund,L V G,Variuosbenzothiazolotriazole derivatives possess good microbial activity. Indian J Chem.8,1998,23.

[13]. GopkumarP,ShivakumarB,JaychandranE,Nagappa, A.N.Nargund,L V G and Guru-Padaiah,Some 6-fluoro-7-(substituted)-(2-N-p-anilinosulfonamido)benzothiazoles were synthesized and studied for their antimicrobial and antifungal activities.IndianJ.Heterocyclic chem.,11.2001,39.

[14]. KashiyarnaE,HutchinssonI,ChauM.S,Stinson S.F,Phillips,L.R.Kaur,G.Sausville,E.A. Br-Adshow ,T.D.Westwell A.D. and Stevens M.F.G,2-(4-aminophenyl)benzothiazol-antitumor agents,Med.Chem,43,1999,4172.

[15]. Nargund,L V G, Few novel 8-fluoro-9-substituted(1,3)benzothiazolo(5,1-b-)-1,3,4-triazoles studied for their anthelmintic activity,Indin Drugs.36,1999,137.

[16]. DelmasF,GiorgioC.D,RobinM,Gasquest,N A M Detang,CCosta,M.Timon,David and Galy J.P. Position 2-substitution-bearing-6nitroand 6-aminobenzothiazoles and their corresponding anthranillic acids and assessed the in vitro antiparasitic activity.Antimicrob.AgentsChmother.46,2002,2588.

[17]. SiddiquiN,Pandeya S N,Sen A P and Singh G S A series of benzothiazolylguanidiness Were synthesized for their significant anticonvulsant activity.Pharmak Eftiki,4,1992,121.

[18]. Singh S P,Misra R S,Parmar S S and Brumleve S J, Some 2-(4-arylthiosemicarazidocarbo-nylthio) benzothiazoles screened for their anticonvulsant activity.J.Pharm.Sci.64,1978,1245.

International Journal of Pharmaceutical Research and Applications
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[19]. SawhneyS.N,Bhutani S. and Dharanvir,Somenobel 2-(2-benzothiazolyl)-6-aryl-4,5-dihydro-3(2H)-pyridazinone screening for their anti-inflammatory activity.Indian J.Chem.25B,1986,288.
[20]. ShivakumarB,SojanK,NagrendraRaoR,Jaychandran E, Synthesis and microbial evaluationOf 6-fluoro-7-substituted-1,2,3,4-tetrazolo[5,1b]benzothiazoles.Indian J.Heterocyclic Chem15,2005,71-72.
[21]. JaychandranE,NaragundL.V.G,Shivakumar B,KamalBhatia.Synthesis and pharmacologicalScreening of 2-(3-amino-5-S-methyl-4-carboxamido pyrazol-1-yl)-6-fluoro-7-substituted(1,3)benzothiazoles. Oriental J Chem,19(1),2002,139.
[22]. Levinson WE,GawetzE,Medical microbiology and immunology.Web publication 3rd ed.Appleton and language,1910-40.