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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED DIIMINO PYRIMIDO PYRIMIDO BENZOTHIAZOLES AND IMINO PYRAZOLO THIAZOLO PYRIMIDINES

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Abstract:
6-Cyano-5-imino-7-(methylthio)-5H-thiazolo[3,2-*a*] pyrimidine on reaction with substituted 2-amino benzothiazoles and substituted hydrazino compounds in presence of weak base anhydrous K_2CO_3 and N,N-dimethyl formamide as solvent afford 5,6-diimino thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazoles and 3-amino-4-imino-2-N-substituted pyrazolo[3,4-*d*] thiazolo[3,2-*a*]pyrimidines respectively, which were further screened for their antimicrobial activities.

Keywords: 2-aminobenzothiazoles, 6-cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3, 2-*a*] pyrimidine, hydrazine, potassium carbonate and thiazolo pyrimidines.

Introduction:

Benzothiazole is biologically potent bicyclic ring containing group like nitrogen , sulphur as heteroatom and formed by thiazole ring fused with benzene ring which behave as weak base, the hetrocyclic compounds possessing benzothiazole ring have versatile pharmacological properties and which act as drug in different places of pharmaceutics time to time.

Particularly different types of 2-amino benzothiazole act as central muscle relaxants and glutamate neurotransmission inhibitor. Fused benzothiazole, thiazolo pyrimidine compounds possess anti-inflammatory activity [i-v], anticancer activity [vi,vii,viii], analgesic activity[ix] antitumor activity, antioxidant activity [xii], antimicrobial activity [xiii-xv] and pyrimido benzothiazole derivatives as antibacterial agent[x,xi]. In the previous study we reported synthesis and antioxidant potential of imino pyrimido thiazole compounds by DPPH and OH radical scavenging assay[xvi], antimicrobial activity and synthesis of benzo[4,5]thiazolo[3,2-*a*]pyrazolo [3,4-*d*]pyrimidine compounds [xvii].

These suitable observations have fascinated significant interest to synthesis of compounds containing thiazolo pyrimidine fused through nitrogen atom with biologically active ring like benzothiazolo, hydrazeno benzothiazole compounds. Herein we report one pot simple and efficient synthesis of fused thiazolo pyrimido benzothiazole, thiazolo pyrimido pyrazole compounds with their antimicrobial activity.

Result and Discussion:

In present work we report the suitable method for synthesis of substituted 5,6-diimino thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazoles (**3a-3f**) from the reaction of 6-cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3,2-*a*] pyrimidine (**1**) and substituted 2-amnio benzothiazoles (**2**). Where as the synthesis of substituted 2-N-phenyl substituted 3-amino-4-imino pyrazolo[3,4-*d*] thiazolo [3,2-*a*]pyrimidines **(5a-5f)** from the reaction of 6-cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3,2-*a*] pyrimidine (**1**) with substituted hydrazines(**4**),the yield of these prepared compounds in the range of 65 to 81% with simple separation method. The structure of these compounds was confirmed on the basis of mass, infrared and proton magnetic resonance spectral data, which clearly show that these compounds are stable and do not show tautomerism.

6-Cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3,2-*a*] pyrimidine (**1**) possess a replaceable active thiomethyl group at the 7-position which is activated electron withdrawing cyano group at 6-postion,which on reaction with selected substituted 2-amino benzothiazoles and hydrazines independently in presence of catalytic amount (0.005 mol)of anhydrous potassium carbonate and N,N-dimethyl formamide as solvent with formation of **3a-3f** and **5a-5f** respectively.

Mass spectra shows that molecular ion peak corresponds to molecular mass of which shows that formation of stable compounds **3a-f** and **5a-f**. Infrared spectra show absorption band in the range of 3340-3120 cm^{-1}, 2240-2170 cm^{-1} for =NH, CN stretching for compounds **3a –f** respectively, compounds **5a-f** shows absorption band at 3430 cm^{-1}, 2210 cm^{-1} due to NH_2, CN stretching respectively. Proton magnetic resonance spectral data also is in accord with structures assigned to compounds **3a-f** and **5a-f**.

The result of antifungal and antibacterial activity of synthesised compounds **3a-f** and **5a-f** are given in table 2. Compounds **3b**, **3d**, **3e**, **3f**, **5b**, **5d**, **5e**, **5f** shows moderate to good antifungal activity against *A.niger* species as compared to value of standard *Fluconazole* while **3a**, **3c**, **3f**, **5a**, **5d**, **5e**, **5f** shows antifungal activity against *penicillium chrysogenum* as compared to value of standard *Fluconazole.*

All the newly prepared compounds were screened for antibacterial activity against gram negative bacterial strain *E.coli* and gram positive bacterial strain *B. substilis*, the compounds **3a**, **3b**, **3c**, **3d**, **3f**, **5a**,**5b**, **5d** and **5f** shows moderate to good zone of inhibition as compared to standard *Ampicillin* against gram negative bacterial strain *E.coli* while the compounds **3a**, **3b**, **3e**, **5a**, **5b**, **5c**, **5d** and **5e** shows moderate to good zone of inhibition against gram positive bacterial strain *B. substilis* as compared to standard *Ampicillin*.

Experimental:

Material and Methods

The entire chemical used are of analytical grade and used without further purification Physical constant like melting point were taken in electro thermal IA 9000 series digital melting point apparatus and were uncorrected. All the reactions monitored by thin layer chromatography, carried out on pre-coated sheets of silica-C plates of 0.25 mm thickness using ultra violet chamber for detection. Infrared spectra were recorded in Nujol or as potassium bromide pallets on Shimadzu infrared spectrophotometer, ^{1}H-NMR spectra were taken on Brukner avance spectrophotometer 400 MHz in deuterated dimethyl sulphoxide using tetramethyl silane as internal standard, mass spectra were recorded on FT-VC-7070 H mass spectrometer using the EI technique at 70 eV. All the reactions were carried out under room condition.

General procedure

8/10-substituted 5,6-diimino thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazoles(3a-3f)

A mixture of 6-cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3,2-*a*] pyrimidine **1** (0.01 mol) and substituted 2-amnio benzothiazole **2** (0.01mol) independently in 15 mL of N, N'-dimethyl formamide and anhydrous potassium carbonate (0.005mol) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to 100 ml crushed ice. The separated solid product was filtered, washed with water and recrystallized from ethanol to give pure **3a-3f**.

2-N-phenyl substituted 3-amino-4-imino pyrazolo[3,4-*d*] thiazolo [3,2-*a*]pyrimidine (5a-5f)

A mixture of 6-cyano-5-imino-7-(methylthio)-5*H*-thiazolo [3,2-*a*] pyrimidine **1** (0.01 mol) and substituted hydrazines **4** (0.01mol) independently in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (0.005mol) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to 100 ml crushed ice. The separated solid product was filtered, washed with water and recrystallized from ethanol to give pure **5a-5f**.

5,6-diimino-10-methoxy thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazole(3c)

Brown powder, IR (KBr / cm^{-1}) 3340-3120(=NH), 2240-2170(CN); ^{1}H-NMR (DMSO-d6) δ 3.8 (s, 3H, OCH_3), 6.9-7.8(m, 5H,Ar-H),8.1-8.5(S,2H, two =NH). EI-MS (m/z: RA %): 355 (M+1,100%).

5,6-diimino thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazole(3e)

Brown powder, IR (KBr / cm^{-1}) 3340-3120(=NH), 2240-2170(CN); ^{1}H-NMR (DMSO-d6) 6.9-7.8(m, 6H,Ar-H),8.1-8.5(S,2H, two =NH). EI-MS (m/z: RA %): 325(M+1,100%).

5,6-diimino-8,10-dimethyl thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazole(3f)

Brown powder, IR (KBr / cm^{-1}) 3340-3120(=NH), 2240-2170(CN). EI-MS (m/z: RA %): 353 (M+1, 100%).

3-amino-4-imino-2-N-(3'-methyl phenyl) pyrazolo[3,4-*d*] thiazolo [3,2-*a*]pyrimidine (5c)

Brown powder, IR (KBr / cm^{-1}) 3430(NH_2), 2210 (CN); ^{1}H NMR (DMSO-d6) δ 2.6 (s, 3H, CH_3),5.8(s,2H,NH_2) 6.5-7.8(m, 6H,Ar-H),10.2(s,1H,=NH). EI-MS (m/z: RA %): 297 (M+1, 100%).

3-amino-4-imino-2-N-(2',4'-dinitro phenyl) pyrazolo[3,4-*d*] thiazolo [3,2-*a*]pyrimidine(5e)

Brown powder, IR (KBr / cm^{-1}) 3430(NH_2), 2210 (CN); EI-MS (m/z: RA %): 373 (M+1, 100%).

Anti-fungal and Anti-bacterial Activity

Antifungal and antibacterial activities were carried out by disc diffusion method using Mueller-Hinton agar medium as per procedure described by M.Turck[xviii]. Antifungal activity was taken against *A.niger* and *Penicillium chrysogenum* where as antibacterial activity against gram negative species *E.coli* gram positive species *B.substilis*. All the newly synthesized compounds were dissolved in dimethyl sulphoxide and the diameter in mm of zone of inhibition is given in table 2.

Conclusion:

In present work, we report simple method for one pot synthesis of fused substituted 5,6-diimino thiazolo[2,3-*b*]pyrimido[5,6-*e*]pyrimido[2,3-*b*]benzothiazoles and 3-amino-4-imino-2-N-substituted pyrazolo[3,4-*d*] thiazolo[3,2-*a*]pyrimidines compounds with good yield. The

antifungal and antibacterial activity of these compounds were moderate to good as compared to standard drug *Fluconazole* and *Ampicillin* , the newly synthesised compounds with on modification may act as antifungal and antibacterial agent in medicinal market in future.

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Table 1: Analytical data

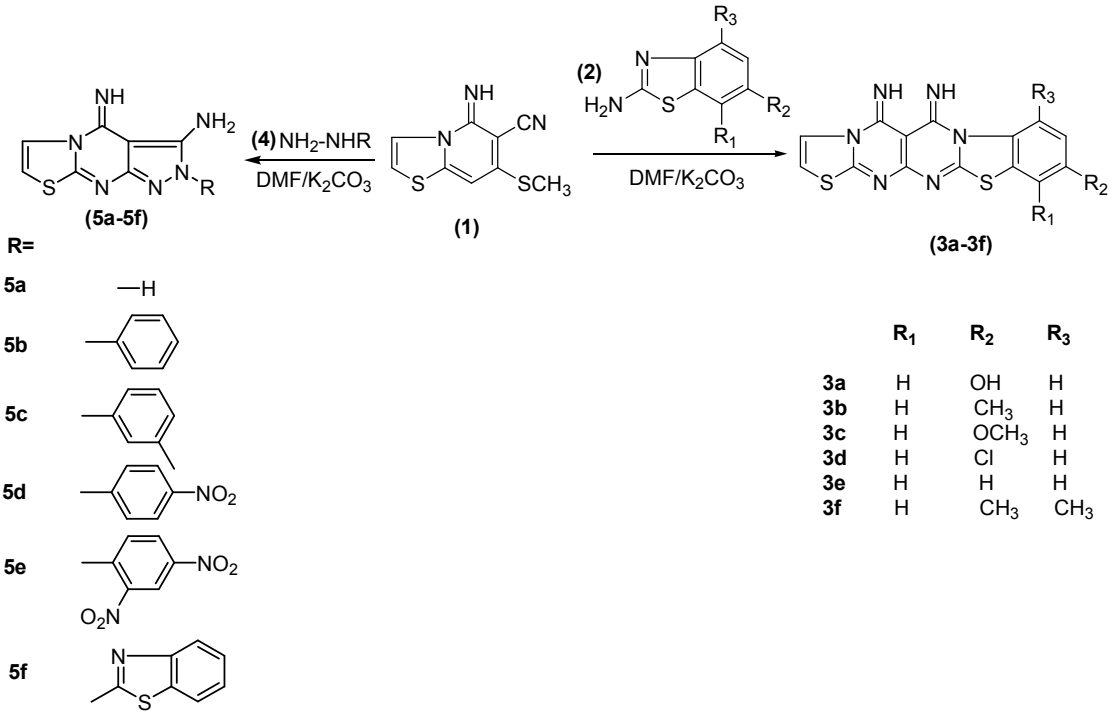
Compound	Molecular Formula	Yield (%)	Melting Point(°C)
(3a)	$C_{14}H_8N_6OS_2$	72	272
(3b)	$C_{15}H_{10}N_6S_2$	78	295
(3c)	$C_{15}H_{10}N_6OS_2$	69	281
(3d)	$C_{14}H_7ClN_6S_2$	74	222
(3e)	$C_{14}H_8N_6S_2$	65	274
(3f)	$C_{16}H_{12}N_6S_2$	79	>300
(5a)	$C_7H_6N_6S$	81	264
(5b)	$C_{13}H_{10}N_6S$	67	280
(5c)	$C_{14}H_{12}N_6S$	67	277
(5d)	$C_{13}H_9N_7O_2S$	69	269
(5e)	$C_{13}H_8N_8O_4S$	77	287
(5f)	$C_{14}H_9N_7S_2$	78	294

Table 2. Antifungal and antibacterial activity

Compound	**Diameter in mm of zone of inhibition (MIC 10 µg/ml)**			
	Antifungal activity		**Antibacterial activity**	
	A.niger	***P.chrysogenum***	***E.Coli***	***B. substilis***
(3a)	**-**	**13**	**12**	**17**
(3b)	**10**	**-**	**15**	**14**
(3c)	**-**	**10**	**10**	**-**
(3d)	**10**	**-**	**17**	**-**
(3e)	**12**	**-**	**-**	**12**
(3f)	**10**	**12**	**12**	**-**
(5a)	**-**	**10**	**17**	**10**
(5b)	**20**	**-**	**11**	**16**
(5c)	**-**	**-**	**-**	**13**
(5d)	**18**	**11**	**14**	**15**
(5e)	**14**	**10**	**-**	**11**
(5f)	**17**	**10**	**16**	**-**
Fluconazole	**18**	**22**	**-**	**-**
Ampicillin	**-**	**-**	**20**	**16**

(-)No Activity

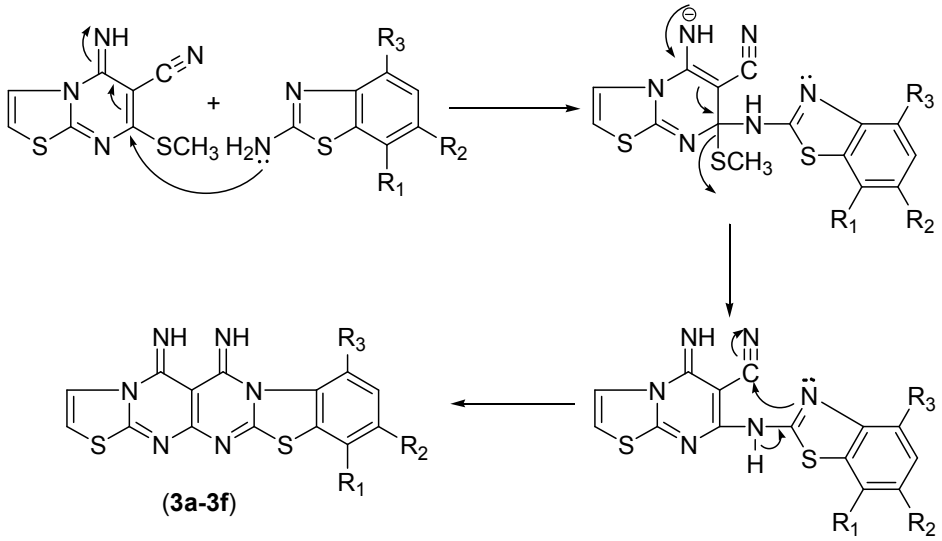
Reaction Scheme:

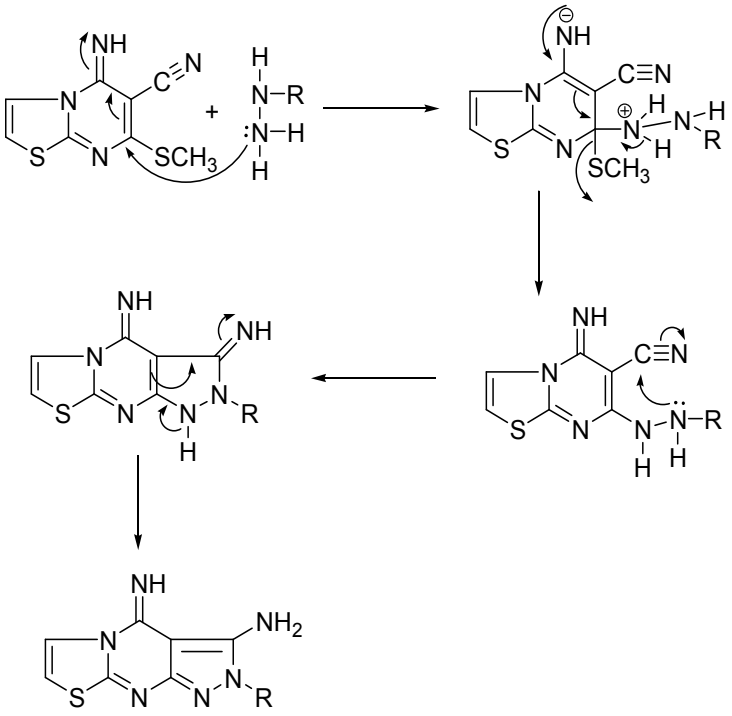


	R_1	R_2	R_3
3a	H	OH	H
3b	H	CH_3	H
3c	H	OCH_3	H
3d	H	Cl	H
3e	H	H	H
3f	H	CH_3	CH_3

Scheme 1

Mechanism:





(**5a-5f**)

Scheme 2