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SYNTHESIS OF BENZIMIDAZOLO PYRIMIDO PYRIMIDO BENZOTHIAZOLE DERIVATIVES AND STUDY OF THEIR PHARMACEUTICAL IMPORTANCE

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ABSTRACT

A mixture of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole was condensed with different substituted benzothiazole in presence of catalytic amount of anhydrous potassium carbonate and N, N'- dimethyl formamide as a reaction solvent, to get corresponding 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*]pyrimido [2, 3-*b*][1, 3] benzothiazole and their substituted derivatives. All the products were confirmed by their IR, ^{1}H NMR and mass spectroscopic measurements. All this compounds were screened for their antimcribial and antioxidant activity.

KEYWORDS

Benzothiazole, Pyrimido, Antioxidant activity and Spectroscopic measurements.

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INTRODUCTON

The bridged heterocyclic compounds which contains nitrogen and sulphur is present in bridged position has a wide scope in medicine. The fused benzimidazole, benzothiazole, pyrimido benzothiazoles are one of the compounds which contain bridged nitrogen atom. Benzimidazoles and benzothiazoles are structural analogues. Both benzimidazoles and benzothiazoles are biological interesting nucleus. These moieties are present in many medicinal drugs.

Organic chemists are very much interested in synthesis of fused benzimidazoles, pyrimidines and benzothiazoles which shows pharmacologically

active role in medicinal chemistry. That's why we are also intended to prepare the novel compounds which contain benzimidazole, benzothiazole as well as pyrimidine moieties.

A different substituted or fused benzothiazoles are used against different types of vital diseases such as antitumor[1], anticancer[2], antimalerial[3], antifungal[4], antiinflamatory[5], antihelmintic activity[6], anti-HIV activity[7], anticonvulsant activity[8], anti-allergic activity[9] and anti diabetic activity[10] etc.

The fused pyrimido benzimidazole is the three to four nitrogen containing compounds. Pyrimido benzimidazole have wide range of application in medicinal chemistry such as antimicrobial[11], antimalerial[12], T-cell activation[13], P-receptor binding agent[14], anti-inflammatory, antiamoebic and analgesic activity[15] and antioxidant[16] etc.

Owing to this interesting work, we carried out the synthesis of benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido[2, 3-*b*] [1, 3] benzothiazole by condensation of substituted pyrimido [1, 2-*a*] benzimidazole with different substituted benzothiazoles. But according to literature review study very few references are available on this compound.

METHODS

General Procedure

3-Cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3)

The parent compound, 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3) prepared by treating an equimolar mixture of 2-amino benzimidazole (0.01 mole) and ethyl-2-cyano-3, 3-bis (methylthio) acrylate (0.01mole) in 25 ml of N, N-dimethyl formamide (DMF) and anhydrous potassium carbonate (10mg) was refluxed for 5 to 6 hours (Scheme No.1).

Synthesis 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazole and their substituted derivatives (5a-g)

An equimolar mixture of 3-cyano -2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (0.01 mole) is condensed with different substituted benzothiazole (0.01 mole) in presence of catalytic amount of anhydrous potassium carbonate and N, N'- dimethyl formamide as reaction solvent (25 ml). The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from ethanol to give pure (5a-g) to get corresponding 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazole and their substituted derivatives (5a-g). (Scheme No.2).

DPPH Radical scavenging activity

The DPPH (1, 1-diphenyl-2-picryl hydrazine) radical scavenging action of different chemical compounds was measured according to the method explained by Kato et al 1998 with some modifications.

OH Radical scavenging activity

The scavenging ability of OH free radical was calculated as per the Yu et al. (2004) method with slight changes. Reaction cocktail included 60 µl of 1mM, $Fecl_3$, 90 µl of 1M 1,10-phenanthroline, 2.4 ml of 0.2 M phosphate buffer (pH 7.8), 150 µl of 0.17 M H_2O_2 and 1.5 ml different concentration of individual product.

Disc diffusion method

Kirby-Bauer method was followed for disc diffusion assay. *In vitro* antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Himedia (Mumbai). The MHA plates were prepared by pouring 15 ml of molten media into sterile petriplates. Solidification of plates were done in 5 min and 0.1 % inoculum suspension was wiped down homogeneously and the inoculum kept to dry for 5 min. The concentration of compounds were set at (10 µg/disc) were loaded on 5 mm sterile individual discs and allowed to diffuse for 5 min followed by incubation at 37°C for 24 h. Penicillin (10 µg/disc) was used as positive control. At the end of incubation, inhibition zones formed around the disc were measured with transparent ruler in millimetre.

RESULTS AND DISCUSSION

Chemistry

In present work, we have reported one pot synthesis of 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido

[5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazole (5a-g). Reaction started with 2-amino benzimidazole (1) and ethyl 2-cyano-3, 3-bis (methylthio) acrylate (2) were refluxed in N, N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afford compound (3) shown in scheme No.1.

Compound (3) posses a repliecable active methylthio group at 2- position which is a good leaving group and activated by adjacent electronegative ring nitrogen atom and negative inductive effect of cyano (-CN) group. The susceptibility of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3) towards cyclization with 2-amino benzothiazole and their different substituted derivatives have been prepared by condensing with 2-amino benzothiazole, 2-amino 6-methyl benzothiazole, 2-amino 6-methoxy benzothiazole, 2-amino 6-chlorobenzothiazole, 2-amino-6-nitro benzothiazole, 2-amino, 2-amino 6-chloro benzothiazole, 2-amino-6-fluro-7-bromo benzothiazole independently to afford 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazolesS (5a-g) given in scheme No.2.

SPECTRAL AND PHYSICAL DATA

The structures of newly synthesized compounds were confirmed on the basis of spectral analysis such as IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectra of compounds (5a-g) showed the absence of -CN stretching absorption band in the region 2214 cm^{-1} which point out that cyclization takes place and showed the presence of absorption bands between 3240-3495 cm^{-1} which can be assigned to (>NH and =NH stretch). The ^{1}H NMR showed a singlet at δ 3.8 and δ 8.7-9.7 which can be assigned to (>NH and =NH) proton. Mass spectra of compounds exhibited the molecular ion peaks which correspond to their molecular weights**.**

3-Cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3)

IR (KBr/cm-1) 1643 cm-^{1} (>CO), 2214 cm-^{1} (-CN); ^{1}H NMR (400 MHz, DMSO-*d6*) δ 2.6 (s, 3H, -SCH_3), 3.9 (s, 1H,-NH), 7.2-8.6(m, 4H,Ar-H) ppm; ^{13}C NMR (300MHz, CDCl3) δ:12.8, 111.1, 115.2, 116.0, 122.3, 122.6, 125.6, 126 , 133.1, 149.5, 157.3, 171.9 ppm; EI-MS (m/z:RA%): 256(M^+).

6-Imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazole (5a)

IR: 1658 cm^{-1}(>C=O), 3248 cm^{-1} & 3464 cm^{-1} (>NH and =NH); ^{1}H NMR : (500 MHz, DMSO) δ : 3.8 (s, 1H, -NH), 7.4 to 8.3 (m, 8H, =C-H) 8.7 (s, 1H ,=NH) ppm; Mass: m/z = 358 (M^+).

6-Imino-2-methoxy-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazole (5c)

IR: 1643 cm^{-1}(-C=O), 3358 cm^{-1} and 3464 cm^{-1} (>NH and =NH stretch); ^{1}H NMR: (500 MHz, DMSO) δ : 3.7 (s, 3H, OCH_3) 3.8 (s, 1H, -NH), 7.2 to 8.5 (m, 7H, =C-H) 9.7 (s, 1H, = NH) ppm; Mass: m/z = 388 (M^+).

ANTI-OXIDANT ACTIVITY

Both DPPH and Hydroxy radical scavenging activity of tested 6-imino-7-oxo-benzimidazolo[2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazoles (5a-5g) were in the range of 22.1 $\pm$ 0.722 to 54.5 $\pm$ 0.412% against DPPH radical and in case of hydroxyl radical in the range of 32.2 $\pm$ 0.252 to 46.9$\pm$ 0.221 as compared to the standard ascorbic acid 78.48 $\pm$ 0.29.% and 02.68 $\pm$ 0.24 respectively. Overall it could be suggested that our synthesized compounds shows good antioxidant properties which were given in Table No.1.

Antimicrobial activity

Selected compounds among newly synthesized compounds were screened for their antibacterial activity against gram-positive bacteria, *B.subtilis* and gram-negative bacteria,

E. coli using the penicillin as a standard drug.

The synthesized compounds like 5a, 5b, 5c, 5d, 5e, and 5g exhibited moderate antibacterial activity against *E. Coli* while 5f not detected in zone of inhibition. Similarly compounds 5a, 5b, 5d, 5e and 5f were exhibited good zone of inhibition against *B. subtillis* as compared with standard drug whereas compound 5c and 5g were inactive shown in below Table No.2.

S.No	Comp. No.	R_1	R_2	R_3
1	5a	-H	-H	-H
2	5b	-H	$-CH_3$	-H
3	5c	-H	$-OCH_3$	-H
4	5d	-H	$-NO_2$	-H
5	5e	-H	-F	-H
6	5f	-H	-Cl	-H
7	5g	-F	-Br	-H

Table No.1: Physico-chemical properties of newly synthesized compounds

S.No	Comp. code	Color	M.F.	M.Wt.	M.P.(^{0}C)	Yield (%)
1	3	Yellow	$C_{12}H_8N_4O_2S$	256	228230	82
2	5a	Yellow	$C_{18}H_{10}N_6OS$	358	316-318	75
3	5b	Pale Yellow	$C_{19}H_{12}N_6OS$	372	328-330	72
4	5c	Brick red	$C_{19}H_{12}N_6O_2S$	388	318-321	73
5	5d	Yellow	C18H9N7O3S	403	325-327	61
6	5e	Golden Yellow	$C_{18}H_9FN_6OS$	376	290-292	71
7	5f	Brown	$C_{18}H_9ClN_6OS$	392	300-303	68
8	5g	Dark brown	$C_{18}H_9BrN_6OS$	455	310-313	70

Table No.1: Antioxidant potential of 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazoles (5a-5g)

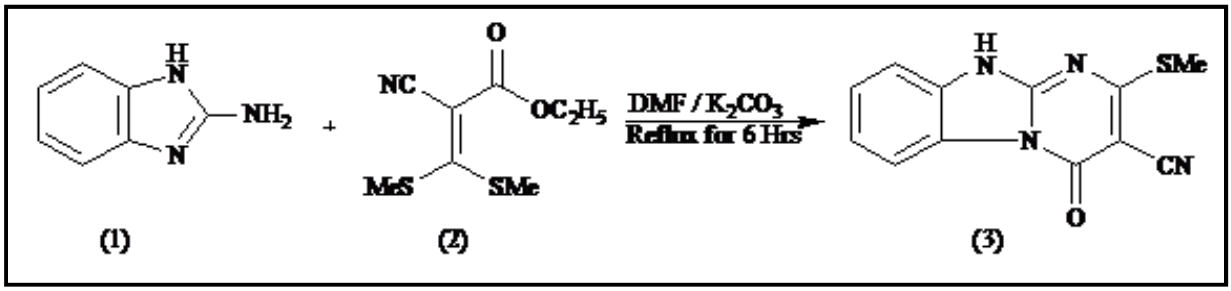
S.No	Compound	DPPH radical scavenging activity (%)	OH radical scavenging activity (%)
1	5a	45.4 $\pm$ 0.722	33.4 $\pm$ 0.142
2	5b	40.2 $\pm$ 0.531	39.2 $\pm$ 0.224
3	5c	44.4 $\pm$ 0.431	46.9$\pm$ 0.221
4	5d	54.5 $\pm$ 0.412	42.3+ 0.944
5	5e	33.1 $\pm$ 0.211	32.2 $\pm$ 0.252
6	5f	30.3 $\pm$ 0.112	33.6+ 0.342
7	5g	22.1 $\pm$ 0.722	36.6 $\pm$ 0.428
8	Ascorbic Acid	78.48 $\pm$ 0.29	02.68 $\pm$ 0.24

Table No.2: Antimicrobial activity 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazoles (5a-5g)

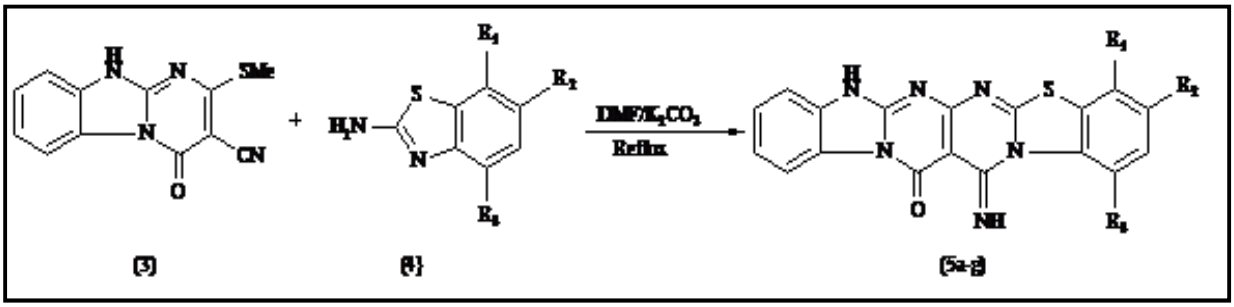
S.No	Compound code	Zone of inhibition in mm	
		E. coli	*B. subtilis*
1	5a	18	23
2	5b	16	12
3	5c	11	NR
4	5d	15	16
5	5e	19	24
6	5f	NR	21
7	5g	09	NR
8	*penicillin*	26	28

NR = No response in zone of inhibition.

Scheme No.1



Scheme No.2



CONCLUSION

In the present work we have synthesized different 6-imino-7-oxo-benzimidazolo [2, 3-*b*] pyrimido [5, 6-*e*] pyrimido [2, 3-*b*] [1, 3] benzothiazoles (5a-5g) in good yields. Selected newly synthesized derivatives were evaluated in vitro to determine their free radical scavenging activities using DPPH and OH free radical model. It is important to note that the series of novel benzimidazolo pyrimido pyrimido benzothiazole derivatives were showed comparatively good in stabilizing both the free radical as compared with the standard ascorbic acid and also exhibited good antimicrobial activity against both the bacteria *E. Coli* and *B. Subtilis* respectively.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

BIBLIOGRAPHY

1. Schnur R C, Anton F J,.Kajim F S, Pollack V A. N-(5-fluorobenzothiazol-2-yl)-2-guanidinothiazole-4-carboxamide. A novel, systemically active antitumor agent effective against 3LL Lewis Lung carcinoma, *J. Med. Chem*, 34(3), 1991, 914-918.
2. Kok S H L, Gambari R. Chui C H, Yuen M C W, Lin E, Wong R S M. Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines, *Bioorg Med. Chem.*, 16(7), 2008, 3626-3631.
3. Hout S, Azas N, Darque A, Robin M, Giorgio C, Gasquet M, Galy J and David P. Activity of benzothiazoles and chemical derivatives on Plasmodium falciparum, *Parasitology*, 129(5), 2004, 525-542.
4. Singh S P, Seghal S. *Indian J. Chem*, 27 B Pt2, 1988, 941.
5. Venkatesh P and Pandeya S N. Synthesis, Characterisation and Anti-Inflammatory activity of some 2-Amino Benzothiazole Derivatives, *International Journal of Chem Tech research,* 1(4), 2009, 1354-1358.
6. Sawhney S N, Bansal O P. *Indian Journal of Chemistry,* 15B Pt1, 1977, 121.

7. Hutchinson I, Jennings S A, Vishnuvajjala B R, Westwell A D and Stevens M F G. Antitumor benzothiazoles. 16. Synthesis and pharmaceutical properties of antitumor 2-(4-aminophenyl)benzothiazole amino acid prodrugs, *J. Med. Chem,* 45(3), 2002, 744-747.
8. Siddiqui N, Pandeya S N, Khan S, Stables J, Rana A, Alam M, Arshad M and Bhat M. Synthesis and anticonvulsant activity of sulfonamide derivatives-hydrophobic domain, *Bioorganic and Medicinal Chemistry Letters*, 17(1), 2007, 255-259.
9. Musser J H, Brown R E, Love B, Baily K, Jones H, Kahen R, *et al.* Synthesis of 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl) benzo heterocycles. A novel series of orally active antiallergic agents, *J. Med. Chem*istry, 27(2), 1984, 121-125.
10. Pattan S R, Suresh C, Pujar V D, Reddy V V K, Rasal V P, Koti B B. Synthesis and Antidiabetic activity of 2-amino[5'(4-sulphonylbenzylidine)-2, 4- thiazolidione]-7-chloro-6-fluorobenzothiazole, *Indian Journal of Chemistry*, 44B, 2005, 2404-2408.
11. Abdelhamid Abdou O, Abdelall Emam, Abdel-Riheem K A, Nadia A. Ahmed sayed. Phosphorous, *sulphur and silicon and the related elements*, 185(4), 2010, 709-718.
12. Werbel L M, Curry A, Elslager E F, Hess C A, Hutt M P, Youngstrom C. *Journal of Heterocyclic Chemistry*, 6(6), 1969, 787-96.
13. Nunes J J, Zhu X T, Amouzegh P, Ghiron C, Johnston D N, Power E C. *Chemical Abstract,* 142, 2005, 198088.
14. Bhaskar R. Venepalli, Lisa D. Aimone, Kenneth C. Appel, Malcolm R. Bell, John A. Dority, Ramanuj Goswami, Patricia L. Hall, Virendra Kumar, Kristine B. Lawrence. Synthesis and substance P receptor binding activity of androstano[3,2-b]pyrimido[1,2-a]benzimidazoles, *J. Med. Chem*, 35(2), 1992, 374–378.
15. Sham M. Sondhi, Shefali Rajvanshi, Monika Johar, Neelam Bharti, Amir Azam, Ashok Kumar Singh. Anti-inflammatory, analgesic and antiamoebic activity evaluation of pyrimido[1, 6-a]benzimidazole derivatives synthesized by the reaction of ketoisothiocyanates with mono and diamines, *European Journal of Medicinal Chemistry*, 37(10), 2002, 835-843.
16. Neochoritis C G, Zarganes-Tzitzikas T, Tsoleridis C A, Stephanidou-Stephanatou J, Kontogiorgis C A, Hadjipavlou-Litina D J, Choli-Papadopoulou T. One-pot microwave assisted synthesis under green chemistry conditions, antioxidant screening, and cytotoxicity assessments of benzimidazole Schiff bases and pyrimido[1,2-a]benzimidazol-3(4H)-ones, *European Journal of Medicinal Chemistry,* 46(1), 2011, 297-306.

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