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Synthesis of 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole derivatives and evaluation of their biological activity

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Abstract

The broad spectrum biological importance of sulphur and nitrogen containing heterocycles were constantly encouraged chemists to synthesize their large number of derivatives during last few decades. one of the most significant compound among these are benzothiazole derivatives which was found to be biologically and medicinally potent. in this study we condensed a mixture of 3-cyano-2-methylthio-6-methyl-4, 8-dioxo-9H-pyrimido [1, 2-a] pyrimidine and differently substituted benzothiazoles in the incidence of K_2CO_3 and DMSO as a reaction solvent, to get corresponding 14-imino-11-methyl-9, 13-dioxo-8H-pyrimido [1, 2-a] pyrimido - pyrimido [2, 1-b] [1, 3] benzothiazole derivatives. All the products were confirmed on the basis of IR, ^1H NMR and mass spectroscopic techniques and evaluate their biological activity.

Keywords: Potassium carbonate, Nitrogen, benzothiazoles**,** Biological activity, Spectroscopic techniques.

Introduction

Benzothiazoles derivatives are significant class of fused heterocycles due to their extensive range of biological and pharmacological potential, in addition to this its value in the synthesis of drug molecules and natural products. It shows anti-inflammatory[1], analgesic[2], antioxidant[3], antidiabetics[4], antimicrobial[5], antituberculosis[6], vasodilator[7], antitumor[8], antiproliferative[9], anticancer activity[10]. Vartale S.P. et. al.[11] achieved the synthesis of Pyrido [1, 2-a] pyrimido [5, 6-e] pyrimido [2, 3-*b*] benzothiazole derivatives starting from pyrido [1, 2-*a*] pyrimidine and 2-amino substituted benzothiazoles. Serkan Yavuz et. al[12] extended the synthesis of 4-imino-3, 4-dihydro-2H-pyrimido [2, 1-b][1, 3] benzothiazole-2-one. A very few references and wide biological significance inspire us to synthesize some pyrimido-benzothiazole derivatives.

Materials and methods

Material: Each and every chemicals utilized in the present research works are from A.R. grade and used without further purification. M.P of the products was determined in open tube on an electrothermal instrument. All the reactions were monitored by TLC. IR spectra were recorded on Shimadzu FT-IR spectrophotometer, ^{1}H-NMR spectra were obtained on Bruker avance spectrophotometer 500 MHz in DMSO-d6 using tetramethylsilane as an internal standard. Mass spectra were recorded on GC-MS spectrometer using the ESI technique.

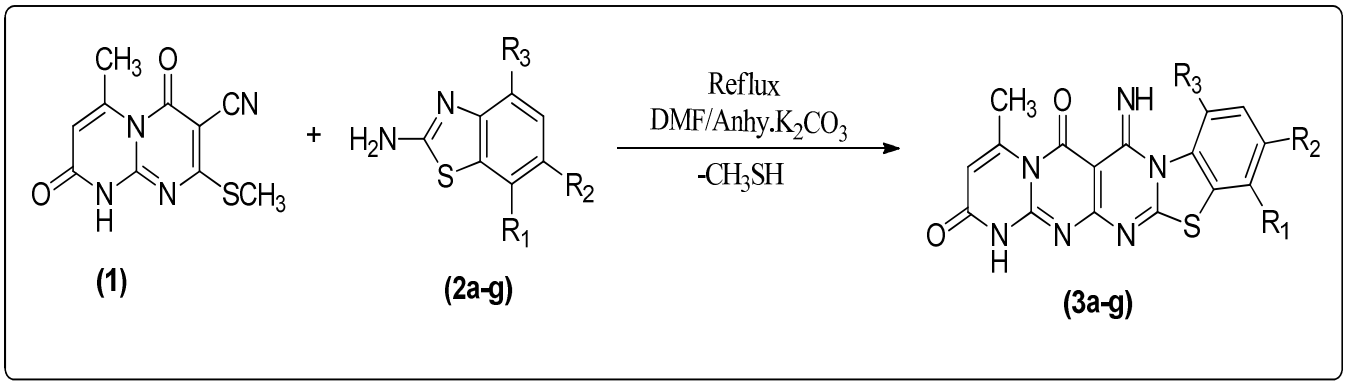
General Procedure: Synthesis of 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole and their 1/3/4 substituted derivatives (5B.12a-g): A parent compound (1) (0.001 mol) treated independently with 2-aminobenzothiazole (2a), 2-amino-6-methylbenzothiazole(2b), 2-amino-6-methoxy-benzothiazole (2c), 2-amino-7-methyl -6-nitrobenzothiazole(2d), 2-amino-6-fluoro-benzothiazole(2e), 2-amino-6-chlorobenzothiazole (2f), 2-amino-6-bromo-4-flurobenzothiazole (2g), (0.001 mol) in 15 ml of DMF as a boiling solvent and anhydrous K_2CO_3 (10 mg) catalyst were refluxed for 4-5 hours.

The reaction material was cooled and added to the crushed ice. The separated solid products were filtered, wash down and clean with water and recrystalized from ethanol to give pure (3a-g) respectively.

Result and discussion

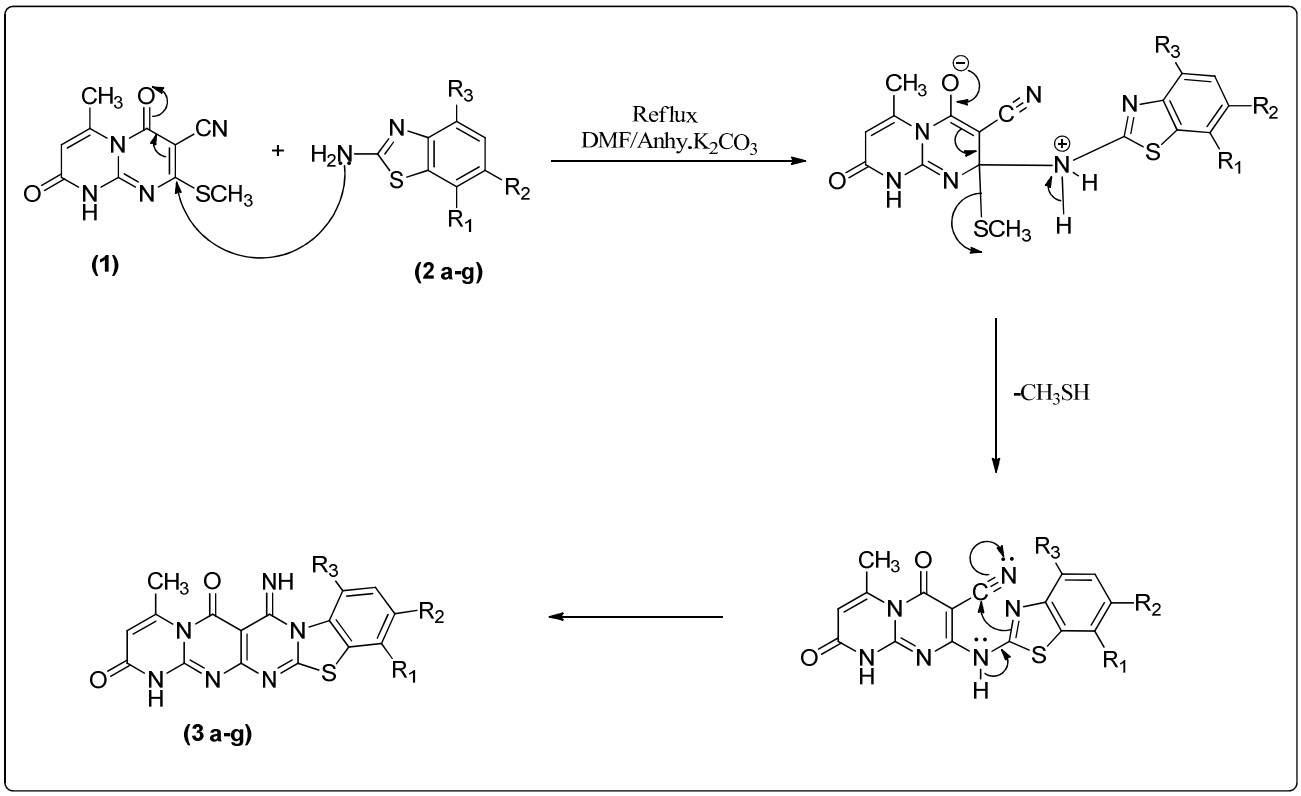
In the present research, we reported one pot synthesis of 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole and their 1/3/4 substituted derivatives (3a-g). The reaction started with 3-cyano-2-methylthio-6-methyl-4, 8-dioxo-9*H*-pyrimido [1, 2-*a*] pyrimidine (1) and differently substituted amino benzothiazoles (2a-g) in DMF and K_2CO_3 to get corresponding target compounds (3a-g).

The reaction start on with opening attack of amino group of benzothiazole derivatives on dynamic carbon bounded to $-SCH_3$ group end result in the loss of $-SCH_3$ group in the form of $-CH_3SH$. The resultant amine polarizes and attack on carbon of cyano group to give ring product (3a-g).



R1 = – H, – H, – H, – H, – H, – H, – F
R2 = – H, – CH_3 – OCH_3 – NO_2, – F, – Cl, – Br
R3 = – H, – H, – H, – CH_3, – H, – H, – H,

Scheme-1: Synthesis of 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole and their 1/3/4 substituted derivatives (3a-g).



Scheme-2: A plausible mechanism of formation of 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole and their 1/3/4 substituted derivatives (3a-g).

All structure of novel ring substances (3a-g) were established on the foundation of spectral data, The IR spectra of compounds (3a-g) demonstrate the missing of cyanide stretching absorption band in the region 2206 cm^{-1} which indicates that ring formation took place and showed the IR spectrum in the region of 3282-3298 cm^{-1} to (=NH). The ^1H NMR spectra exhibited a singlet at δ 12 to 12.5 which can be assigned to (=NH) proton.

14-imino-11-methyl-9,13-dioxo-*8H*-pyrimido[1,2-*a*]pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole (3a). Color: Brown solid. Yield:70%. M.P: 315^0C - 318^0C. M.W. 350. M.F. $C_{16}H_{10}N_6O_2S$. IR: 3282 cm^{-1}(=NH), 1670, 1724 cm^{-1}(>C=O strech), 1454-1639(aromatic C=C strech). ^{1}HNMR: (500 MHz, DMSO-d_6) δ: 2.5 (s, 3H, -CH_3), 7.9 (s, 1H,C-NH), 5.8 (s, 1H,

ethylene C-H), 12.5 (s, 1H,=NH) 6.7-7.7 (m, 4H, Ar-H), ppm; Mass:m / z= 351 (M+1).

14-imino-3,11-dimethyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*]pyrimido[2, 1-*b*] [1, 3] benzothiazole (3b). Color: Brown solid, Yield: 64%, M.P: 310-312°C, M.W. 364, M.F. $C_{17}H_{12}N_6O_2S$

14-imino-3-methoxy-11-dimethyl-9,13-dioxo-*8H*-pyrimido [1,2-*a*] pyrimido[4,5-*d*] pyrimido[2, 1-*b*] [1, 3] benzothiazole (3c). Color: Faint brown solid, Yield:68%, M.P:305^{0}C - 307^{0}C, M.W. 380, M.F.$C_{17}H_{12}N_6O_3S$, IR: 3191,3298cm^{-1}(-NH, =NH), 1675,1738cm^{-1}(>C=O strech), 1438-1601(aromatic C=C strech). ^{1}HNMR: (500 MHz, DMSO-d_6) δ: 2.8 (s, 3H, -CH_3), 3.7 (s, 3H, -OCH_3), 8 (s, 1H, C-NH), 5.2 (s 1H, ethylene C-H), 12.0(s, 1H,=NH) 7.2-7.6 (m, 3H, Ar-H), ppm; Mass:m/z= 381 (M+1).

14-imino-1,11-dimethyl-3-nitro-9,13-dioxo-*8H*-pyrimido[1,2-*a*]pyrimido[4,5-*d*]pyrimido [2, 1-*b*] [1, 3] benzothiazole(3d). Color: Dark brown solid, Yield: 74 %, M.P: 321-323°C, M.W. 409, M.F. $C_{17}H_{11}N_7O_4S$.

14-imino-3-fluoro-11-methyl-9,13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4,5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole(3e). Color: Brown solid, Yield: 67 %, M.P: 306-308°C, M.W. 368, M.F. $C_{16}H_9FN_6O_2S$

3-chloro-14-imino-11-methyl-9,13-dioxo-*8H*-pyrimido[1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole(3f). Color: Brown solid, Yield: 69%, M.P: 317-320°C, M.W. 384, M.F. $C_{16}H_9ClN_6O_2S$

3-bromo-14-imino-4-fluoro-11-methyl-9,13-dioxo-*8H*-pyrimido[1,2-*a*]pyrimido[4,5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole (3g). Color: Yellow solid, Yield: 65%, M.P: 322-325°C, M.W. 447, M.F. $C_{16}H_8BrFN_6O_2S$.

Antioxidant activity: The DPPH radical scavenging assay has been used for preliminary screening of the samples for antioxidant activity**.** The DPPH radical scavenging activity done by proton radical mechanism, the DPPH radical becomes paired with hydrogen then it changes purple color turns into yellow color with strong absorption maximum at 517nm using standard Ascorbic acid (78.48 ± 0.13) drug.

The overall DPPH radical scavenging activity of tested benzothiazole derivatives were in a range of 16.31±0.60 to 29.67±0.51 % as compared to the standard ascorbic acid (78.48 ± 0.13 %).

The novel synthesized compounds 3a, 3b, 3c, 3d, 3e, 3f and 3g shows good DPPH radical scavenging activity as compared with Ascorbic acid (78.48 ± 0.13 %). It is important to note that highest DPPH radical scavenging activity was exhibited by compound 3a is (29.67±0.51).

Table-1: Antioxidant potential of pyrimido – benzothiazoles.

Sr. No	Compound	DPPH radical scavenging activity (%)
1	3a	29.67±0.51
2	3b	21.34±0.44
3	3c	16.31±0.60
4	3d	20.74±0.52
5	3e	18.30±0.62
6	3f	22.12±0.73
7	3g	17.56±0.77
8	**Ascorbic Acid**	**78.48 ± 0.13**

Conclusion

In the present work we synthesized 14-imino-11-methyl-9, 13-dioxo-*8H*-pyrimido [1, 2-*a*] pyrimido [4, 5-*d*] pyrimido [2, 1-*b*] [1, 3] benzothiazole and their 1/3/4 substituted derivatives (3a-g) excellent quantity. Selected novel analogues were determined their free radical scavenging activities using DPPH free radical model. It is significant to note that benzothiazole derivatives were comparatively good in stabilizing the DPPH free radical as compared with the standard ascorbic acid.

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