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An Efficient method for Synthesis of Novel Iminothiazolo Pyrimidines and Plausible Antioxidant Potential

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Abstract

2-aminothiazole on treatment with bis(methylthio)methylene malononitrile in *N, N'*-dimethyl formamide (DMF) and anhydrous potassium carbonate afforded 6-Cyano-5-imino-7-(methylthio)-*5H*-thiazolo[3,2-*a*] pyrimidinewhich on further reacted with selected N–, O– and C–nucleophiles such as aryl and heteryl amines, substituted phenols and compounds with an active methylene group and synthesized 7-substituted derivatives of 6-Cyano-5-imino-*5H*-thiazolo [3,2-*a*] pyrimidine. These newly synthesized derivatives were further screened for their antioxidant potential.

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2-aminothiazole, bis(methylthio)methylene malononitrile.

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INTRODUCTION

The synthesis of condensed fused heterocyclic compounds is an important task for heterocyclic chemist from pharmacological effectiveness point of view. The survey of literature reveals that, fused heterocyclic compounds especially pyrimido fused compounds shows pharmacological properties like antimicrobial [1-2], anti-inflammatory, antituberculosis[3] andantitumor[4]. Additionally condensed fused pyrimidine exhibited important activities likepesticides[5], herbicides[6], and plant growth regulators[7].Heterocyclic compounds containing thiazole rings represent a very important group of organic compounds, which are also found in

certain natural productssuch as vitamin B1 (thiamine) and the penicillin thiazoles.In fusion with other aromatic systems thiazole ring is also potential bioactive scaffolds such as Riluzole(A)-a benzothiazole analogue is known to intervene in epilepsy[8]. Thiazole ring system is an important class of compounds in medicinal chemistry. This structure has found applications in drug development for the treatment of cardiotonic[9], fungicidal[10], HIV infection[11], mental retardation in children, age related and neurodegenerative brain damage (Alzheimer is disease, Parkinsonism disease).Various thiazole derivatives have been reported to posses broad spectrum of pharmacological activities like antidiabetic[12], CNS depressant[13], analgesic[14], antifilarial[15], antifungal &antibacterial[16]activity. Thiazoles obtained from microbial and marine origins were found to exhibit antitumor and antiviral activities[17]. The present investigation was based on careful and extensive review on literature available with an aim to synthesize new bioactive fused thiazolo pyrimidine derivatives. The compound 3 was prepared by the reaction of 2-amino thiazole 1 reaction with bis(methylyhio) methylene malononitrile 2 in presence of *N, N*'-dimethyl formamide (DMF) and anhydrous potassium carbonate Scheme-1. A plausible mechanism for the formation of parent compound 3can be adduced as shown in Scheme-2. Compound 3 possesses an active methylthio group at the 7-position that is activated by the ring 1-nitrogen atom and the electron withdrawing 6-cyano group. Compound 3 was reacted with selected N-, O-, and C-nucleophiles like aryl amines, substituted phenols, heteryl amines and compound containing active methylene group. Hence, compound 3 independently react with different substituted anilines, substituted phenols, active methylene compounds and heteryl amines in presence of N, N'-dimethyl formamide (DMF) and anhydrous potassium carbonate affords new compounds 4a-c,5a-c,6a-6c,7a-7c.Scheme 3.

MATERIAL AND METHODS

Melting points were determined by open capillary tubes and were uncorrected. All the reactions monitored by thin layer chromatography, carried out on 0.2 mm silica gel-C plates using iodine vapors for detection. Infrared spectra were recorded in Nujol or as potassium bromide pallets on infrared spectrophotometer, nuclear magnetic resonance spectra were obtained on brukner avance spectrophotometer 400 MHz, 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 ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

General procedure

6-Cyano-5-imino-7-(methylthio)-5H-thiazolo[3,2-*a*]pyrimidine (3)

A mixture of 2-aminothiazole (1) (0.01 mol) and bis(methylthio) methylene malanonitrile (2) (0.01 mol) in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 6 hours. 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 recrystallized from N, N'- dimethyl formamide- ethanol mixture to give pure (3).

7-Substituted derivative of 6-Cyano-5-imino-5H-thiazolo [3,2-*a*] pyrimidine(4a-7c)

A mixture of 3 (0.001 mol) and independently with aromatic amines, aromatic Phenols, Active methylene groups, Hetryl amines (0.001mol) in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 6 hours. 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 recrystallized from N, N'- dimethyl formamide- ethanol mixture to give pure (4a-7c).

6-Cyano-7-(methylthio)-5-Imino-5H-thiazolo[3,2-*a*]pyrimidine (3)

Brown powder, Yield 80 %, M.P.194-196 °C (dec.). IR (KBr / cm^{-1}) 3522 (=NH), 2210 (CN); ^1H NMR (400

MHz, DMSO-d_6) δ 2.62 (s, 3H, SCH_3), 7.4-8.0 (dd, 2H, J=6.2-7.6 Hz), 8.2 (br s, 1H, =NH). EI-MS (m/z: RA %): 222 M^+ 100%). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 16, 79, 98, 116,144,163,164,165, Anal. Calcd. For: $C_8H_6N_4S_2$; C, 43.23; H, 2.72; N, 25.20. Found: C, 43.02; H, 2.42; N, 24.90.

6-Cyano-5-imino-7-(p-toluidino)-5H-thiazolo [3,2-*a*]pyrimidine (4a)

Brown powder, Yield 85 %, M.P. 204-206°C (dec.). IR (KBr / cm^{-1}) 3345 (=NH), ^1H NMR (400 MHz,DMSO-d_6) δ 2.5 (s, 3H, Ar-CH_3), 4.1(s, 1H, -NH), 5.6-6.1 (dd, 2H,-CH=CH-), 6.3-7.2(m, 4H, Ar-H), 8.6 (s, 1H, =NH). EI-MS (m/z: RA %): 281. Anal. Calcd. For $C_{14}H_{11}N_5S$: C, 59.77; H, 3.94; N, 24.89. Found: C, 59.30; H, 3.52; N, 24.61.

6-Cyano-5-imino-7-(p-anisidino)-5H-thiazolo [3,2-*a*]pyrimidine (4b)

Brown powder, Yield 88 %, M.P.140°C (dec.). IR (KBr/cm^{-1}) 3532 (=NH). ^1H NMR (400 MHz,DMSO-d_6) δ 3.6 (s, 3H, Ar-OCH_3), 4.3 (s, 1H, -NH), 5.1-6.5 (dd, 2H,-CH=CH-), 6.2-7.1 (m, 4H, Ar-H), 8.7 (s, 1H, =NH). EI-MS (m/z: RA %): 298 M+1. Anal. Calcd. For $C_{14}H_{11}N_5OS$: C, 56.55; H, 3.73; N, 23.55; Found: C, 56.25; H, 3.33; N, 23.21.

6-Cyano-5-imino-7-(p-chloro anilino)-5H-thiazolo [3,2-*a*]pyrimidine(4c)

Brown powder, Yield 79 %, M.P.197-199°C (dec.). IR (KBr / cm^{-1}) 3552 (=NH). ^1H NMR (400 MHz, DMSO-d_6) δ 4.2 (s, 1H, -NH), 5.1-6.2 (dd, 2H,-CH=CH-), 6.4-7.4(m, 4H, Ar-H), 8.6 (s, 1H, =NH). EI-MS (m/z: RA %): 302 M+1. Anal. Calcd. For $C_{13}H_8ClN_5S$; C, 51.74; H, 2.67; N, 23.21. Found: C, 51.32; H, 2.31; N, 21.98.

6-Cyano-5-imino-7-phenoxy-5H-thiazolo [3,2-*a*]pyrimidine(5a)

Brown powder, Yield 87 %, M.P.203°C (dec.).IR (KBr/cm^{-1}) 3546 (=NH). ^1H NMR (400 MHz, DMSO-d_6) δ 5.2-6.3 (dd, 2H,-CH=CH-), 6.1-7.6 (m, 5H, Ar-H), 8.7 (s, 1H, =NH). EI-MS (m/z: RA %): 268. Anal. Calcd. For: $C_{13}H_8N_4OS$;C, 58.20; H, 3.01; N, 20.88. Found: C, 57.89; H, 2.76; N, 20.52.

6-Cyano-5-imino-7-(p-methoxy phenoxy)-5H-thiazolo [3,2-*a*]pyrimidine (5b)

Brown powder, Yield 79 %, M.P.207°C (dec.). IR (KBr/cm^{-1}) 3552 (=NH). ^1H NMR (400 MHz, DMSO-d_6) δ 5.2-6.1 (dd, 2H, -CH=CH-), 6.4-7.8 (m, 4H, Ar-H), 8.6 (s, 1H, =NH). EI-MS (m/z: RA %): 298; Anal. Calcd. For $C_{14}H_{10}N_4O_2S$: C, 56.37; H, 3.38; N, 18.78; Found: C, 56.06; H, 3.27; N, 18.42.

6-Cyano-5-imino-7-(o-chloro phenoxy)-5H-thiazolo [3,2-*a*]pyrimidine (5c)

Brown powder, Yield 74 %, M.P.197°C (dec.). IR (KBr/cm^{-1}), 3543 (=NH). ^1H NMR (400 MHz, DMSO-d_6)δ 5.3-6.2 (dd, 2H, -CH=CH-), 6.5-7.6(s, 4H,Ar-H), 8.5 (s, 1H, =NH). EI-MS (m/z: RA %): 302; Anal. Calcd. For: $C_{13}H_7ClN_4OS$; C, 51.58; H, 2.33; N, 18.51. Found: C, 51.20; H, 2.01; N, 18.14.

6-Cyano-5-imino-7-malonyl-5H-thiazolo [3,2-*a*]pyrimidine (6a)

Brown powder, Yield 74%, M.P.214°C (dec.).IR (KBr/cm^{-1}), 3535(=NH), 2208 (CN), ^1H NMR (400MHz, DMSO-d_6), δ 3.1 (s, 1H, -CH-), 5.1-6.0 (dd, 2H, -CH=CH-), 8.4 (s, 1H, =NH) . EI-MS (m/z: RA %):241 (M+I).Anal. Calcd. For: $C_{10}H_4N_6S$; C, 49.99; H, 1.68; N, 34.98. Found: C, 49.45; H, 1.38; N, 34.54.

6-Cyano-5-imino-7-ethyl acetoacetyl-5H-thiazolo [3,2-*a*]pyrimidine (6b)

Brown powder, Yield 72 %, M.P.216°C(dec.).IR (KBr/cm^{-1}) 3564(=NH). ^1H NMR (400 MHz, DMSO-d_6), 1.5(t, 3H,-CH_3), 2.8 (s, 3H,-$COCH_3$), 3.9 (s, 1H,-CH-), 4.3 (q, 2H, -CH_2-),5.2-6.2 (d d, 2H,-CH=CH-), 8.4 (s, 1H, =NH) . EI-MS (m/z: RA %): 304. Anal. Calcd. For: $C_{13}H_{12}N_4O_3S$; C, 51.31; H, 3.97; N, 18.41; Found: C, 51.01; H, 3.45; N, 18.03.

6-Cyano-5-imino-7-ethyl cyanoacetyl-5H-thiazolo [3,2-*a*]pyrimidine (6c)

Brown powder, Yield 80 %, M.P.210°C (dec.).IR (KBr/cm^{-1}) 3560 (=NH). ^1H NMR (400MHz, DMSO-d_6), 1.2 (t, 3H,-CH_3), 4.1 (s,1H,-CH-), 4.4 (q, 2H, -CH_2-), 5.1-6.4 (dd, 2H, -CH=CH-), 8.6 (s, 1H, =NH) . EI-MS (m/z: RA %): 287. Anal. Calcd. For:

$C_{12}H_9N_5O_2S$; C, 50.17; H, 3.16; N, 24.38; Found: C, 50.02; H, 3.07; N, 24.13.

6-Cyano-5-imino-7-pyrolidino-5H-thiazolo [3,2-*a*]pyrimidine (7a)

Brown powder, Yield 74 %, M.P.220°C (dec.).IR (KBr/cm^{-1}) 3548 (=NH). ^{1}H NMR (400MHz, DMSO-d_6), 1.6 (d,4H,-CH_2-), 2.9 (d,4H,-NCH_2-), 5.2-6.3 (dd, 2H, -CH=CH-), 8.5 (s, 1H, =NH). EI-MS (m/z: RA %): 245. Anal. Calcd. For: $C_{11}H_{11}N_5S$; C, 53.86; H, 4.52; N, 28.55; Found: C, 53.28; H, 4.02; N, 28.05.

6-Cyano-5-imino-7-piperidino-5H-thiazolo [3,2-*a*]pyrimidine (7b)

Brown powder, Yield 77 %, M.P.216°C (dec.).IR (KBr/cm^{-1}) 3558 (=NH). ^{1}H NMR (400MHz, DMSO-d_6), 1.8 (m,6H,-CH_2-), 2.6 (d,4H,-NCH_2-), 5.1-6.2 (dd, 2H, -CH=CH-), 8.8 (s, 1H, =NH). EI-MS (m/z: RA %): 259. Anal. Calcd. For: $C_{12}H_{13}N_5S$; C, 55.58; H, 5.05; N, 27.01; Found: C, 55.18; H, 4.61; N, 26.52.

6-Cyano-5-imino-7-morpholino-5H-thiazolo [3,2-*a*]pyrimidine (7c)

Brown powder, Yield 86 %, M.P. 214-215°C (dec.).IR (KBr/cm^{-1}) 3546 (=NH). ^{1}H NMR (400 MHz, DMSO-d_6), 2.9 (d, 4H,-NCH_2-), 3.8 (d, 4H,-OCH_2-), 5.0-6.4 (dd, 2H, -CH=CH-), 8.3 (s, 1H, =NH). EI-MS (m/z: RA %): 261. Anal. Calcd. For: $C_{11}H_{11}N_5OS$; C, 50.56; H, 4.24; N, 26.80; Found: C, 50.02; H, 3.74; N, 26.44.

RESULTS AND DISCUSSION

The results of antioxidant potential of novel synthesized thiazolo pyrimidine compounds are summarized in Table 1. The efficacy of antioxidant potential was determined in terms of percent DPPH and OH radical scavenging assay. The DPPH radical scavenging assay has been used for preliminary screening of the samples for antioxidant activity. The proton radical scavenging action is known as an important mechanism of antioxidants. The overall DPPH radical scavenging activity of tested thiazolo pyrimidine compounds were in a range of 14.89± 1.35 to 51.09± 0.85 % as compared with the standard ascorbic acid (78.45 ± 0.17 %). The highest proton radical scavenging activity was exhibited by 6-Cyano-7-(ethyl cyanoacetyl)-5-imino-*5H*-thiazolo [3,2-*a*]pyrimidine while 6-Cyano-7-(ethyl acetoacetyl)-5-imino-*5H*-thiazolo [3,2-*a*]pyrimidine demonstrated minimum activity. Out of twelve tested compounds, compound 6-Cyano-7-(p-toluidino)-5-imino-*5H*-thiazolo [3,2-*a*]pyrimidine and 6-Cyano-7-(p-chloro anilino)-5-imino-*5H*-thiazolo [3,2-*a*]pyrimidine failed to stabilize proton radical under experimental condition.

The perusal of Table 1 clearly indicates comparatively good OH radical scavenging activity of newly synthesized thiazolo pyrimidine compounds in a range of 71.88± 0.89 to 301.17± 1.67 % as compared with standard ascorbic acid (02.82 ± 0.42 %). The 6-Cyano-7-(o-chloro phenoxy)-5-imino-*5H*-thiazolo [3,2-*a*]pyrimidine demonstrated highest OH radical scavenging activity (301.17 ± 1.67 %). It is imperative to state that the series of thiazolo pyrimidine compounds were comparatively good in stabilizing the hydroxyl free radical as compared with the proton radical stabilization. In light of present work it can firmly concluded that the thiazolo pyrimidine fused derivatives are essential to boost the antioxidant activity. The present investigation opens a path for researchers to find out the different plausible pharmacological activities by using or modifying the novel series of thiazolo pyrimidine compounds.

Antioxidant Activity

1) DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay

DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay was carried out as per reported method[18]. In brief, 1 ml(1 mM) of the test sample is added to equal quantity ofo.1 mM solution of DPPH in ethanol. After 20 min of incubation at room temperature, the DPPH reduction was measured by reading the absorbance at 517 nm. Ascorbic acid (1 mM) was used as the reference compound.

2) OH radical scavenging assay

The OH radical scavenging activity was demonstrated with Fenton's reaction[19-20]. The reaction mixture contained, 60 µl of $FeCl_2$ (1 mM), 90 µl of 1–10

phenathroline (1 mM), 2.4 ml of phosphate buffer (0.2 M, pH7.8), 150 µl of H_2O_2 (0.17 M) and 1.5 ml of individual compound (1 mM). The reaction was started by adding H_2O_2.After 5 min. incubation at room temperature, the absorbance was recorded at 560 nm. Ascorbic acid (1 mM) was used as a reference compound.

CONCLUSION

It is concluded that the present work provides a convenient and efficient route for the preparation of new thiazolo [3,2-*a*] pyrimidine derivatives. The results of the present study may serve as a ready reference for the researchers to take advantage of proficient procedure applied for the synthesis of novel series of derivatives and further plausible modifications which will augment the therapeutic potential of thiazolo [3,2-*a*] pyrimidine derivatives.

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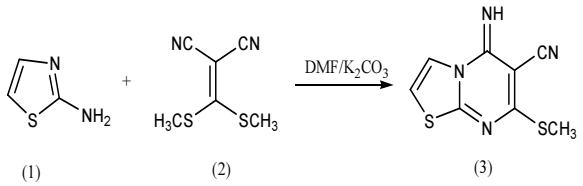
***Table* 1.** Antioxidant potential of tested thiazolo pyrimidine compounds.

Sr. No.	Compound Tested	Antioxidant Potential (%)	
		DPPH radical scavenging activity	OH radical scavenging activity
1	4a	NR	176.17 ± 1.47
2	4b	16.85 ± 0.15	178.13 ± 0.69
3	4c	NR	198.05 ± 0.58
4	5a	23.70 ± 1.11	71.88 ± 0.89
5	5b	22.61 ± 1.54	116.80 ± 1.87
6	5c	16.52 ± 0.45	301.17 ± 1.67
7	6a	26.09 ± 0.47	NR
8	6b	14.89 ± 1.35	266.41 ± 0.79
9	6C	51.09 ± 0.85	117.19 ± 0.97
10	7a	NR	77.52 ± 1.68
11	7b	NR	NR
12	7c	NR	72.87 ± 1.25
13	Ascorbic acid (Vit. C)	78.45 ± 0.17	02.82 ± 0.42

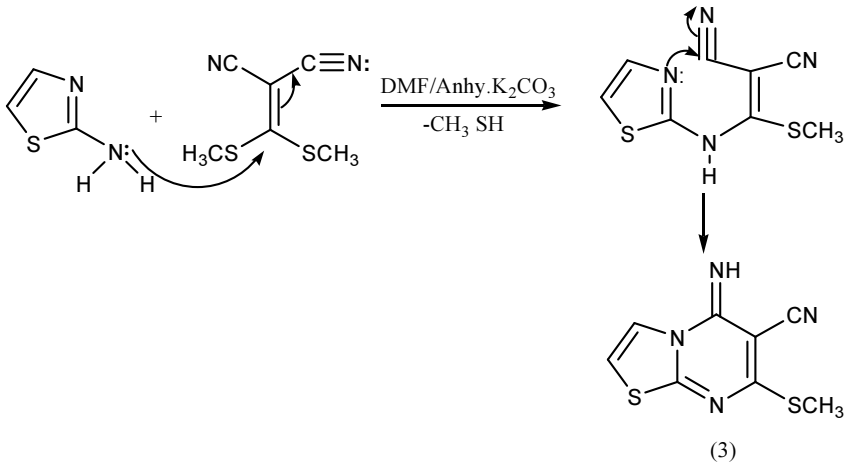
Results presented here are the mean values from three independent experiments ± S.D., NR = No reaction under experimental condition

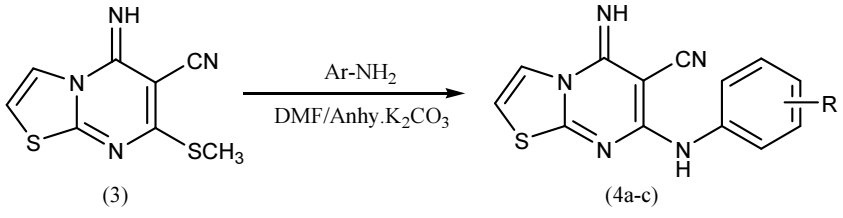


Scheme

Plausible reaction mechanism for the formation of 6-Cyano-5-imino-7-(methylthio)-*5H*-thiazolo[3,2-*a*] pyrimidine

Mechanism of 6-Cyano-5-imino-7-(methylthio)-*5H*-thiazolo[3,2-*a*] pyrimidine



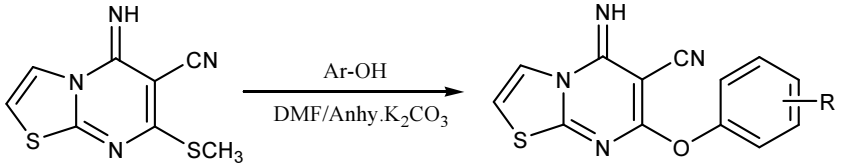


(3) (4a-c)

4a H_2N–C_6H_4–CH_3

4b H_2N–C_6H_4–OCH_3

4c H_2N–C_6H_4–Cl

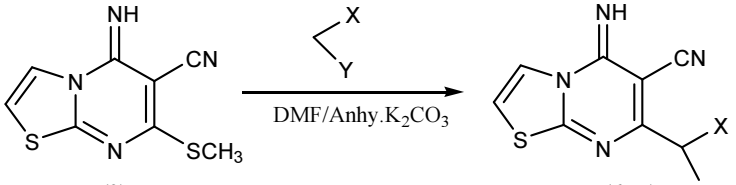


(3) (5a-c)

5a HO–C_6H_4–

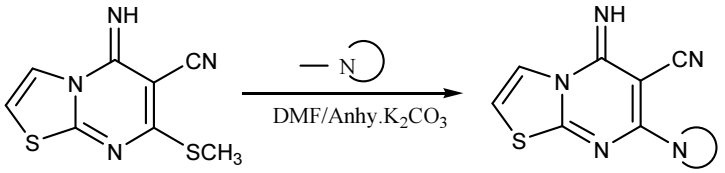
5b HO–$C_6H_3(OCH_3)$–

5c HO–$C_6H_3(Cl)$–

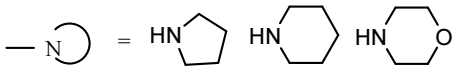


(3) (6a-c)

	X	Y
6a	-CN	-CN
6b	$-COOC_2H_5$	$-COCH_3$
6c	-CN	$-COOC_2H_5$



(3) (7a-c)



7a 7b 7c

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