

SYNTHESIS, STRUCTURAL ELUCIDATION AND ANTIBACTERIAL POTENTIAL OF 6-CYANO-5-OXO-7-(METHYLTHIO)-5H-THIAZOLO[3,2-*a*]PYRIMIDINE AND ITS SUBSTITUTED DERIVATIVES

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Article Info:

Received: 16 July 2026,

Revised: 06 August 2026,

Accepted: 26 August 2026

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DOI: <https://doi.org/10.5281/zenodo.22211791>



Citation:

Digambar B. Kadam*. (2026). Synthesis, Structural Elucidation And Antibacterial Potential Of 6-Cyano-5-Oxo-7-(Methylthio)-5h-Thiazolo[3,2-A]Pyrimidine And Its Substituted Derivatives. International Journal of Clinical and Pharmaceutical Innovations, 1(6), 150-154.

ABSTRACT

The 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-*a*]pyrimidine (3) is prepared by condensing 2-amino thiazole (1) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate under reflux condition. The latter were further reacted with selected nucleophiles such as substituted aryl amines to afford 7-aryl amino derivatives of parent thiazolo[3,2-*a*]pyrimidine. The newly synthesized compounds were further screening of antibacterial activity.

KEYWORDS: 2-amino thiazole, ethyl 2-cyano-3,3-bis(methylthio)acrylate, 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-*a*]pyrimidine, DMF.

INTRODUCTION

Fused heterocyclic ring structure play crucial role in the enhancement of pharmacological action. Pyrimidine nucleus contains nitrogen as electron rich heterocycle. The pyrimidine nucleus forms the different derivatives which includes numerous pyrimido core containing pyrimidine compounds.^[3] The synthesis and biological potential of pyrimidine and its derivatives has been studied extensively ever since the last century due to their diverse applications. Because of the wide spectrum of biological and pharmacological actions that pyrimidines exhibit, it is regarded as important heterocyclic group. The number of naturally occurring molecules that contain this six-membered 1, 3-diazine ring with nitrogen at the 1 and 3 positions like nucleotides, nucleic acids, vitamins, coenzymes, purines and uric acids. Thiazolopyrimidines are fused heterocyclic molecules bearing thiazole and pyrimidine ring system. The wide medicinal application of pyrimidine fused heterocycles may be elaborated by the fact that it is a component of DNA and RNA.^[5] It includes anticancer^[6], anti-HIV^[7], anti-inflammatory^[8], antifungal^[9], analgesic^[10], antibacterial^[11],

tuberculosis^[12] and antioxidant^[13] properties. Due to their valuable biological applications, the use of thiazolo pyrimidines in reactions for the development of new heterocyclic compounds can certainly offer further opportunities. However, these compounds have not been tested for their antimicrobial activity.

In the present article we reported the synthesis of 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-*a*]pyrimidine (3) is prepared by condensing 2-amino thiazole (1) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate and its 7-aryl amino derivatives in one-pot cost effective method and evaluated their anti-microbial activity.

Experimental

All the chemicals used in present works are from analytical grade and used without additional purification. Melting points of the products were determined in open capillary tubes on an electro thermal melting point apparatus and were uncorrected. The progress of reactions and the purity of the isolated compounds were

monitored by thin layer chromatography on Ultra Violet active silica gel plate (Merck). Infrared spectra were recorded on Shimadzu FT-IR spectrophotometer, ^1H NMR spectra were obtained on Bruker advance spectrophotometer 500 MHz in DMSO-d_6 using tetramethyl silane (TMS) as an internal standard. Mass spectrums were analyzed on GC-MS spectrometer using the electron spray ionization technique.

General Procedure

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

A mixture of 2-aminothiazole (1) (0.01 mol) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) (0.01mol) in 15 mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with cold water and recrystallized from N, N'- dimethyl formamide- ethanol mixture to give pure (3) (Scheme 1).

7-Substituted derivative of 6-Cyano-5-oxo-5H-thiazolo [3,2-a] pyrimidine (5a-5d)

A mixture of (3) (0.001 mol) and independently with aromatic amines (0.001mol) in 15 mL of N, N'-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with cold water and recrystallized from N, N'- dimethyl formamide- ethanol mixture to give pure (5a-5d) (Scheme 3).

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

Brown solid, yield-78%, M.P. 194-196°C, IR spectrum: ($\text{KBr} / \text{cm}^{-1}$) 1735.42 (C=O stretch), 2206.41(CN stretch), ^1H NMR spectrum: (DMSO-d_6 , δ ppm) 2.65 (s, 3H, $-\text{SCH}_3$), 7.4-7.8 (dd, 2H, thiazolic-H), Mass spectrum: m/z 223 $[\text{M}^+]$.

6-Cyano-5-oxo-7-(anilino)-5H-thiazolo[3,2-a]pyrimidine (5a)

Brown solid, yield-87%, M.P. 203°C, IR spectrum: ($\text{KBr} / \text{cm}^{-1}$) 1724.31 (C=O stretch), 2214.23 (CN stretch), 3472.35 (N-H stretch), ^1H NMR spectrum: (DMSO-d_6 , δ ppm) 5.2-6.3 (dd, 2H, $-\text{CH=CH-}$), 6.4-7.6 (m, 5H, Ar-H), Mass spectrum: m/z 268 $[\text{M}^+]$.

6-Cyano-5-oxo-7-(4-methyl anilino)-5H-thiazolo[3,2-a]pyrimidine (5b)

Brown solid, yield-80%, M.P. 204-206°C, IR spectrum: ($\text{KBr} / \text{cm}^{-1}$) 1732.64 (C=O stretch), 2226.54 (CN stretch), 3470.55(N-H stretch), ^1H NMR spectrum: (DMSO-d_6 , δ ppm) 2.4 (s, 3H, Ar- CH_3), 4.3(s, 1H, -NH), 5.6-6.1 (dd, 2H, $-\text{CH=CH-}$), 6.3-7.2(m, 4H, Ar-H), Mass spectrum: m/z 282 $[\text{M}^+]$.

6-Cyano-5-oxo-7-(4-methoxy anilino)-5H-thiazolo[3,2-a]pyrimidine (5c)

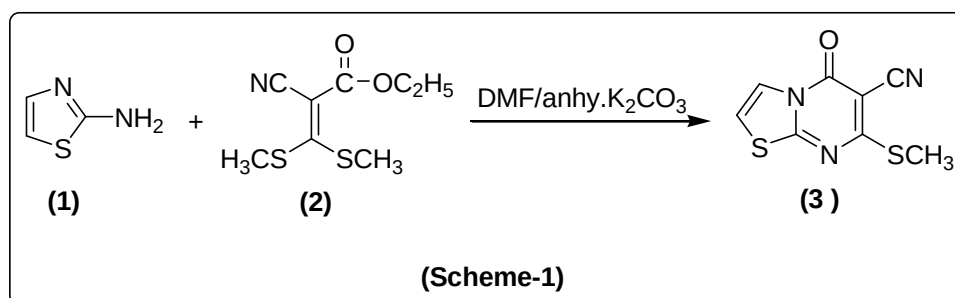
Brown solid, yield-88%, M.P. 209°C, IR spectrum: ($\text{KBr} / \text{cm}^{-1}$) 1722.35 (C=O stretch), 2218.27 (CN stretch), 3485.15 (N-H stretch), ^1H NMR spectrum: (DMSO-d_6 , δ ppm) 3.7 (s, 3H, Ar- OCH_3), 4.1(s, 1H, -NH), 5.1-6.5 (dd, 2H, $-\text{CH=CH-}$), 6.2-7.1(m, 4H, Ar-H), Mass spectrum: m/z 298 $[\text{M}^+]$.

6-Cyano-5-oxo-7-(4-nitro anilino)-5H-thiazolo[3,2-a]pyrimidine (5d)

Brown solid, yield-84%, M.P. 196°C, IR spectrum: ($\text{KBr} / \text{cm}^{-1}$) 1715.42 (C=O stretch), 2210.05 (CN stretch), 3479.34 (N-H stretch), ^1H NMR spectrum: (DMSO-d_6 , δ ppm) 4.2 (s, 1H, -NH), 7.581-8.345 (m, 6H, Ar-H & thiazolic-H), Mass spectrum: m/z 313 $[\text{M}^+]$.

RESULT AND DISCUSSION

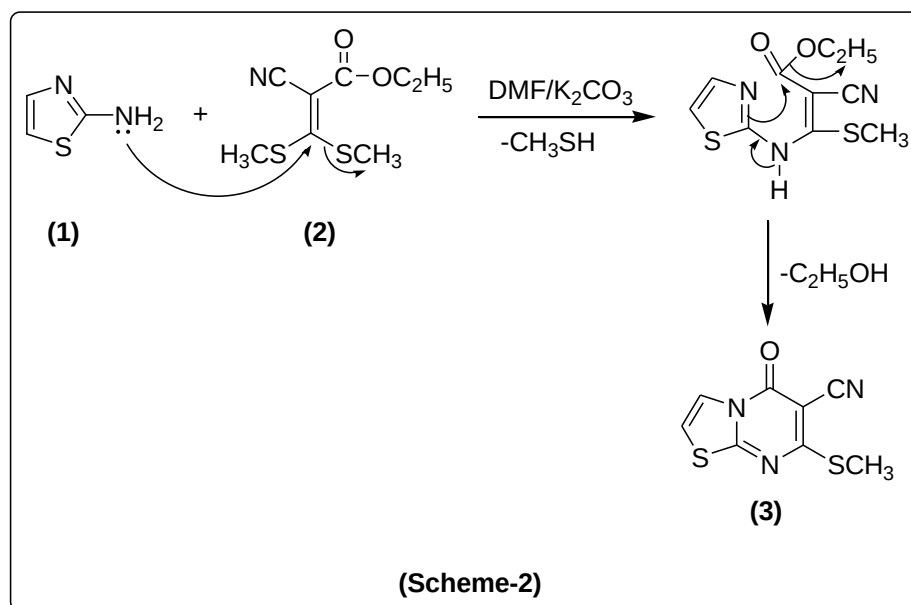
In present work, we reported the synthesis of 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-a]pyrimidine (3) and its 7-substituted derivatives (5a-d). The reaction start with 2-amino thiazole (1) with ethyl 2-cyano-3,3-bis(methylthio)acrylate (2) in DMF and anhydrous K_2CO_3 to afford compound (3) (Scheme 1).



The structure of the newly synthesized compound (3) was assigned on the basis of analytic and spectral data. IR spectrum shows absorption bands at 1735.42 cm^{-1} and 2206.41 cm^{-1} which can be assigned to $>\text{C=O}$ (carbonyl), $-\text{CN}$ stretching respectively. The ^1H NMR spectrum of the compound was recorded in DMSO-d_6 , shows singlet peak at δ 2.65 ppm assignable to $-\text{SCH}_3$

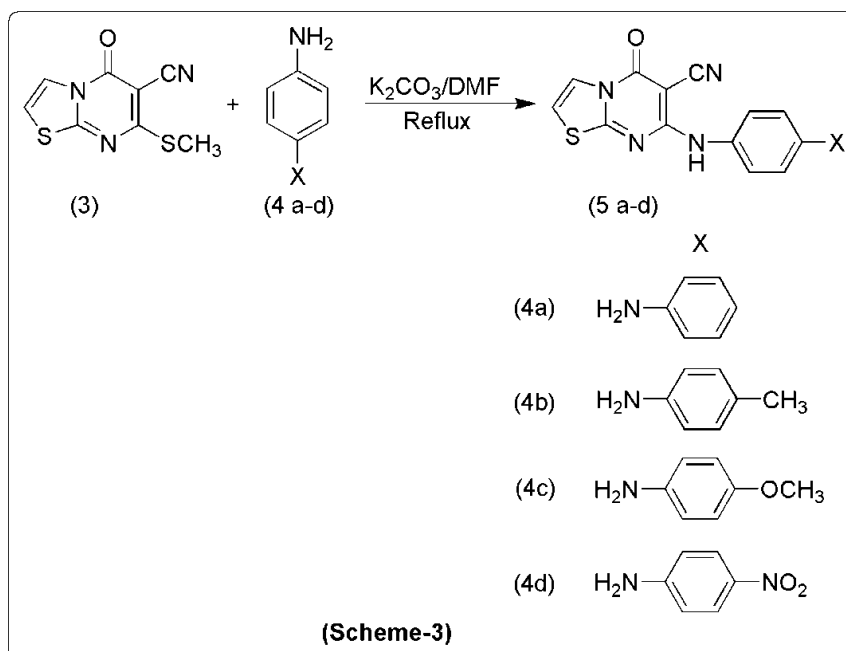
group, singlet at δ 7.4- δ 7.8 ppm due to thiazole ring proton. Mass spectrum exhibits molecular ion peak at m/z 223 (M^+) which corresponds to its molecular weight. Since parent compound (3) possess best leaving active thiomethyl group at 7-position which is hence, its reaction towards nucleophilic substitution with different nucleophilic reagents like substituted aryl amines has been

investigated. The mechanism for the synthesis of compound (3) can be given as (Scheme 2).



Amino derivatives of (3) were synthesized by reacting it independently with aniline, p-toulidine, p-anisidine and p-nitro aniline in DMF and anhydrous K_2CO_3 as a catalyst to yield compounds (5a-d) (Scheme 3). All compounds show strong absorption bands in the range of $2226-2206\text{ cm}^{-1}$ which can be assigned to $-CN$ stretch

and absorption in the range $3485-3470\text{ cm}^{-1}$ are due to $-NH$ stretch. Mass spectra showed the molecular ion peak which corresponds to their respective molecular weight. 1H NMR spectra showed absence of singlet at $\delta 2.65$ which shows that substitution of active thiomethyl group takes place.



Antibacterial activity

The antibacterial activity was carried out as per reported method.^[14] In brief the antibacterial properties of newly synthesized compounds (3), (5a-5d) were evaluated by the disc diffusion assay using *Ampicillin* (10 $\mu\text{g}/\text{disc}$) as the reference compound. Disc diffusion method was

carried by Kirby-Bauer method. 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. The plates were allowed to solidify for 5 minute and 0.1 % inoculum suspension was

swabbed uniformly and the inoculum was allowed to dry for 5 min. The concentrations of compounds were set at 10 µg/disc and were loaded on 5 mm sterile individual discs. The loaded discs were placed on the surface of medium and the compounds were allowed to diffuse for

5 min and the plates were kept for incubation at 37°C for 24 hrs. *Ampicillin* (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 millimeter.

Table No. 1: Antibacterial activity of 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-a]pyrimidine (3) and its 7-substituted derivatives.

Sr. No.	Compound	Zone of inhibition in mm	
		Antibacterial activity	
		<i>E. coli</i>	<i>B. subtilis</i>
01	3	13	15
02	5a	16	09
03	5b	15	11
04	5c	17	12
05	5d	16	14
	<i>Ampicillin</i>	20	16

The compounds (3),(5a-5d) exhibit zone of inhibition against the tested bacteria, some of tested compounds like 5a, 5c,5d displayed 16 mm, 17 mm, 16 mm zone of inhibition respectively against *E. coli*, while compounds 3, 5c, 5d impart 15 mm, 12 mm, 14 mm zone of inhibition respectively against *B. subtilis* as compared with standard *Ampicillin*.

CONCLUSION

In conclusion we have reported a convenient and efficient method for the synthesis of 6-Cyano-5-oxo-7-(methylthio)-5H-thiazolo[3,2-a]pyrimidine compound through K₂CO₃ catalyzed reaction. This method provides diverse advantages, including the use of a reusable catalyst, affording high yields, employing a simple reaction procedure, and provides the simple isolation procedure. Moreover, we conducted a screening of the antibacterial properties of all the synthesized compounds. Particularly, some of these synthesized compounds show significant properties in inhibiting the growth of tested bacteria, in particular *E. coli* and *B. subtilis*.

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