

Heteryl Amine and Activemethylene Derivatives of Pyrido Pyrimidines as Potent Antimicrobial Activity

Avinash V Pawde

Department of Chemistry, A.E. S's Arts, Commerce and Science College, Hingoli-431513, Maharashtra, India

Email: pawdeavi@gmail.com

DOI: <https://doi.org/10.5281/zenodo.22744023>

ABSTRACT

The previously synthesized compound, 7-bromo-3-cyano-4-imino-2-(methylthio)-4H-pyrido[1,2-a] pyrimidine (1), was further subjected to condensation reactions with various heteryl amines and active methylene compounds to afford a series of 7-bromo-3-cyano-4-imino-2-(substituted)-4H-pyrido[1,2-a] pyrimidine derivatives. The synthesized compounds were subsequently evaluated for their antimicrobial activity

Keywords: DMF, pyrido[1,2-a]pyrimidine, bis(methylthio)methylene malononitrile.

INTRODUCTION:

Compounds having Pyrido [1,2-a] pyrimidine nucleus shows potent pharmacological activities¹. They exhibit antitumor², antibacterial³, anti-HIV⁴ activities considering these importance of different pharmacological activities of pyrido pyrimidines their different derivatives will give the hoprful results.

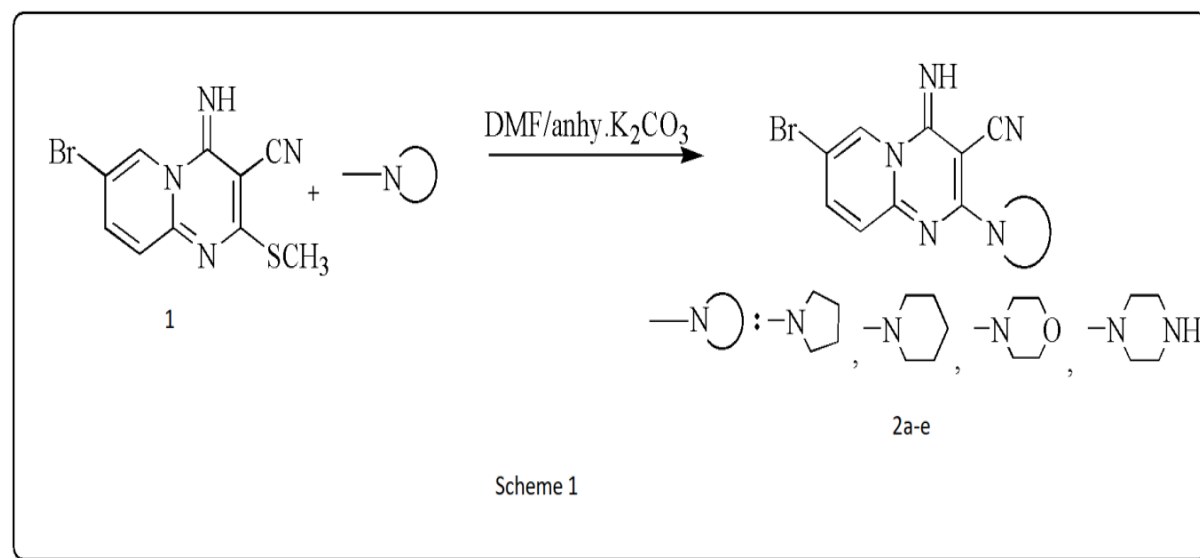
Alan R. Katritzky et al⁵ reported pyrido [1,2-a] pyrimidin-2-ones by reactions of N (phenylpropioyl) benzotriazole with substituted 2-amino pyrimidines. Maria Tsankopoulou et al.⁶ described the synthesis of indeno [1,2-d] pyrido [1,2-a] pyrimidine derivatives by reacting with differently substituted 2- aminopyridines. These indenopyridopyrimidines are good receptor tyrosine kinase inhibitors. Mohammed Abass et al⁷ described the preparation of 2-azido- 4H-pyrido [1,2-a] pyrimidine-4-one and 2-hydrozinyll -4H- pyrido [1,2-a]pyrimidine -4-one by treating 2-chloro-4H-pyrido [1,2-a] pyrimidine-4-one with sodium azide and hydrazine hydrate respectively . One-pot and three component reaction of diamines, α -oxoketenedithioacetals and dimethyl acetylenedicarboxylate to get tetrahydropyrido [1,2-a]

pyrimidines were reported by Langpoklakpam et al⁸. Raghunath et al⁹ described the synthesis of pyrido [1,2-*a*] pyrimidines from aminopyrimidines. Kai Yang et al¹⁰ presented preparation of pyrido [1, 2-*a*] pyrimidines by condensation of 2-aminopyridines, chlorobenzaldehyde, and cyclohexanone under trifluoromethane sulfonic acid catalysis.

RESULT AND DISCUSSION:

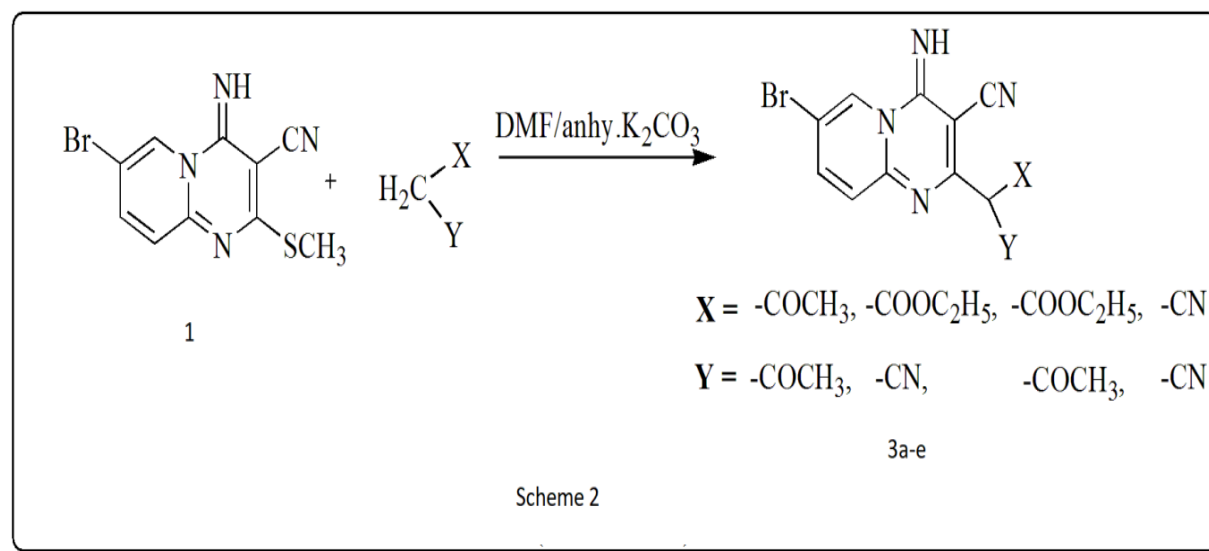
The compound **(1)** contains active methylthio group at 2-position which is easily replaceable, hence its susceptibility towards substitution with different reagents like heteryl amines and active methylene group and have been investigated.

The treatment of **(1)** with selective heteryl amines like pyrrolidine, piperidine morpholine and piperazine in DMF and anhydrous K₂CO₃ yield 7-bromo-3-cyano-4-imino-2-[pyrrolidino/ piperidino/ morpholino/ piperazino] -4*H*-pyrido [1,2-*a*] pyrimidine **(2a-d)** (**Scheme 1**). All these compounds show IR absorption bands in the range **2204-2205** cm⁻¹ and **3215-3419** cm⁻¹ due to –CN and =NH group respectively. Mass spectrum showed ion peaks, which showed their respective molecular weights. ¹H NMR spectra are in agreement with the structure of the compounds.



Different 7-bromo-3-cyano-4-imino-2-(substituted active methylene)-4*H*-pyrido [1,2-*a*] pyrimidine **(3 a-d)** were prepared by treating the parent compound **(1)** independently with acetyl acetone, ethyl cyano acetate, ethyl aceto acetate and malanonitrite in DMF and anhydrous K₂CO₃ under reflux condition (**Scheme 2**). All these compounds show absorption bands in the range **2204-2208** cm⁻¹ and **3056-3392** cm⁻¹ due to –CN and =NH stretching respectively. Mass spectra of **(2.32 a-d)** showed peaks which shows their respective molecular weight. ¹H NMR spectrum shows signals in the range δ **3.8-3.9** ppm for –CH- and absence

of signal at δ 2.63 ppm for $-\text{SCH}_3$, indicating replacement of $-\text{SCH}_3$ group by active methylene compounds



EXPERIMENTAL SECTION

Synthesis of 7-Bromo-3-cyano-4-imino-2-(substituted)-4H-pyrido[1,2-a] pyrimidine Derivatives (2a–e) and (3a–e)

A mixture of compound 1 (0.295 g, 0.001 mol) and, separately, various aromatic amines, substituted phenols, active methylene compounds, and heteroaryl amines (0.001 mol) was treated with anhydrous K_2CO_3 (10 mg) in DMF (15 mL). The reaction mixture was refluxed for 4–5 h and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was cooled to room temperature and poured into ice-cold water. The resulting solid was separated by filtration, washed thoroughly with water, and recrystallized from an ethanol–DMF mixture to obtain the corresponding 7-bromo-3-cyano-4-imino-2-(substituted)-4H-pyrido[1,2-a]pyrimidine derivatives (2a–e) and (3a–e), respectively.

ANTIMICROBIAL ACTIVITY

Infectious diseases remain among the major causes of mortality worldwide and represent a significant public health concern. Disease-causing microorganisms, including bacteria, fungi, viruses, and protozoa, are collectively referred to as pathogenic or infectious microorganisms. These microorganisms can be inhibited or eliminated by substances of biological or non-biological origin, commonly known as antimicrobial agents. Such agents are widely employed for the prevention and treatment of microbial infections.

The discovery and development of antimicrobial agents represented a major advancement in modern medicine. However, the extensive and often inappropriate use of antimicrobial compounds has contributed significantly to the development and dissemination of antimicrobial resistance. Drug-resistant microorganisms are those that are no longer effectively inhibited or killed by antimicrobial agents. The increasing prevalence of antimicrobial resistance, together with the emergence and re-emergence of pathogenic microorganisms, poses a serious threat to public health. The global spread of antimicrobial resistance is largely associated with the genetic adaptability of microorganisms.

DISC DIFFUSION METHOD

The Kirby–Bauer disc diffusion method was employed to evaluate the in vitro antimicrobial activity of the synthesized compounds. Mueller–Hinton Agar (MHA) obtained from HiMedia, Mumbai, was used as the culture medium. MHA plates were prepared by dispensing approximately 15 mL of molten medium into sterile Petri plates. The medium was allowed to solidify for approximately 5 min.

A 0.1% inoculum suspension was uniformly spread over the surface of the agar plates using a sterile swab and allowed to dry for approximately 5 min. The synthesized compounds were prepared at a concentration corresponding to 10 µg/disc and loaded onto sterile discs of 5 mm diameter. The impregnated discs were carefully placed on the surface of the inoculated agar medium and allowed to diffuse for approximately 5 min.

The plates were subsequently incubated at 37 °C for 24 h. Penicillin (10 µg/disc) was used as the positive control. Following incubation, the zones of inhibition produced around the discs were measured in millimetres (mm) using a transparent ruler. The antimicrobial activity of the synthesized compounds was assessed based on the diameter of the resulting zones of inhibition.

ANTIMICROBIAL ACTIVITY OF NEWLY SYNTHESIZED COMPOUNDS:

Table: Antimicrobial potential of 7-Bromo-3-cyano-4-imino-2-methylthio-4*H* pyrido [1,2-*a*] pyrimidine and its 2-substituted derivatives

Sr.no.	Name of compound	Zone of inhibition in mm	
		<i>E. coli</i>	<i>B. subtilis</i>
1	2a	NR	09
2	2b	11	08
3	2c	NR	NR

5	2d	07	11
6	3a	NR	07
7	3b	NR	NR
8	3c	10	11
9	3d	NR	13
10	Penicillin	15	22

NR: No Response

CONCLUSION:

In conclusion, a series of heteroaryl amine- and active methylene-condensed pyrido[1,2-a]pyrimidine derivatives were successfully synthesized and evaluated for their antimicrobial activity. The biological studies revealed that several of the synthesized compounds exhibited promising antibacterial activity against the tested bacterial strains.

Compounds 2d and 3c demonstrated notable antibacterial activity against both tested bacterial strains. Compounds 2b and 3c showed stronger activity against *E. coli* compared with the standard drug. Similarly, compounds 2d, 3c, and 3d exhibited good zones of inhibition against *B. subtilis* compared with the standard drug.

On the other hand, compounds 2a, 2c, 3a, 3b, and 3d showed no significant activity against *E. coli*, whereas compounds 2c and 3b were inactive against *B. subtilis*. Overall, the findings indicate that some of the synthesized pyrido[1,2-a]pyrimidine derivatives possess promising antibacterial potential and may serve as useful lead structures for further antimicrobial studies.

REFERENCES:

1. Katritzky A.R., Rogers J.W., Witek R.M., Nair S.K., *ARKIVOC*, **2011**, 2: 297-309.
2. 72Yao P, Zhai X, Liu D, Qi BH, Tan H.L, *Arch Pharm (Weinheim)*, **2010**, 343: 17-23.
3. Ferrarini P.L., Mori C, Armani G, Rossi L., *Farmaco*, **1995**, 50: 69- Joseph S., Burke J.M., *J Biol Chem.*, **1993**, 268: 24515-24518.
4. Jasinski J.P., Butcher R.J., Hakim Al-Arique Q.N., Yathirajan H.S., Narayana B., *Acta Crystallogr Sect E Struct Rep Online*, **2009**, 65: 2201-2202.
5. Maria Tsankopoulou, Thomas Cottin, Anita buttner, Vasiliki Sarli, Elizabeth Malamidou- Xenikari, Spyros Spyroudis and Athanassios Giannis ., *Med. Chem.*, **2008**, 3, 429-433

6. Mohamed Abass, Mostafam M.ismail, Wafaar R.abdel-monem and Aisha S.Mayas ., *J. Serb.Chem.Soc.*, **2010**,75(1)11-17, JSCS-3936
7. Gullu M. and Utley J.H.P.,*Commun.Fac.Sci.Uni.Ank.Series B.*, **1999**, V. 45, 93-99.
8. Langpoklakpam Gellina Chanu, Thokchom Prasanta Singh, Yong Ju Jang, Yong-Jin Yoon,Okram Mukherjee Singh, and Sang-Gyeong Lee., *Bull. Korean Chem. Soc.*, **2014**, Vol. 35, No. 4. 994
9. Raghunath B. Toche, Bhausahab K. Ghotekar, Muddassar A. Kazi,Shivaraj P. Patil, and Madhukar N. Jachak., **2008**, Article ID 434329 doi:10.3814/**2008**/434329
10. Kai Yang, Jinbao Xiang, Guochen Bao, Qun Dang, and Xu Bai, *ACS Comb. Sci.*, **2013**, 15, 519–524.