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REVIEW ARTICLE

2-Sulfanylidene-2,3-dihydropyridopyrimidin-4(1*H*)-one Derivatives: Synthesis, Reactions and Biological Activities

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2-Sulfanylidene-2,3-dihydropyridopyrimidin-4(1H)-one Derivatives: Synthesis, Reactions and Biological Activities

SUMMARY

This review presents a comprehensive examination of the synthesis, structural modifications, and biological activities of the 2-sulfanylidene-2,3-dihydropyridopyrimidin-4(1H)-one ring systems. The study is organized into four main sections covering compounds possessing the core structures of pyrido[2,3-d]-, pyrido[3,4-d]-, pyrido[4,3-d]-, and pyrido[3,2-d]pyrimidines. Common synthetic strategies frequently used in the synthesis of these fused rings, such as reactions of aminopyridinecarboxylic acid derivatives with thiourea, ammonium thiocyanate, or isothiocyanates, are summarized, with a particular focus on structural modifications performed at the 2- and 3-positions of the rings. In the case of pyrido[2,3-d]pyrimidine derivatives, the reactions of the widely reported 6-amino-2-sulfanylpyrimidin-4(3H)-one compound with β-dicarbonyl compounds or α,β-unsaturated carbonyl derivatives are comprehensively discussed. In addition, the pharmacological effects of the 2-sulfanylidene-2,3-dihydropyridopyrimidin-4(1H)-one ring system, particularly its anticancer activities, are highlighted, underscoring the importance of this scaffold in medicinal chemistry.

Keywords: *Pyrido[2,3-d]pyrimidine, pyrido[3,4-d]pyrimidine, pyrido[4,3-d]pyrimidine, pyrido[3,2-d]pyrimidine, 2-sulfanylidene-2,3-dihydropyridopyrimidin-4(1H)-one*

2-Sülfaniliden-2,3-dihidropiridopirimidin-4(1H)-on Türevleri: Sentezi, Reaksiyonları ve Biyolojik Aktiviteleri

ÖZ

Bu inceleme, 2-sülfaniliden-2,3-dihidropiridopirimidin-4(1H)-on halka sistemlerinin sentezlerini, yapısal modifikasyonlarını ve biyolojik aktivitelerini kapsamlı bir şekilde ele almaktadır. Çalışma, pirido[2,3-d]-, pirido[3,4-d]-, pirido[4,3-d]- ve pirido[3,2-d] pirimidin ana yapısına sahip bileşiklerin ele alındığı dört ana bölüme ayrılmıştır. Halkaların sentezinde aminopiridinkarboksilik asit türevlerinin tiyoüre, amonyum tiyosiyanat veya izotiyosiyanat ile reaksiyonları gibi yaygın olarak kullanılan sentetik stratejiler özetlenmiş; özellikle halkaların 2 ve 3 nolu konumlarından gerçekleştirilen yapısal modifikasyonlara odaklanılmıştır. Pirido[2,3-d]pirimidin türevi özelinde, literatürde geniş olarak yer bulan 6-amino-2-sülfanilpirimidin-4(3H)-on bileşiğinin, β-dikarbonil bileşikleri veya α,β-doymamış karbonil türevleri ile tepkimeleri kapsamlı bir biçimde değerlendirilmiştir. Bunun yanı sıra, 2-sülfaniliden-2,3-dihidropiridopirimidin-4(1H)-on halka sisteminin farmakolojik etkileri, özellikle antikanser aktivitelerine vurgu yapılarak, bu yapı sisteminin medisinal kimya alanındaki önemi ortaya konulmuştur.

Anahtar Kelimeler: *Pirido[2,3-d]pirimidin, pirido[3,4-d] pirimidin, pirido[4,3-d]pirimidin, pirido[3,2-d]pirimidin, 2-sülfaniliden-2,3-dihidropiridopirimidin-4(1H)-on*

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INTRODUCTION

Uracil is a pyrimidine derivative and one of the four nucleobase constituents of ribonucleic acid (RNA). Uracil and its sulfur analogue, thiouracil, are regarded as privileged scaffolds in medicinal chemistry, playing a crucial role in the design and development of therapeutic agents (Kaur et al., 2025; Ramesh, Vijayakumar & Kannan, 2020). 5-Fluorouracil, an uracil analogue, is widely used as an anticancer agent. In addition, several structurally related uracil derivatives, including tegafur and floxuridine, have also been approved for clinical use (Ghafouri-Fard et al., 2021; Kaur et al., 2025; Power & Kemeny, 2009; Ramesh et al., 2020; Vodenkova et al., 2020). With respect to thiouracil derivatives, although anticancer activities of thiouracil derivatives have also been reported, their most prominent biological property, especially for 6-alkylthiouracils, is their antithyroid activity. Propylthiouracil, a representative thiouracil derivative, is clinically employed as an antithyroid drug (He et al., 2004; Kaur et al., 2025; Lee et al., 2023; Marinova & Tamahkyarova, 2024; Miao et al., 2022; Ramesh et al., 2020) (Figure 1.)

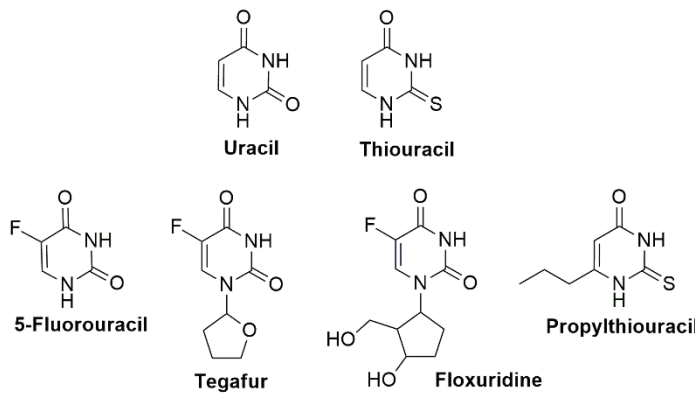


Figure 1. Uracil, thiouracil, and their derivatives

The established clinical relevance of biologically active uracil and thiouracil derivatives has stimulated extensive research on these heterocyclic frameworks. This research has led to the development of numerous compounds exhibiting anticancer, antiviral, antithyroid, antidiabetic, and anti-Alzheimer's disease activities. In addition to these studies, bicyclic and tricyclic systems formed by the fusion of aryl or heteroaryl groups with uracil and thiouracil cores have also been widely explored. Examples of these systems include quinazoline-2,4(1*H*,3*H*)-dione, purine-2,6-dione, thiazolo[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione, pyrrolo[2,3-*d*]pyrimidine-2,4-(3*H*,7*H*)-dione, 2-sulfanylidene-2,3-dihydroquinazolin-4(1*H*)-one, 2-sulfanylidene-1,2,3,5-tetrahydro-6*H*-purin-6-one and others. In particular, anticancer investigations of these ring systems have attracted increasing attention in recent years (Aly et al., 2025; Backer et al., 2024; Jian et al., 2021; Kaur et al., 2025; Kuyrukcu Ozturk, Oyardi & Dundar, 2025; Kuyrukcu Ozturk, Oyardi, Ilikci Sagkan & Dundar, 2026; Kuyrukcu Ozturk & Dundar, 2026; Pałasz & Cież, 2015; Ramesh et al., 2020; Sanduja, Gupta & Virmani, 2020).

In view of the biological significance and structural versatility of uracil- and thiouracil-based heterocycles, increasing attention has been directed toward fused ring systems incorporating these cores. Accordingly, this review focuses on the synthesis, reactions, and biological activities of 2-sulfanylidene-2,3-dihydropyridopyrimidin-4(1*H*)-one ring systems derived from pyridine-annulated thiouracil frameworks. For clarity and systematic discussion, these systems are classified into four distinct groups based on the position of the nitrogen atom within the pyridine

moiety: pyrido[2,3-*d*]pyrimidine (**1**), pyrido[3,4-*d*] pyrimidine (**2**), pyrido[4,3-*d*]pyrimidine (**3**), and pyrido[3,2-*d*]pyrimidine (**4**) (Figure 2.). Despite the growing number of reports on pyridopyrimidine derivatives, a comprehensive and systematic comparison of all four pyridopyrimidine isomers incorporating a thiouracil core—particularly with respect to synthetic diversity—has not yet been systematically reviewed. This review aims to address this gap by critically summarizing synthetic strategies, post-functionalization reactions, and reported biological activities of these heterocyclic systems.

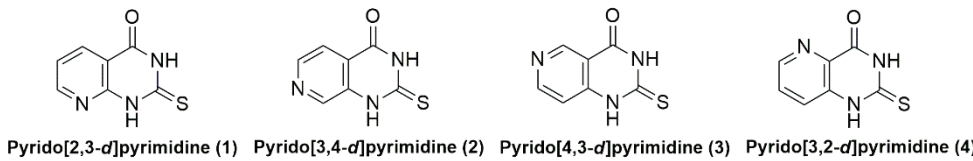


Figure 2. 2-Sulfanylidene-2,3-dihydropyridopyrimidin-4(1*H*)-one derivatives

2-Sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (1)

The synthesis and structural modifications of 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**1**), the most extensively studied heterocyclic framework among the four structural isomers, are outlined in Figures 3–20.

The earliest and most widely reported synthetic approaches employ 2-aminopyridine-3-carboxylic acid (**5**) as the starting material. Cyclocondensation of compound 5 with thiourea (**6**), either under solvent-free conditions at 200 °C (Hitchings, Tuckahoe, Robins & Yonkers, 1954; Hitchings, Yonkers, Robins & Ariz, 1962; Jian et al., 2021; Robins & Hitchings, 1955; The Wellcome Foundation Limited Company, 1957) or by heating in polyethylene glycol at 150 °C (Li, Deng, Wu & Yan, 2022; Nikpour, Mozafari & Paibast, 2009) affords the target compound (**1**) (Figure 3.).

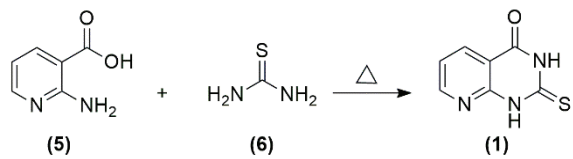


Figure 3. Reaction of 2-aminopyridine-3-carboxylic acid and thiourea

In an alternative synthetic approach, 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**1**) has been obtained by heating 4-aminopyrido[2,3-*d*]pyrimidin-2(1*H*)-thione (**7**) either in 2N hydrochloric acid (Hitchings et al., 1954, 1962; The Wellcome Foundation Limited Company, 1957) or in 2N sodium hydroxide solution (Robins & Hitchings, 1955). In addition, the reaction of 2-chloro-4-hydroxypyrido[2,3-*d*]pyrimidine (**8**) with sodium hydrosulfide (4N NaSH (Hitchings et al., 1954, 1962; The Wellcome Foundation Limited Company, 1957) or 2N NaSH (Robins & Hitchings, 1955)) provides an alternative route to the compound 1 (Figure 4.).

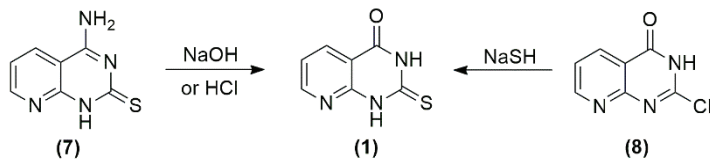


Figure 4. Reactions of 4-aminopyrido[2,3-*d*]pyrimidin-2(1*H*)-thione and 2-chloro-4-hydroxypyrido[2,3-*d*]pyrimidine

In synthetic routes using methyl or ethyl 2-aminopyridine-3-carboxylate (**9** or **10**) as the starting material, the key transformations have been achieved with either thiourea (**6**) (Deng, Zhang, Chen & Li, 2023) or ethoxycarbonyl isothiocyanate (**11**) (Jeges et al., 2011; Stanovnik & Tisler, 1972). More recently, Deng et al. (2025) reported a two-step procedure in which methyl 2-aminopyridine-3-carboxylate (**9**) was first treated with ammonium thiocyanate and benzoyl chloride (**12**), followed by cyclization under basic conditions to afford the target scaffold (**1**) (Figure 5.)

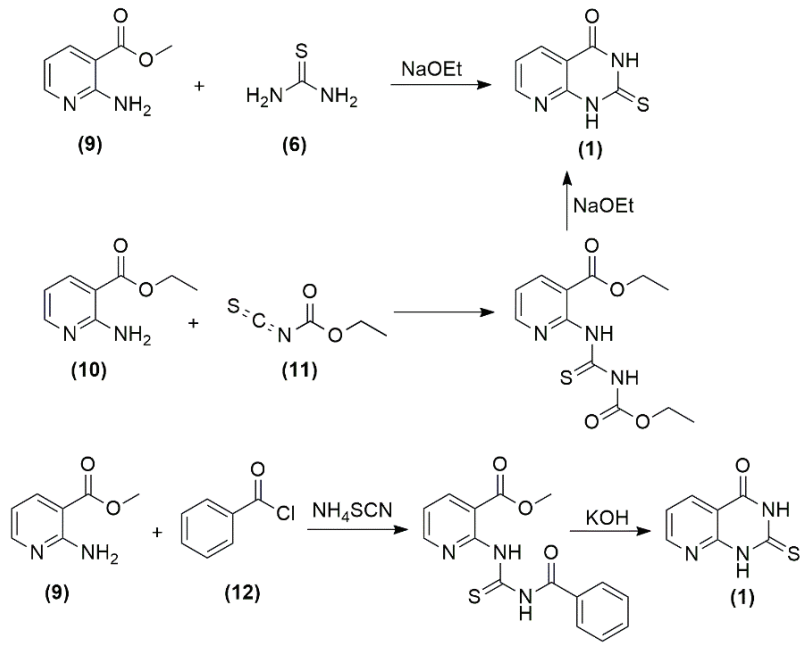


Figure 5. Synthesis of 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one via ester derivatives

Another method involving isothiocyanates was employed to synthesize compound 1 and its N1-substituted derivatives (**13**), as reported by Koscik et al. (1983). In this approach, 2-chloronicotinyl isothiocyanate (**14**) was used as the starting material, and cyclization proceeded via a thiourea intermediate formed through the addition of primary amines to this compound (Figure 6.).

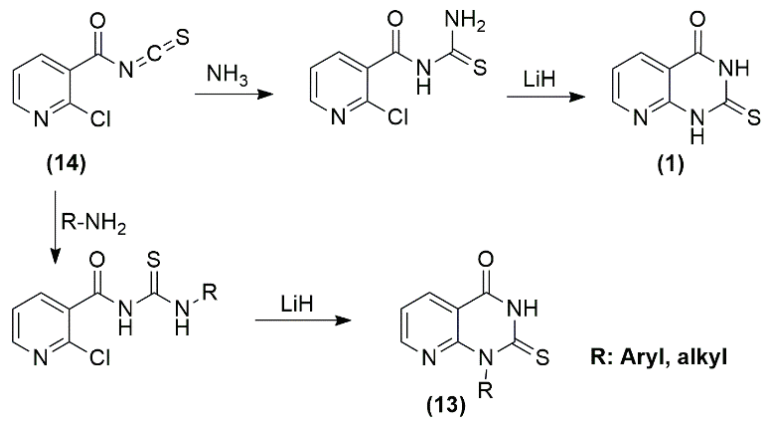


Figure 6. Synthesis of 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one from 2-chloronicotinyl isothiocyanate

In a study reported by Koren, Stanovnik and Tisler (1987), it was demonstrated that 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**1**) can be obtained via ring expansion during the alkaline hydrolysis of a thiadiazolopyridine derivative (**15**) (Koren et al., 1987; Sako, 2004) (Figure 7.).

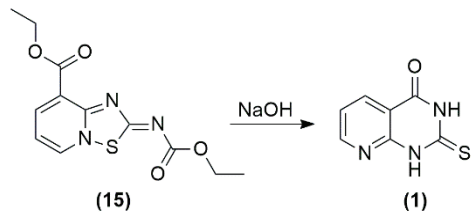


Figure 7. Ring expansion reaction via hydrolysis of thiadiazolopyridine derivative

The synthesis of 5-, 6-, and 7-substituted 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one derivatives has been achieved starting from 6-amino-2-sulfanylpyrimidin-4(3*H*)-one (**16**). In particular, the reaction of this amino derivative with 1,3-diketones in 85% phosphoric acid has been shown to afford 5,7-disubstituted derivatives (**17**) (Hitchings, Tuckahoe, Robins & Yonkers, 1956; Hitchings et al., 1962; Moawad, Abou-El-Regal & El-Metwally, 2025; Mukarramov, Urakov & Shakhidoyatov, 2007; Ridi, Checchi & Papini, 1955; Robins & Hitchings, 1958; Zhang, Wang, Wen, Li, & Quan, 2016). It has also been reported that the introduction of substituents at the *α*-positions of the corresponding carbonyl compounds leads to the formation of 5,6,7-trisubstituted derivatives. However, the yields obtained were generally low. In related studies, reactions with 2-alkyl/aryl-3-ketoaldehyde derivatives predominantly afforded 6,7-disubstituted compounds (**18**), whereas *β*-ketoaldehydes were reported to provide either 7-substituted derivatives (**19**) or structurally related tricyclic compounds (**20**) (Robins & Hitchings, 1958) (Figure 8.)

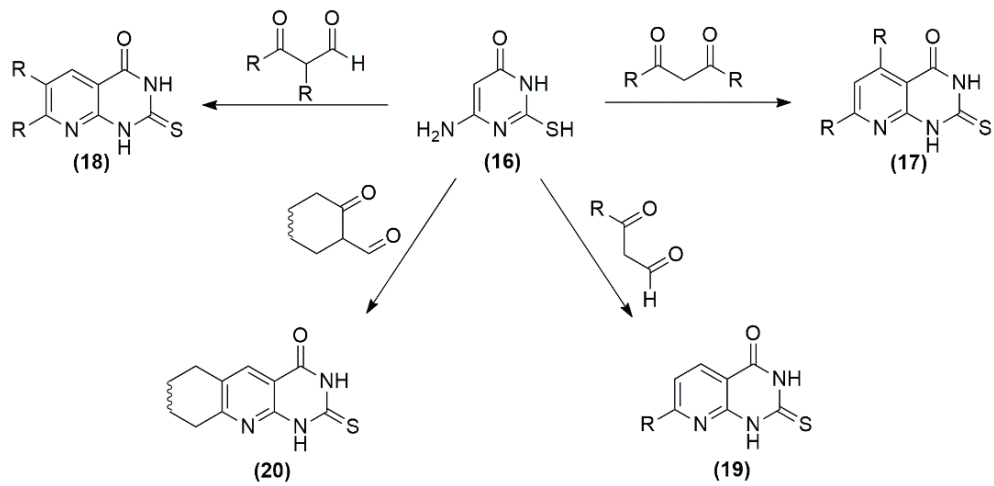


Figure 8. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives from 6-amino-2-sulfanylpyrimidin-4(3*H*)-one

In addition to these approaches, the synthesis of 4-hydroxy-2-sulfanyl-6,7-disubstitutedpyrido[2,3-*d*] pyrimidine (**18**) via the reaction of 5,6-disubstituted-2-aminonicotinic acid (**21**) with thiourea (**6**) has also been documented in the literature (Hitchings et al., 1962) (Figure 9.).

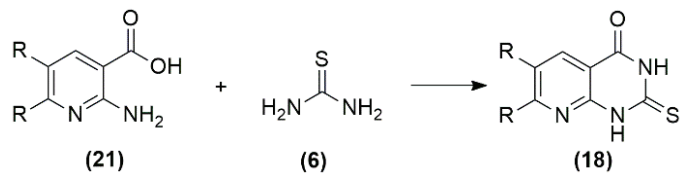


Figure 9. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives from 5,6-disubstituted-2-aminonicotinic acid

Numerous studies have reported that substituted 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one derivatives can also be obtained through the reaction of 6-amino-2-sulfanylpyrimidin-4(3*H*)-one (**16**) with *α,β*-unsaturated carbonyl derivatives, analogous to reactions involving 1,3-diketones and alkyl/aryl-3-ketoaldehyde derivatives. In particular, the reactions of 6-amino-2-sulfanylpyrimidin-4(3*H*)-one (**16**) with *α,β*-unsaturated ketones afford 5,7-disubstitutedpyrido[2,3-*d*]pyrimidine derivatives (**17**) (Abosalim et al., 2025; Fares et al., 2017; Gomha, Ahmed & Abdelhamid, 2015; Moawad et al., 2025; Quiroga, Insuasty, Sanchez, Nogueras, & Meier, 1992). Furthermore, condensation reactions involving malononitrile and aromatic aldehyde have been described to produce 7-amino-5-substituted-4-oxo-2-sulfanylidene-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives (**22**) (Rad & Mokhtary, 2015). The reaction of compound **16** with 3-(dimethylamino)-2-substitutedprop-2-enenitrile results in the formation of 5-substituted-7-aminopyrido[2,3-*d*]pyrimidine derivatives (**23**) (Fadda, Bayoumy & El-Sherbiny, 2016). In addition, the use of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one as a reagent leads to the formation of 7-substituted derivatives (**19**) (Baharfar & Azimi, 2011). The reaction of compound **16** with 1,1-dimethoxy-*N,N*-dimethylmethanamine yields *N,N*-dimethyl-*N*'-(6-oxo-2-sulfanyl-1,6-dihydropyrimidin-4-yl)methanimidamide (**24**), which subsequently reacts with appropriate *α,β*-unsaturated carbonyl compounds to give 5-substituted derivatives (**25**) (Mohamed, ElHefny & Abdelmomem, 2015). In addition, 5/7-substituted derivatives (**19** or **25**) can also be obtained via the reaction of compound **16** with 3-(dimethylamino)-1-substitutedprop-2-en-1-ones (Ali, Said, Allam, Abdel-Aziz, & Abou-Seri, 2025; Churchill, Raw & Powell, 2011; Hassneen & Abdallah, 2003; Kawade & Khedekar, 2014) (Figure 10.)

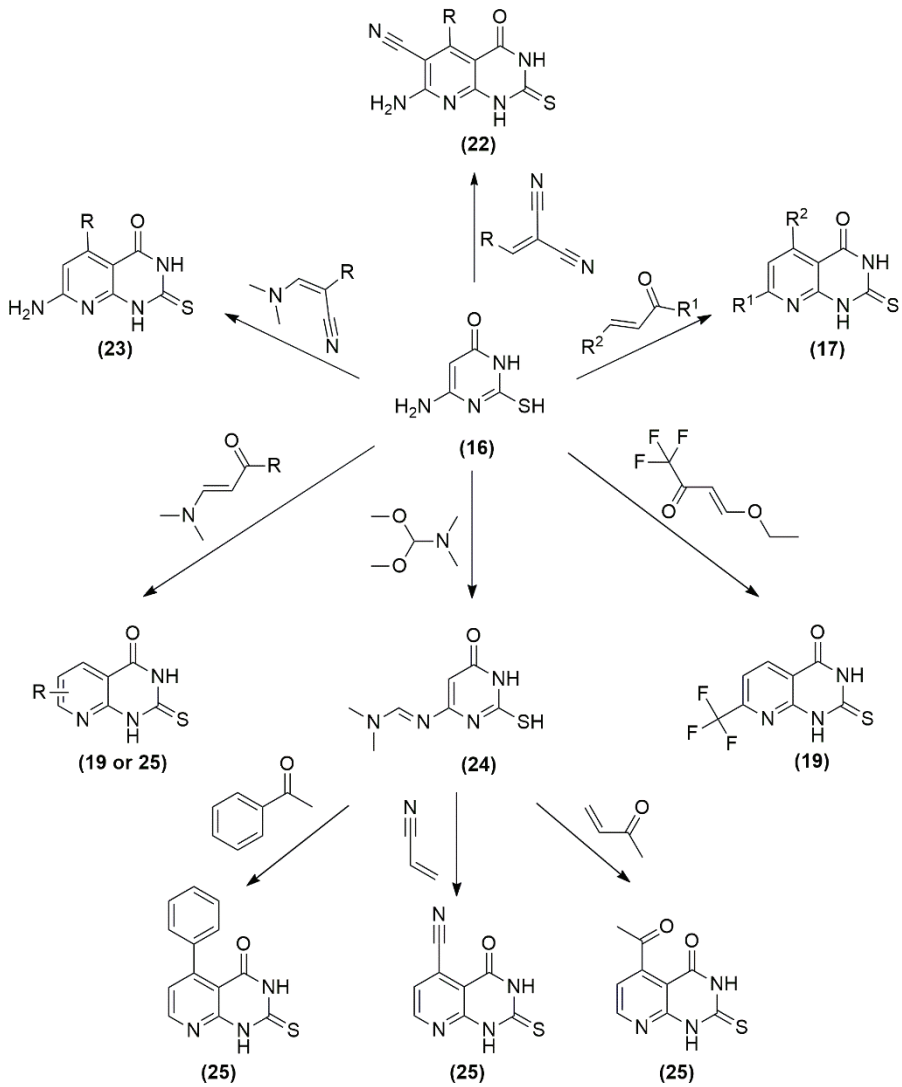


Figure 10. Reaction of 6-amino-2-sulfanylpyrimidin-4(3*H*)-one with *α,β*-unsaturated carbonyl derivatives

He et al. (2024) reported the synthesis of 5,6,7-trichloropyrido[2,3-*d*]pyrimidine (**26**), using 2-amino-4,5,6-trichloronicotinic acid (**27**) as the starting material, with yielded the corresponding ester (**28**) hydrolysis. The resulting acid was then converted to the corresponding acid chloride using thionyl chloride, and cyclization was achieved through reaction with ammonium thiocyanate. A similar strategy was applied for the synthesis of the 5,7-dichloro derivative (Figure 11.)

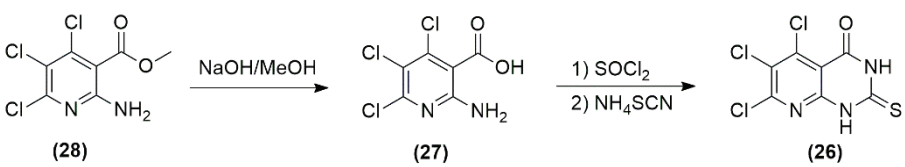


Figure 11. Ring closure with ammonium thiocyanate

It has been reported that derivatives bearing substituents at the N3 position of the pyrido[2,3-*d*]pyrimidine ring can be synthesized by reacting 3-ethoxycarbonyl-2-isothiocyanopyridine (**29**) with various nucleophiles, including hydrazine, phenylhydrazine, alkylamines, ethyl glycinate, or glycine. These reactions afford the corresponding N3-substituted derivatives bearing amino (**30**), phenylamino (**31**), alkyl (**32**), ethoxycarbonylmethyl (**33**), and carboxymethyl (**34**) groups, respectively (Kücükdisli et al., 2023; Modica et al., 2000; Urleb, Stanovnik & Tisler, 1990a) (Figure 12.).

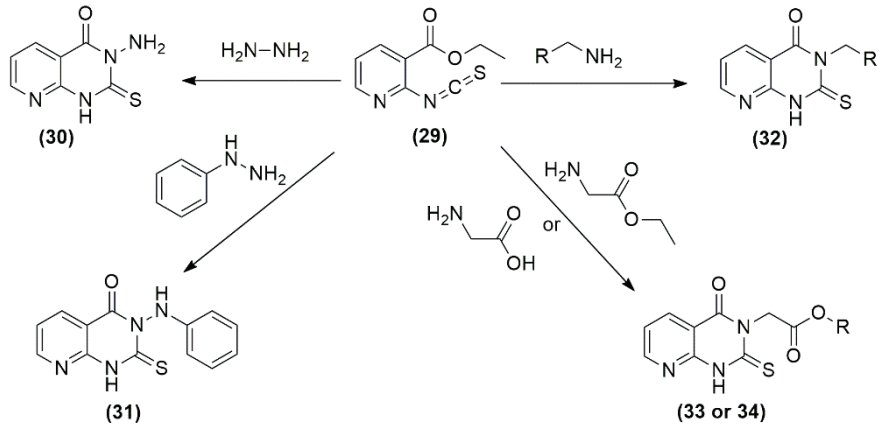


Figure 12. Transition to N3-substituted derivatives

In addition to these studies, N3-substituted derivatives (**35** and **36**) have also been synthesized through the reaction of ethyl 2-aminopyridine-3-carboxylate (**10**) —or its corresponding acid (**5**) or amide (**37,** obtained through nitrile (**38**) hydrolysis) derivatives— with substituted isothiocyanates. This methodology has been documented in several studies (Agrawal, Swati, Yadav & Prakash, 1998; Alverez et al., 2020; Kadunc, Stanovnik & Tisler, 1984; Redondo et al., 2012) (Figure 13.).

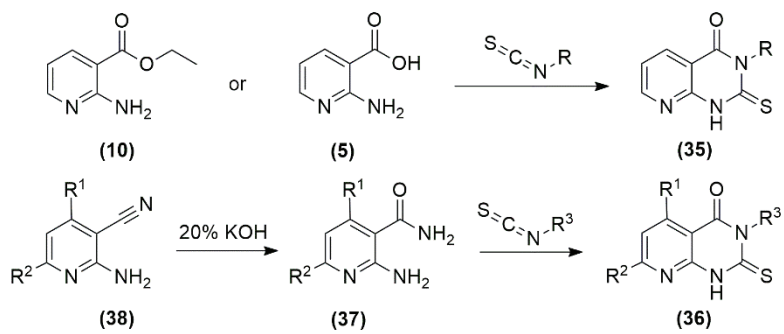


Figure 13. Ring closure with isothiocyanate derivatives

In an alternative approach, the N3-phenyl derivative (**39**) was obtained via the reaction of methyl 2-aminopyridine-3-carboxylate (**9**) with methyl *N*-phenylcarbamodithiolate (**40**) (Garin, Melendez, Merchan & Tejero, 1984) (Figure 14.). In a 2025 study, 2-amino-*N*-phenylnicotinamide (**41**) was first synthesized from 2-aminonicotinic acid (**5**) and subsequently subjected to ring closure with thiocarbonyldiimidazole (Zlotnick, Turner, Vannieuwenhze & Haydar, 2025) (Figure 15.).

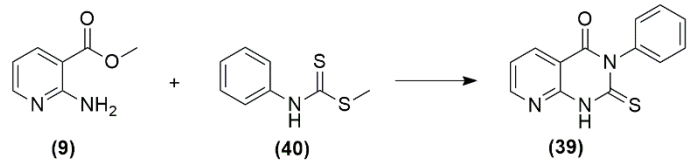


Figure 14. Ring closure with methyl *N*-phenylcarbamodithiolate

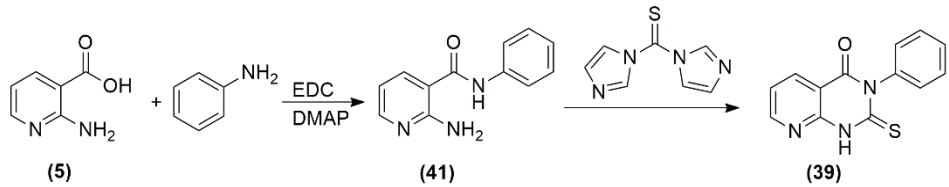


Figure 15. Ring closure with thiocarbonyldiimidazole

Disubstituted derivatives (**42**) via N1 and N3 were obtained by reacting substituted thiourea derivatives with the ethyl 2-chloropyridinecarboxylate derivative (**43**) in 5–15% yield (Sladowska & Zawisza, 1982) (Figure 16.). In another approach to the synthesis of N1,N3-disubstituted derivatives, isoxazolylpyrido[2,3-*d*]pyrimidines (**44**) were reported to be obtained in high yields by reacting (*E*)-methyl 2-((3-methyl-5-styrylisoxazole-4-yl)amino)nicotinates (**45**) with various aryl isothiocyanates in the presence of polyethylene glycol 400 (PEG-400). The corresponding (*E*)-methyl 2-((3-methyl-5-styrylisoxazole-4-yl)amino)nicotinates (**45**) were previously synthesized via the reaction of methyl 2-chloronicotinate (**46**) with appropriate heteroaromatic amine derivatives (**47**), which was also conducted in the presence of PEG-400 (Rani & Kunta, 2021) (Figure 17.). Additionally, ring closure was achieved through the oxidative reaction of 6-amino-2,3-dihydro-1,3-dimethyl-2-thioxo-4(1*H*)-pyrimidinone (**48**) with diarylpropene derivatives (**49**), catalyzed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/*tert*-butylnitrite (TBN)/O_2 (Cheng et al., 2023) (Figure 18.).

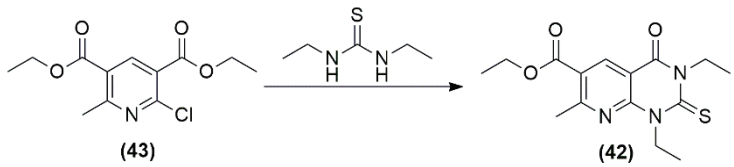


Figure 16. Ring closure with substituted thiourea derivatives

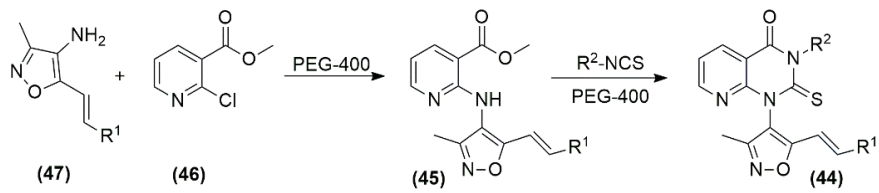


Figure 17. Synthesis of N1,N3-disubstitutedpyrido[2,3-*d*]pyrimidine derivatives

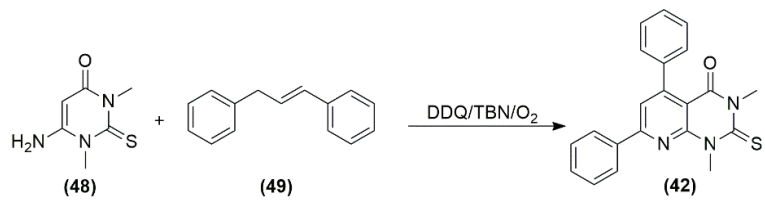


Figure 18. Synthesis of N1,N3-disubstitutedpyrido[2,3-*d*]pyrimidine derivatives by oxidation

Another synthetic approach to pyrido[2,3-*d*]pyrimidine derivatives was reported by Abd-Elaziz et al. (2022), in which barbituric acid derivatives were employed as starting materials. According to their findings, 7-aminopyrido[2,3-*d*]pyrimidinecarbonitrile derivatives (**52**) were successfully synthesized via the reaction of substituted thiobarbituric acids (**50**) with 2-(4-methoxybenzylidene)malononitrile (**51**) in the presence of ammonium acetate (Figure 19.).

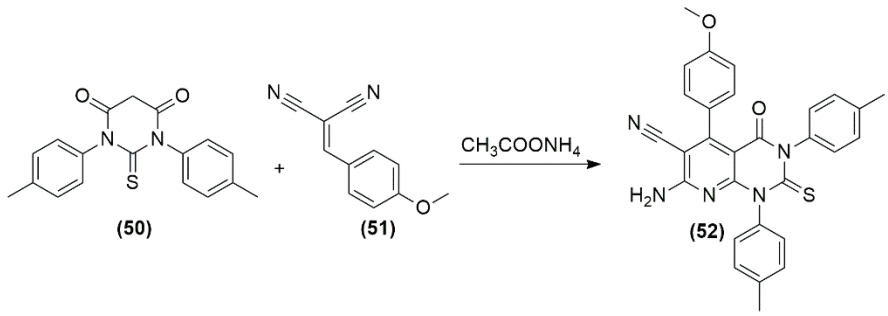


Figure 19. Synthesis of 7-aminopyrido[2,3-*d*]pyrimidine derivatives from thiobarbituric acid

Alkyl substitution (**53**) of the sulfur atom at position two of the pyrido[2,3-*d*]pyrimidine ring can be achieved by reacting the core ring with alkyl halides (Jian et al., 2021; Koren et al., 1987) or sulfonic acid esters (Deng et al., 2023; Li et al., 2022) under basic conditions. It has been reported that increasing the polarity and cation-solvating ability of the solvent enhances the formation of N1- and N3-methylated products while reducing the proportion of S-substituted derivatives (Khodzhaniyazov, Urakov & Shakhidoyatov, 2000). In addition, the sulfur atom undergoes a substitution reaction with sulfuryl chloride or chlorine to yield 2-chloropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**54**) (Deng et al., 2025). Reactions with hydrazine hydrate to produce 2-hydrazino derivatives (**55**) have also been reported in the literature (Khalifa, Alkahtani, Al-Omar, & Bakheit, 2019b) (Figure 20.)

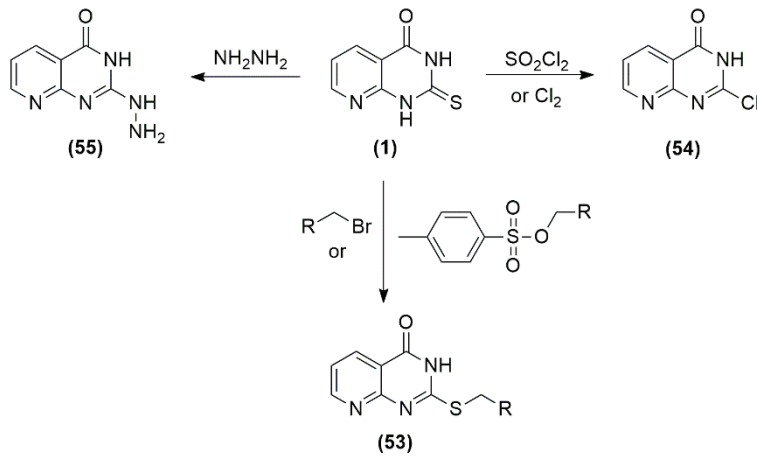
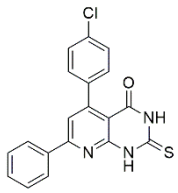
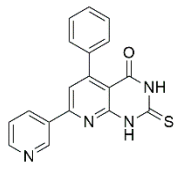
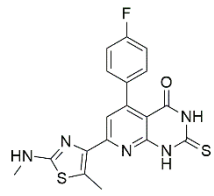
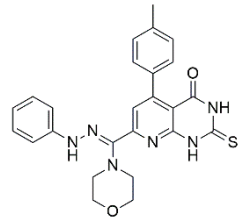
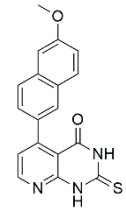
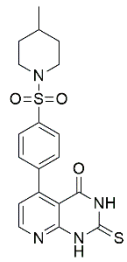
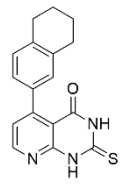
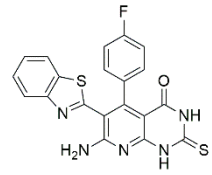
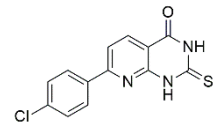
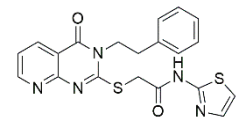
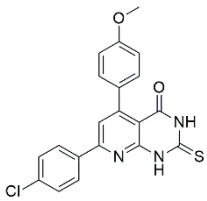
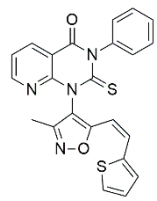
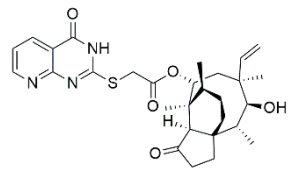
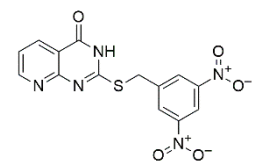


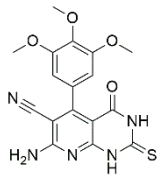
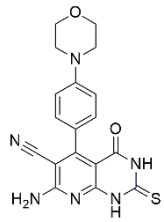
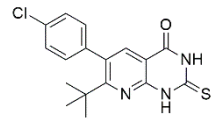
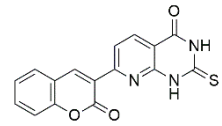
Figure 20. S-substitution of the pyrido[2,3-*d*]pyrimidine ring

Due to its diverse synthetic accessibility and versatile chemical reactivity, this ring system has been extensively investigated since the 1950s, and numerous studies on its biological activities have been reported. In particular, the anticancer potential of 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one derivatives has been widely explored. These compounds have also been described in the literature as exhibiting a broad spectrum of biological activities, including antibacterial, antitubercular, analgesic, anti-inflammatory, antinociceptive, antioxidant, and carbonic anhydrase inhibitory effects.

Representative examples of biological activity studies on 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one and its derivatives, together with relevant activity data, are summarized in Table 1. Despite the investigation of various substitution patterns, the currently available biological data remain insufficient to establish definitive structure–activity relationships. Nevertheless, this heterocyclic scaffold has been frequently employed as a building block in medicinal chemistry research.

Table 1. Representative examples of biological activity of 2-sulfanylidene-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one derivatives

Anticancer activity				
 MCF7 IC_{50}= 5.11 µg/ml (El-Nassan, 2011)	 HepG2 IC_{50}= 9.40 µM PC3 IC_{50}= 10.76 µM HCT116 IC_{50}= 14.90 µM (Khalifa, Al-Omar, Alkahtani & Bakheit, 2019a)	 HepG2 IC_{50}= 8.25 µM A549 IC_{50}= 7.33 µM MCF7 IC_{50}= 10.00 µM (Farghaly, Masaret, Muhammad & Harras, 2020)	 A549 IC_{50}= 5.70 µg/ml HepG2 IC_{50}= 3.54 µg/ml (Muhammad et al., 2017)	 EGFR tyrosine kinase inh. (81% at 25 nM) MCF7 IC_{50}= 8.40 nM (El Sayed et al., 2018)
 MCF7 IC_{50}= 15.62 µM HCT116 IC_{50}= 14.07 µM HepG2 IC_{50}= 14.41 µM (Halawa et al., 2019)	 HCT116 IC_{50}= 0.49 µM HepG2 IC_{50}= 27.00 µM HeLa IC_{50}= 25.30 µM MCF7 IC_{50}= 18.20 µM (Gamal-Eldeen, Hamdy, Abdel-Aziz, El-Hussieny, & Fakhr, 2014)	 NCI-H460 IC_{50}= 0.28 µM HepG2 IC_{50}= 0.39 µM HCT116 IC_{50}= 0.14 µM (Al-Mutairi, Hafez, El-Gazzar & Mohamed, 2022)	 T47D IC_{50}= 1.46 µg/ml inh. kinase activity of PI3K α IC_{50}= 0.18 µg/ml PI3K β IC_{50}= 2.22 µg/ml PI3K δ IC_{50}= 0.61 µg/ml (Ali et al., 2025)	 PI3K-C2α IC_{50}= 0.80 µM (Kücükdisli et al., 2023)
Antibacterial activity				
 *Candida albicans* MIC= 1.95 µg/ml *Streptococcus pneumoniae* MIC= 0.49 µg/ml (Fares et al., 2018)	 *Staphylococcus aureus* MIC= 8.00 µg/ml *Pseudomonas aeruginosa* MIC= 7.00 µg/ml (Rani & Kunta, 2021)	 *MR Staphylococcus aureus* MIC= 2.00 µg/ml (Deng et al., 2023)	 *Mycobacterium tuberculosis* H37Rv MIC= ≥50 µM (Jian et al., 2021)	

Analgesic, antiinflammatory, and antinociceptive activity			Antioxidant and carbonic anhydrase inhibitory activity
			
COX-1 IC_{50}= 4.27 µM, COX-2 IC_{50}= 0.25 µM carrageenan-induced rat paw oedema inhibition (76% at 50 mg/kg) (Abdelgawad, Bakr & Azouz, 2018)	Analgesic activity (66% at 20 mg/kg) carrageenan-induced rat paw oedema inhibition (63% at 20 mg/kg) (El-Gazzar & Hafez, 2009)	Vanilloid receptor 1 antagonists IC_{50}= 18 nM (Culshaw et al., 2006)	ABTS 83.53% (Hamama, Berghot, Baz & Gouda, 2011) CA XII *Ki*= 2.46 µM (Abdelaal et al., 2024)

2-Sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one (2)

The synthetic methods for 2-sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one (2-thiocopazoline-2,4(1*H*,3*H*)-dione, **2**) derivatives are summarized herein.

Among the strategies employed for the construction of this core scaffold, analogous to those used for pyrido[2,3-*d*]pyrimidine systems, one commonly reported route involves the solvent-free heating of 3-aminopyridine-4-carboxylic acid (3-aminoisonicotinic acid, **56**) with thiourea (**6**) at 160 °C. This methodology has been described in several studies (Cox, Raheem, Flores & Whitman, 2011; Fox, 1952; Guo et al., 2022; Westaway et al., 2016). Furthermore, the desired ring system has also been obtained through a cyclocondensation reaction of 3-amino-5-chloropyridine-4-carboxamide (**57**) with carbon disulfide, affording 5-chloro-2-sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one (**58**) (Van Hoof et al., 2023). Ester derivatives (**59**) have also been reported as suitable starting materials for the synthesis of this scaffold; the synthesis of 6-methyl-2-sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one (**60**) using a related methodology was reported by Maguire and McKee (1979) (Figure 21.).

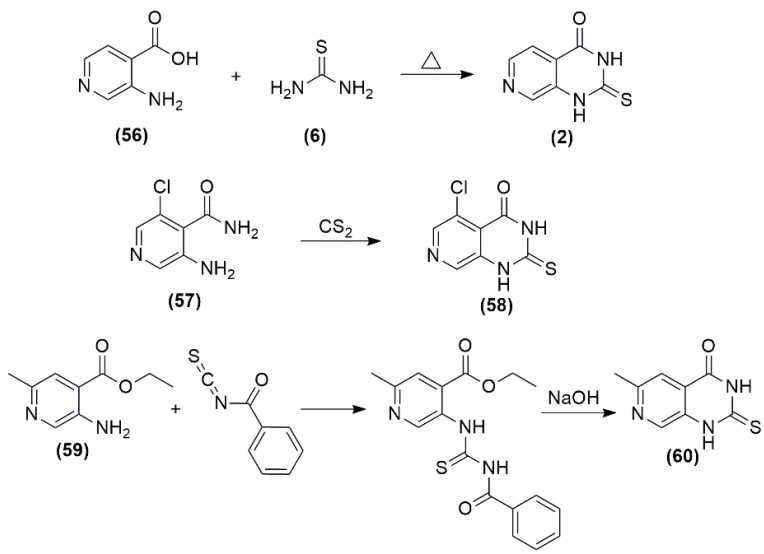


Figure 21. Synthesis of 2-sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one via 3-aminopyridine-4-carboxylic acid/ ester/ amide derivatives

The N3-phenyl derivatives (**61**) have been synthesized using either 1,1′-thiocarbonyldiimidazole (**62**) or phenylisothiocyanates (**63**) with 3-amino-*N*-phenylpyridine-4-carboxamide (**64**) or 3-aminopyridine-4-carboxamide (**65**), respectively (Grosse et al., 2020; Zlotnick et al., 2025) (Figure 22.). Similar to the sulfur substitution reactions observed at the 2-position of the pyrido[2,3-*d*]pyrimidine ring, the core (**2**) undergoes alkylation with alkyl halides under basic conditions to yield S-alkyl derivatives (**66**) (Dyachenko, Vaskevich & Vovk, 2014; Guo et al., 2022; Jian et al., 2021; Murugesan et al., 2018; Vaskevych, Shishkina, Dekhtyar, Smolii, & Vovk, 2024; Westaway et al., 2016). Additionally, treatment of this heterocyclic system with phosphorus oxychloride enables halogenation at the 2- and 4-positions (**67**), as reported in the literature (Cox et al., 2011) (Figure 23.).

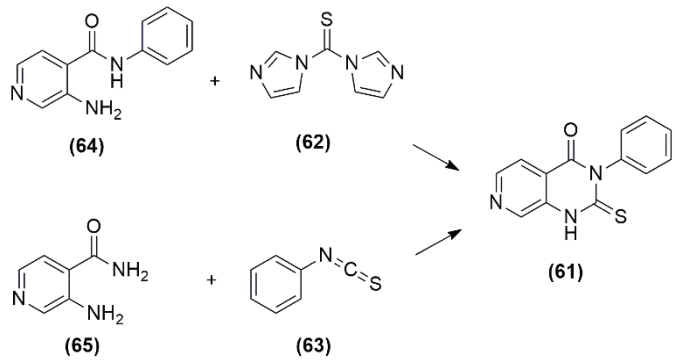


Figure 22. Synthesis of N3-substituted pyrido[3,4-*d*]pyrimidine derivatives

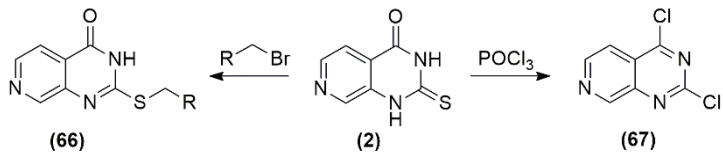
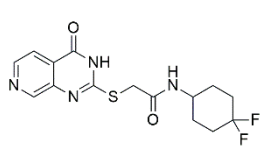
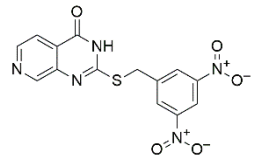
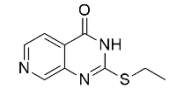


Figure 23. Reactions at the C2 position of pyrido[3,4-*d*]pyrimidine

Studies focusing on compound **2** are extremely limited; consequently, investigations into the biological activities of its derivatives remain scarce. Table 2 summarizes representative examples of compounds reported to exhibit antitubercular activity and cell-penetration inhibitory effects.

Table 2. Representative examples of biological activity of 2-sulfanylidene-2,3-dihydropyrido[3,4-*d*]pyrimidin-4(1*H*)-one derivatives

Antitubercular activity		Cell penetration inhibitor activity
		
Micobacterium tuberculosis H37Rv MIC= 9.40 µM (Murugesan et al., 2018)	*Mycobacterium tuberculosis* H37Rv MIC= >50 µM (Jian et al., 2021)	KDM4C RFMS pIC_{50}= 6.10 IC_{50}= 0.794 µM (Westaway et al., 2016)

2-Sulfanylidene-2,3-dihydropyrido[4,3-*d*]pyrimidin-4(1*H*)-one (3)

Studies focusing on this ring system have remained relatively limited. In the literature, the core scaffold (**3**) has been constructed via treatment of 4-aminopyridine-3-carboxylic acid (**68**) with thionyl chloride or phosphorus oxychloride, followed by reaction with ammonium thiocyanate (Ahmad, Bilodeau, Lajkiewicz & Fernando, 2025a; Fu & Sun, 2024; Jian et al., 2021; Medina & Dong, 2024; Zanaletti, Khan & Chang, 2025) (Figure 24.).

Figure 24. Synthesis of pyrido[4,3-*d*]pyrimidine core via 4-aminopyridine-3-carboxylic acid

Functionalization of this scaffold has also been reported, and within this context, one reported strategy for the construction of the 8-nitro-2-sulfanylidene-2,3-dihydropyrido[4,3-*d*]pyrimidin-4(1*H*)-one (**69**) involved the reaction of a 4-aminopyridine-3-carboxamide derivative (**70**) with 1,1′-thiocarbonyldiimidazole (**62**). The key intermediate, 4-aminopyridine-3-carboxamide derivative (**70**), was obtained through a three-step synthetic sequence starting from 4-hydroxypyridine-3-carboxylic acid (**71**). This sequence included nitration at the 5-position (**72**), conversion of the resulting acid to the corresponding acid chloride (**73**) using thionyl chloride, and subsequent amidation with ammonium hydroxide to afford the desired carboxamide derivative (**70**). The study also included conversion of the thioxo group to the corresponding chloro derivative (**74**), followed by substitution (**75**) with a primary amine derivative (Dai et al., 2024) (Figure 25.).

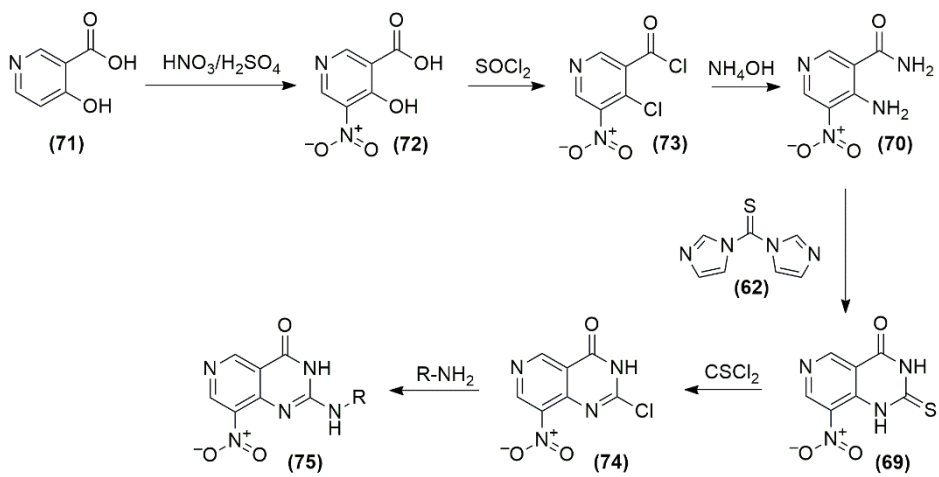


Figure 25. Synthesis of pyrido[4,3-*d*]pyrimidine core via 4-hydroxypyridine-3-carboxylic acid

In a different functionalization strategy, the 3,7-dichloropyrido[4,3-*d*]pyrimidine derivative (**76**) was synthesized through the reaction of 4-amino-2,6-dichloronicotinic acid (**77**) with ethoxycarbonyl isothiocyanate (O-ethyl carbonisothiocyanatidate, **78**) (Ahmad, Fernando & Rui, 2025b; Landry et al., 2025) (Figure 26.).

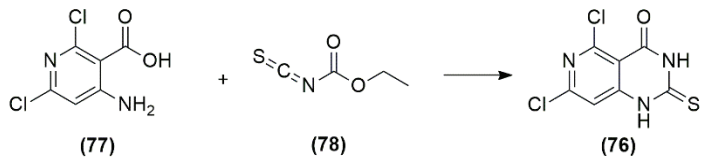


Figure 26. Synthesis of pyrido[4,3-*d*]pyrimidine core via ethoxycarbonyl isothiocyanate

In a study by Shang et al. (2024), an alternative synthetic approach was employed for the preparation of the S-methyl derivative (**79**). In this method, 4-chloropyridine-3-carboxylic acid derivative (**80**) was used as the starting material and was first converted into the corresponding acid chloride (**81**) using thionyl chloride. The resulting intermediate was then reacted with S-methylisothiourea (**82**) to yield methyl *N*-(4,6-dichloro-5-fluoropyridine-3-carbonyl)carbamimidothioate (**83**), followed by a cyclization step carried out in *N,N*-dimethylformamide (DMF) at 120 °C to afford the target compound (**79**) (Shang et al., 2024) (Figure 27.).

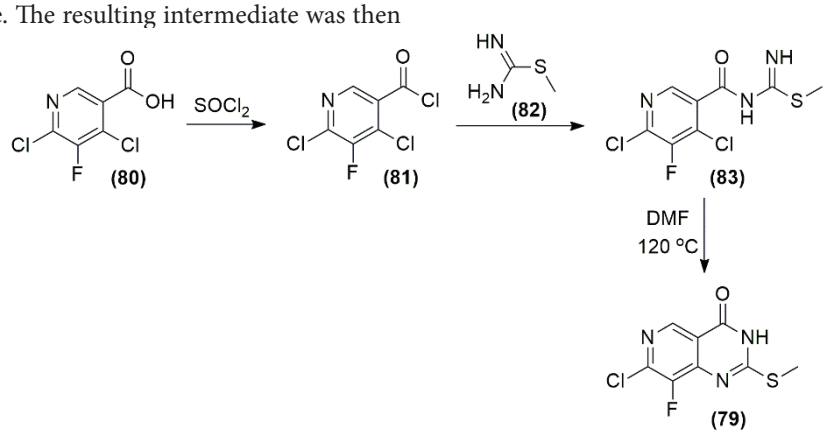


Figure 27. Synthesis of pyrido[4,3-*d*]pyrimidine S-methyl derivative via S-methylisothiourea

Similarly, 4-bromo-2,6-dichloro-5-fluoropyridine-3-carboxylic acid (**84**) was employed as the starting material and initially reacted with *N*-hydroxysuccinimide (NHS). The resulting activated intermediate (**85**) was subsequently treated with S-methylisothiourea (**82**) to yield carbamimidothioate derivatives (**86**), followed by a cyclization step conducted in the presence of *N*-methylimidazole (NMI) to afford the desired heterocyclic compound (**87**) (Chakravarty et al., 2025) (Figure 28.).

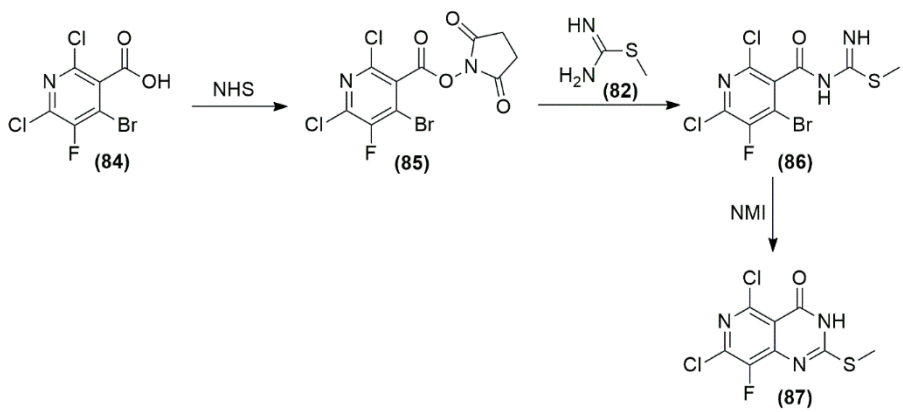


Figure 28. Synthesis of S-methylpyrido[4,3-*d*]pyrimidine via *N*-hydroxysuccinimide and S-methylisothiourea

Despite these synthetic efforts, very limited data exist on the biological activity of this ring system; one study reported that an S-substituted derivative exhibited weak antitubercular activity (*Mycobacterium tuberculosis* H37Rv MIC= >50 μM) (Jian et al., 2021).

2-Sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one (4)

There are only a limited number of studies focusing on the fourth ring of the series, 2-sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one (**4**). Although most reported synthetic routes follow strategies similar to those applied to other pyridopyrimidine systems, several ring-specific synthetic strategies have also been described in the literature.

The earliest report by Korte (1952) employed 3-aminopyridine-2-carboxylic acid (**88**) as the starting material. The acid was first converted to the corresponding thiourea derivative (**89**) via reaction with ammonium thiocyanate, and subsequent heating at 160–180 °C afforded the target heterocycle (**4**) (Figure 29.).

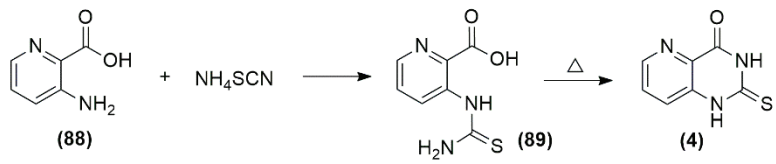


Figure 29. Synthesis of 2-sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one via 3-aminopyridinecarboxylic and ammonium thiocyanate

In a later study, Robins and Hitchings (1956) also utilized compound **88**. Initially, ring closure (**90**) was achieved using urea (**91**), followed by chlorination at the C2- and C4-positions (**92**) with phosphorus oxychloride. Subsequent conversion of the C4-position to the corresponding amino derivative (**93**) was accomplished using ammonium hydroxide, after which reaction with thiourea introduced a sulfanyl group at the C2-position (**94**). Finally, treatment with sodium hydroxide in the fifth step afforded the 2-sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one derivative (**4**) (Robins & Hitchings, 1956). An alternative route involving the reaction of the dichloro derivative first with thiourea (**95**), then with ammonium hydroxide and sodium hydroxide, was also reported in the related literature (Figure 30.).

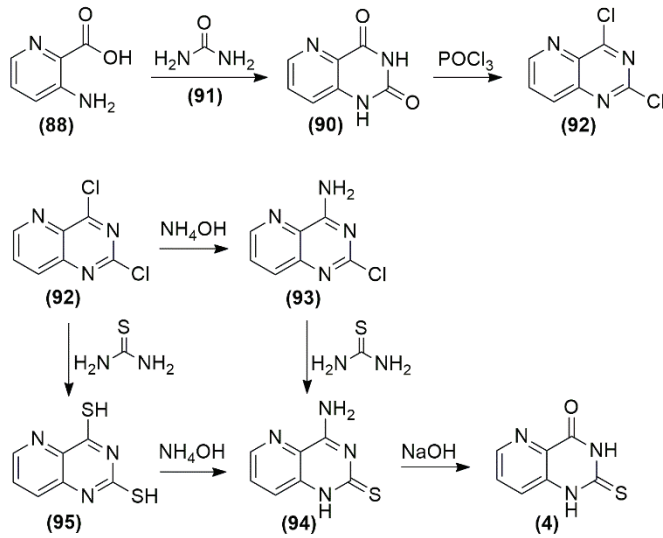


Figure 30. Synthesized of 2-sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one via pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

In another reported method, using 3-aminopyridine-2-carboxylic acid (3-aminopicolinic acid, **88**) as the starting material, ring closure was achieved by solvent-free heating with thiourea (Jian et al., 2021) (Figure 31.).

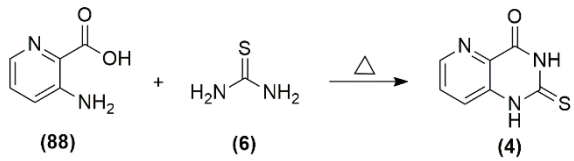


Figure 31. Reaction with 3-aminopyridine-2-carboxylic acid and thiourea

An alternative approach involved the reaction of methyl 3-aminopyridine-2-carboxylate (**96**) with thiophosgene (**97**), yielding methyl 3-isothiocyanatopyridine-2-carboxylate (**98**). The latter underwent cyclization upon heating in a sealed tube under basic conditions. In the same study, methylation (**99**) of the sulfur atom at position two of the core scaffold was carried out using methyl iodide. Subsequently, final compounds (**100**) were obtained through nucleophilic substitution at the same position with piperazine derivatives (Sutton, Walter, East & Perez, 2017) (Figure 32.).

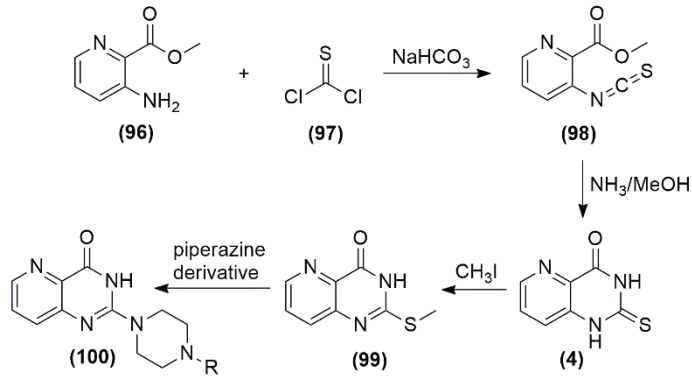


Figure 32. Reaction with methyl 3-aminopyridine-2-carboxylate and thiophosgene

Similarly, reaction of ethyl 3-isothiocyanatopyridine-2-carboxylate (**101**) with hydrazine hydrate affords derivatives bearing an amino group at the 3-position of the ring (**102**). Upon heating with hydrazine hydrate, the sulfanyl group can also be substituted by a hydrazino group (**103**). Furthermore, reaction of the isothiocyanate intermediate with amines enables access to N3-substituted derivatives (**104**) (Urleb, Stanovnik & Tisler, 1990b, 1990c) (Figure 33.).

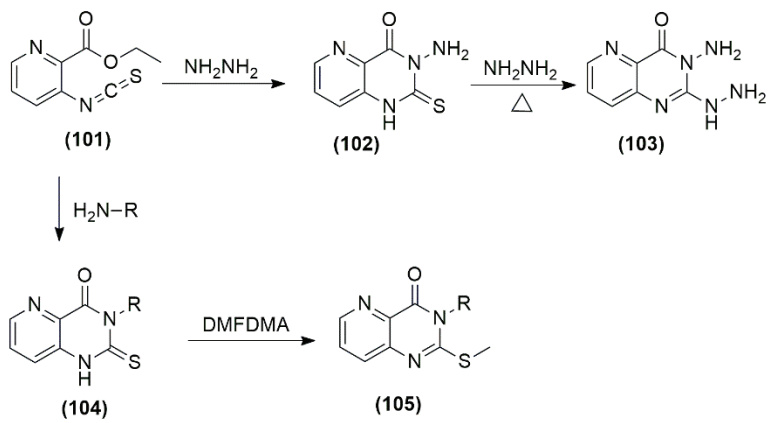


Figure 33. Reaction with ethyl 3-isothiocyanatopyridine-2-carboxylate with hydrazine hydrate and related derivatives

N3-substituted derivatives (**106**) can also be obtained directly through the reaction of 3-aminopyridine-2-carboxylic acid (**88**) with isothiocyanate derivatives (**107**). S-substituted analogues (**108**), as observed for related ring systems, are generally accessible via reactions with alkyl halides under basic conditions (Alverez et al., 2020; El-Sayed, Nossier, Almehizia & Amr, 2022; Lee et al., 2022; Soloducho, 1990; Zlotnick et al., 2025) (Figure 34.). In one study, the S-methyl derivative (**105**) was obtained using *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (Urleb et al., 1990c) (Figure 33.).

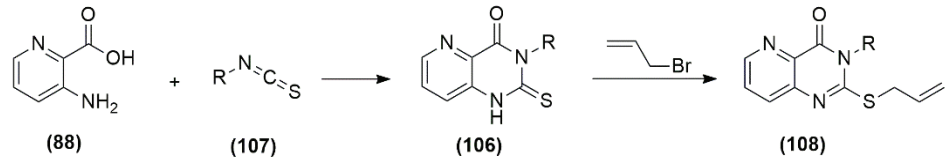


Figure 34. N3- and S-substituted of pyrido[3,2-*d*]pyrimidine derivatives

Among the reactions of N3-substituted pyridopyrimidine derivatives (**106**), one commonly employed transformation involves the replacement of the sulfanyl group at the 2-position with a chlorine atom (**109**) using phosphorus oxychloride. The resulting chloro intermediate can subsequently be reacted with phenolic compounds to afford 2-aryloxy derivatives (**110**). In addition, a variety of coupling reactions can be performed at this same position (**111**) (Bakthavatchalam et al., 2008; Blum, Ghosh, Martinez, Zhang, & Zheng, 2008) (Figure 35.)

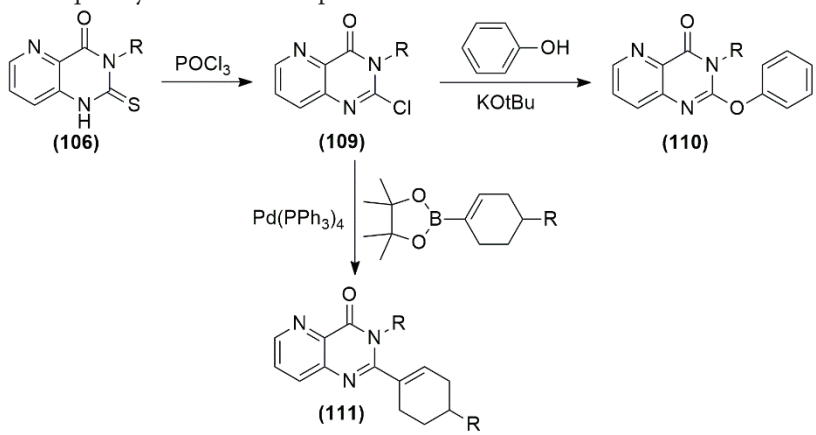
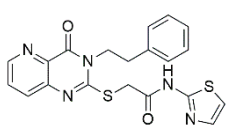
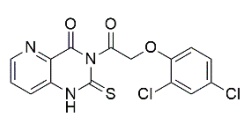
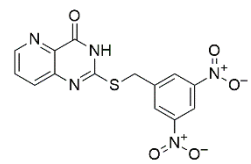


Figure 35. Synthesis of 2-aryloxy/cycloalkylpyrido[3,2-*d*]pyrimidine derivatives

Studies focusing on compound **4** are also limited. Table 3 summarizes representative examples of compounds reported to exhibit anticancer and antitubercular activity.

Table 3. Representative examples of biological activity of 2-sulfanylidene-2,3-dihydropyrido[3,2-*d*]pyrimidin-4(1*H*)-one derivatives

Anticancer activity		Antitubercular activity
 PI3K-C2α IC_{50}= 5.30 μM (Kücükdisli et al., 2023)	 HCT116 IC_{50}= 11.46 μM MCF7 IC_{50}= 8.97 μM CDK-2/cyclin A2 IC_{50}= 1.55 μM (El-Sayed et al., 2022)	 *Mycobacterium tuberculosis* H37Rv MIC= 19.00 μM (Jian et al., 2021)

CONCLUSION

In conclusion, the 2-sulfanylidene-2,3-dihydropyridopyrimidin-4(1*H*)-one ring system, classified into four subgroups—pyrido[2,3-*d*]-, pyrido[3,4-*d*]-, pyrido[4,3-*d*]-, and pyrido[3,2-*d*]pyrimidines—represents an important heterocyclic scaffold in medicinal chemistry. This review provides a systematic comparison of all four pyridopyrimidine isomers incorporating a thiouracil core, which has not previously been presented in a unified manner. Among these subgroups, the pyrido[2,3-*d*]pyrimidine core has been the most extensively investigated, with numerous studies focusing on its synthesis and functionalization, highlighting its prominence in the literature. The limited number of reports on other isomers indicates an opportunity for further exploration.

The synthesis of these ring systems most commonly involves the reaction of aminopyridine carboxylic acids or their derivatives with thiourea. Alternatively, ring closure can be achieved by converting acid derivatives into acid halides, followed by reaction with ammonium thiocyanate. For the pyrido[2,3-*d*] pyrimidine framework in particular, substitutions at the 5, 6, 7, and 8 positions of the rings are frequently introduced using 6-amino-2-sulfanylpyrimidin-4(3*H*)-one as a key starting material. Reactions with β-diketones and α,β-unsaturated carbonyl compounds are widely reported and represent practical and efficient routes to structural diversity. Across all four ring systems, N3 substitution is generally achieved through reactions between aminopyridine carboxylic acid derivatives and isothiocyanates; additionally, substituted thioureas provide an alternative approach for introducing desired groups at the C3 position. In addition, the thione group at C2 can tautomerize to the corresponding thiol, enabling further functionalization. This feature allows the preparation of S-substituted derivatives via reactions with alkyl halides or sulfonic acid esters. C2-chloro intermediates can also be formed in the presence of phosphorus oxychloride and subsequently undergo nucleophilic substitution reactions. Overall, the structural flexibility of these pyridopyrimidine frameworks enables the synthesis of a wide range of novel derivatives, with the pyrido[2,3-*d*]pyrimidine scaffold exhibiting higher synthetic versatility.

Biological studies on pyridopyrimidine derivatives have primarily focused on their anticancer activity; however, compounds exhibiting antibacterial, analgesic, and anti-inflammatory effects have also been reported. Due to the heterogeneity of biological assays and target systems, direct structure–activity relationships could not be conclusively established across all studies. Nevertheless, certain recurring trends suggest that both ring substitution patterns and functionalization at key positions contribute to activity profiles, highlighting the importance of targeted structural modifications. In particular, 5,7-disubstituted or 5- and 7-substituted derivatives are frequently associated with anticancer activity, with these substitutions often consisting of bulky aromatic groups. Taken together, these findings highlight the potential of pyridopyrimidine systems as versatile scaffolds for the design and development of biologically active molecules.

Overall, pyridopyrimidine-based heterocycles represent valuable platforms for medicinal chemistry research and offer significant potential for further structural optimization. Their continued investigation may contribute to the development of novel therapeutic agents, particularly in anticancer drug research. Further systematic structure–activity relationship studies and standardized biological evaluations are required to better understand and fully exploit this potential.

AUTHOR CONTRIBUTION STATEMENT

Concept: FG, YD; Data Collection or Processing: FG, ÖKÖ, YD; Analysis: FG, ÖKÖ, YD; Writing: FG, ÖKÖ, YD; Proofreading: ÖKÖ, YD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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