Pyrido[2,3-d], [3,2-d], [3,4-d] and [4,3-d]pyrimidine Derivatives

Subjects: Chemistry, Applied

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The structures composed of a pyridopyrimidine moiety which have shown a therapeutic interest or have already been approved for use as therapeutics, including pyrido[2,3-d]pyrimidines, pyrido[3,4-d]pyrimidines, pyrido[4,3-d]pyrimidines and pyrido[3,2-d]pyrimidines.

pyridopyrimidines synthesis biological activity N-heterocycles

1. Introduction: Pyridopyrimidines and Their Scaffold

Depending on where the nitrogen atom is located in pyridine, it can be found four possible skeletons for the heterocyclic combination of pyrimidine and pyridine rings (**Figure 1**). Pyridopyrimidines and other *N*-heterocycles are of great interest due to their biological potential. The pyridopyrimidine moiety is present in relevant drugs and, in recent years, it has been studied in the development of new therapies, as evidenced by numerous publications, studies and clinical trials [1][2][3].

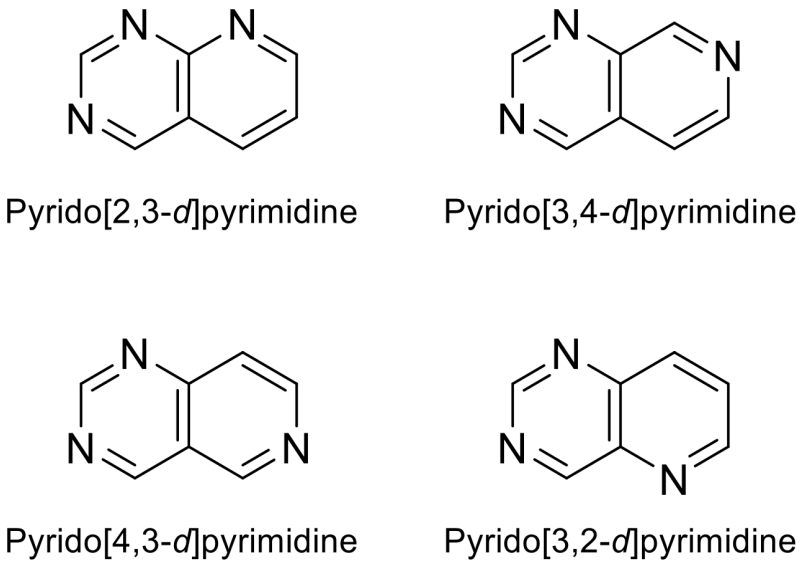


Figure 1. Various pyridopyrimidine structures types.

The various pyridopyrimidines are used on several therapeutic targets. All the synthetic protocols are considered to prepare these pyridopyrimidine derivatives which have shown a therapeutic interest or have been approved for use

as therapeutics according to bibliographic research conducted on Reaxys and Scifinder. Among them, herein can mention in **Figure 2** palbociclib and dilmapimod.

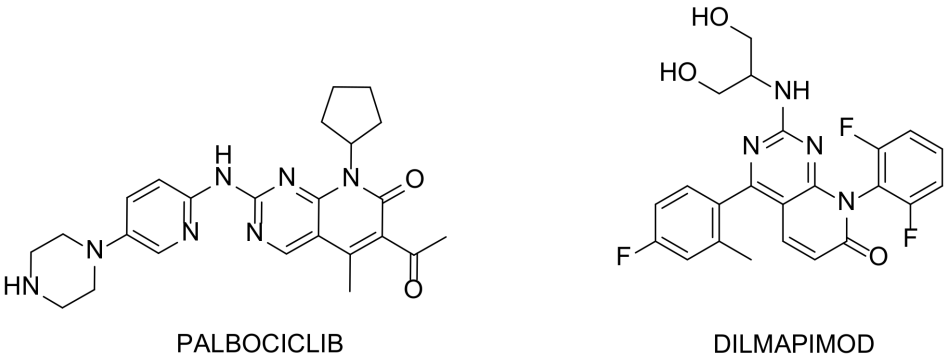


Figure 2. Examples of interesting molecules. Palbociclib: breast cancer drug developed by Pfizer and Dilmapimod: potential activity against rheumatoid arthritis.

Those most frequently mentioned biological targets of pyrido[2,3-d]pyrimidine derivatives are dihydrofolate reductase (DHFR), some kinases, such as the tyrosine-protein kinase transforming protein Abl or MAP kinases, and the biotin carboxylase.

Kinases or protein kinases are the generic names of enzymes involved in the signaling pathways that preside over a large number of cellular functions and are involved in various pathologies, including cancerous pathologies [4][5][6][7].

Pyridopyrimidines are kinase inhibitors and act by competition on the active site or at an allosteric site. Various tyrosine kinase inhibitors, called tyrphostines (e.g., imatinib, gefitinib, sunitinib), which act selectively on one or more receptors with tyrosine kinase activity, are used to treat some specific forms of cancer.

While many inhibitors have already showed great therapeutic potential, intensive research effort is currently underway to discover new molecules able to interact with protein kinases for use in therapy.

Biotin dependent carboxylases can be found in numerous species of fungi, bacteria, plants and, of course, animals and humans. They play an important role in various metabolisms such as fatty acids [8], carbohydrates and amino acids, but also assimilation [9][10][11][12][13][14][15] and fixation [16]. Biotin dependent carboxylases contain acetyl-CoA carboxylase (ACC), propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase (MCC), geranyl-CoA carboxylase (GCC), pyruvate carboxylase (PC), and urea carboxylase (UC). Due to their activity, they are mainly involved in diseases such as type 2 diabetes, obesity and microbial infection [17]. ACC catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA, which is an intermediate substrate. Over the years, ACC inhibitors have attracted great attention in the development of treatments for various human diseases, including microbial infections, metabolic syndrome, obesity, diabetes and cancer [18][19].

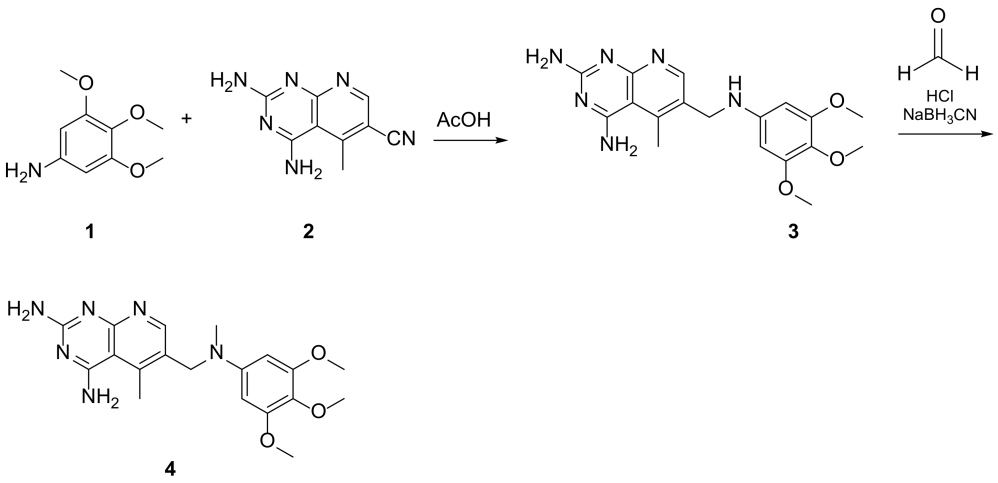
2. Pyridopyrimidines: Therapeutic Potential and Synthesis

This section describes that, for each compound mentioned, the biological activity and the synthetic route reported. The 24 compounds described herein are presented according to the type of pyridopyrimidines (pyrido[2,3-*d*]pyrimidine, pyrido[3,4-*d*]pyrimidine, pyrido[4,3-*d*]pyrimidine and pyrido[3,2-*d*]pyrimidine). For each compound described, the target is indicated and some additional information has been added if different from that mentioned in the introduction.

2.1. Pyrido[2,3-d]pyrimidine

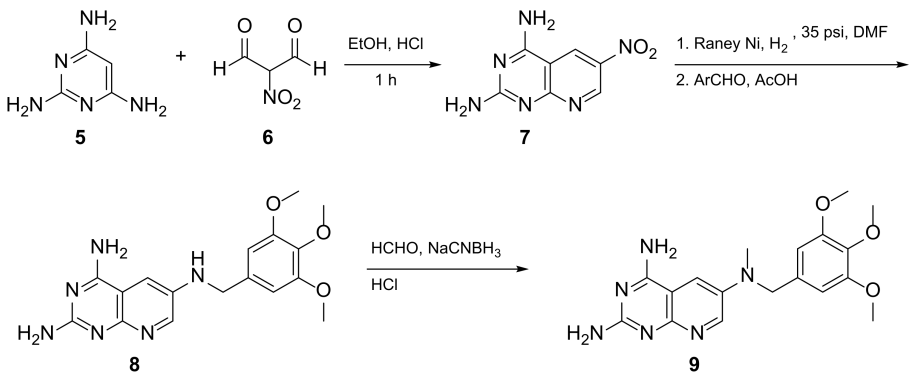
Herein starts with some interesting pyrido[2,3-*d*]pyrimidines. The first one is 5-methyl-6-([methyl(3,4,5-trimethoxyphenyl)amino]methyl)pyrido[2,3-*d*]pyrimidine-2,4-diamine (**Table 1**, entry 1) which has been described to have DHFR dihydrofolate as the target [20].

Kisliuk et al. described, in 1993, the synthesis of pyrido[2,3-*d*]pyrimidine-2,4-diamine (**4**). The reductive condensation of 6-cyano-5-methyl-pyrido[2,3-*d*]pyrimidine-2,4-diamine (**2**) with 3,4,5-trimethoxyaniline (**1**) in the presence of Raney Ni 70% in acetic acid gave the precursor **3** which underwent methylation at the N10 position by reductive alkylation with formaldehyde and sodium cyanoborohydride (Scheme 1) [20].



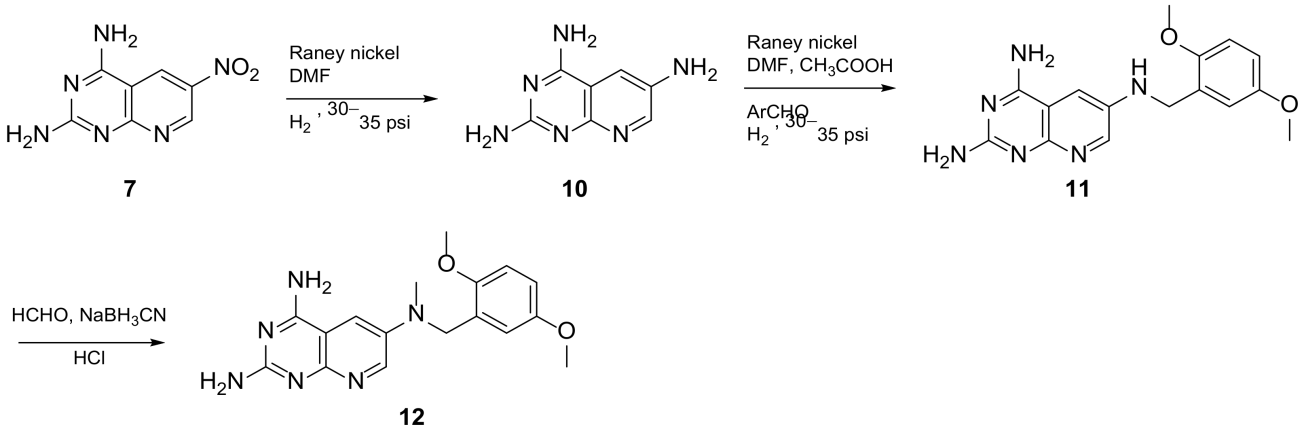
Scheme 1. Synthesis of pyrido[2,3-*d*]pyrimidine-2,4-diamine (**4**) by Kisliuk et al. [20].

Kisliuk et al. also developed another strategy to synthesize pyrido[2,3-*d*] pyrimidine-2,4-diamines as compound **9** (Scheme 2, **Table 1**, entry 2). Starting from 2,4,6-triaminopyrimidine (**5**) with the sodium salt of nitromalonaldehyde, they obtained in a single step the 2,4-diamino-6-nitropyrido [2,3-*d*]pyrimidine (**7**) which was then reduced to its corresponding 6-amino analogue using Raney Ni in DMF. The reductive amination with various aldehydes (ArCHO, in this case 3,4,5-trimethoxybenzaldehyde) provided the desired product **8**. In the last step, **8** was *N*-methylated by treatment with formaldehyde in the presence of sodium cyanoborohydride [15] (Scheme 2). An analog compound (**Table 1**, entry 3) was obtained following the same synthetic pathway (Scheme 2) using 3,5-dimethoxybenzaldehyde.



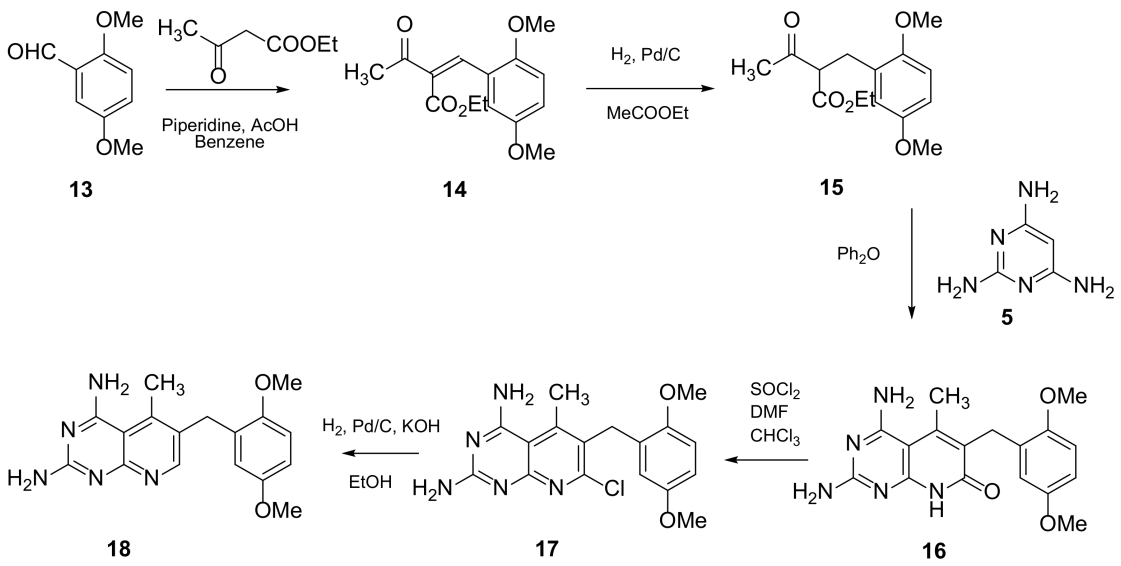
Scheme 2. Synthesis of pyrido[2,3-*d*]pyrimidine-2,4-diamine (**9**) by Kisliuk et al. [15].

In 2008, Queener et al. synthesized **12** starting from 2,4-diamino-6-nitroquinazoline **7** which underwent reduction with hydrogen and Raney nickel at 30-35 psi, providing the desired 2,4,6-triaminoquinazoline (**10**) (Scheme 3). Then, as described above, the 2,5-dimethoxybenzaldehyde ArCHO was added to generate the N9-H precursor **11**. The following step was a reductive N9-alkylation using sodium cyanoborohydride which afforded the final compound [14]. Queener et al. conducted a biological evaluation of this compound **12** (Scheme 3, **Table 1**, entry 4) as a lipophilic inhibitor of dihydrofolate reductase.

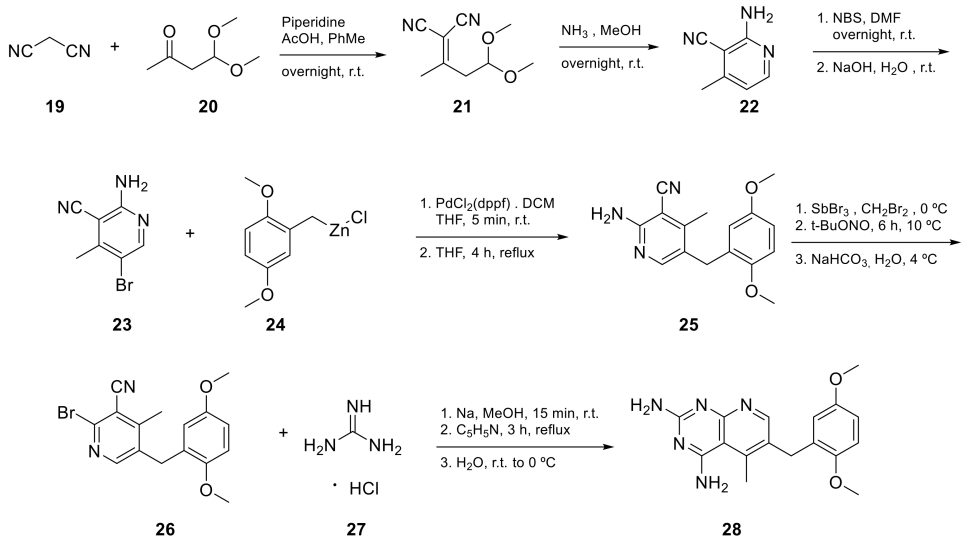


Scheme 3. Synthesis of *N*6-[(2,5-dimethoxyphenyl)methyl]-*N*6-methylpyrido[2,3-*d*]pyrimidine-2,4,6-triamine (**12**) by Queener et al. [14].

Piritrexim (PTX) (Scheme 4 and Scheme 5, **Table 1**, entry 5) is a synthetic antifolate first synthesized by Grivsky, Sigel et al. [21] with anti-parasitic, anti-psoriatic and anti-tumor properties. Piritrexim inhibited dihydrofolate reductase (DHFR) and also showed good antitumor effects on the carcinosarcoma in rats. An advantage of this compound compared to some analogues is that it does not have effects as an inhibitor of histamine metabolism, reducing the potential risk of side reactions on metabolism. Its degree of lipophilicity, i.e., the affinity of this drug for a lipid environment, allows it to diffuse easily into the cells. The various therapeutical activities listed for piritrexim are on melanoma and urothelial cancer, and promising results in head and neck cancer were already obtained in combination with other molecules [16].



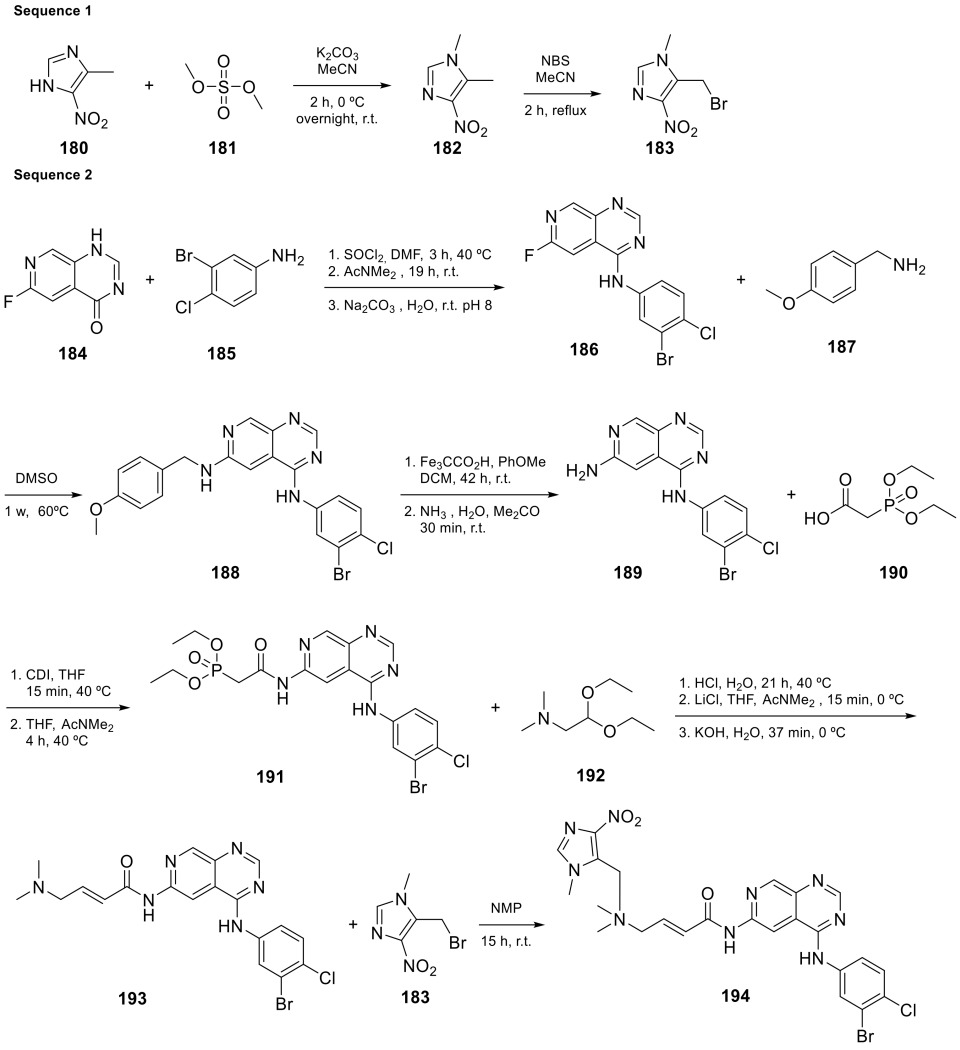
Scheme 4. Synthesis of 6-[(2,5-dimethoxyphenyl)methyl]-5-methylpyrido[2,3-*d*]pyrimidine-2,4-diamine (**18**) by Grivsky, Sigel et al. [21].



Scheme 5. Synthesis of 6-[(2,5-dimethoxyphenyl)methyl]-5-methylpyrido[2,3-*d*]pyrimidine-2-amine (**28**) by Chan and Rosowsky [17].

2.2. Pyrido[3,4-d]pyrimidine

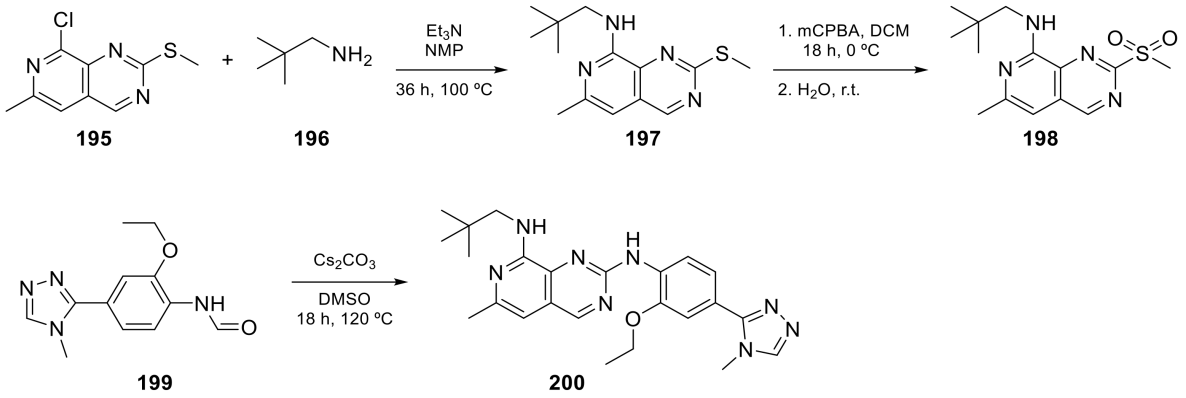
This class of pyridopyrimidine is mainly referenced with kinase activity. The first example mentioned herein is Tarloxotinib (**194** in Scheme 6). It is being studied in the clinical trial NCT03743350 (NSCLC exon 20 or HER2 activating mutation) [22]. This molecule is a kinase inhibitor targeting all members of the HER family, with a novel mechanism of action. It is a hypoxia-activated prodrug that releases an active metabolite irreversibly targeting the kinase. The goal is to inhibit only HER kinases in tumor cells. Tarloxotinib is a Pan-HER kinase inhibitor.



Scheme 6. [(2*E*)-3-({4-[(3-bromo-4-chlorophenyl)amino]pyrido[3,4-*d*]pyrimidin-6-yl}carbamoyl)prop-2-en-1-yl]dimethyl[(1-methyl-4-nitro-1*H*-imidazol-5-yl)methyl]azanium (**194**) [23].

Carlin et al. [23] patented in 2015 the preparation of 4-anilinopyrido[3,4-d]pyrimidine prodrugs (Scheme 6, **Table 1**, entry 19) as kinase inhibitors useful for cancer treatment. The procedure is described in Scheme 6 with classical synthetic methodologies affording the expected compound **194** in twelve steps.

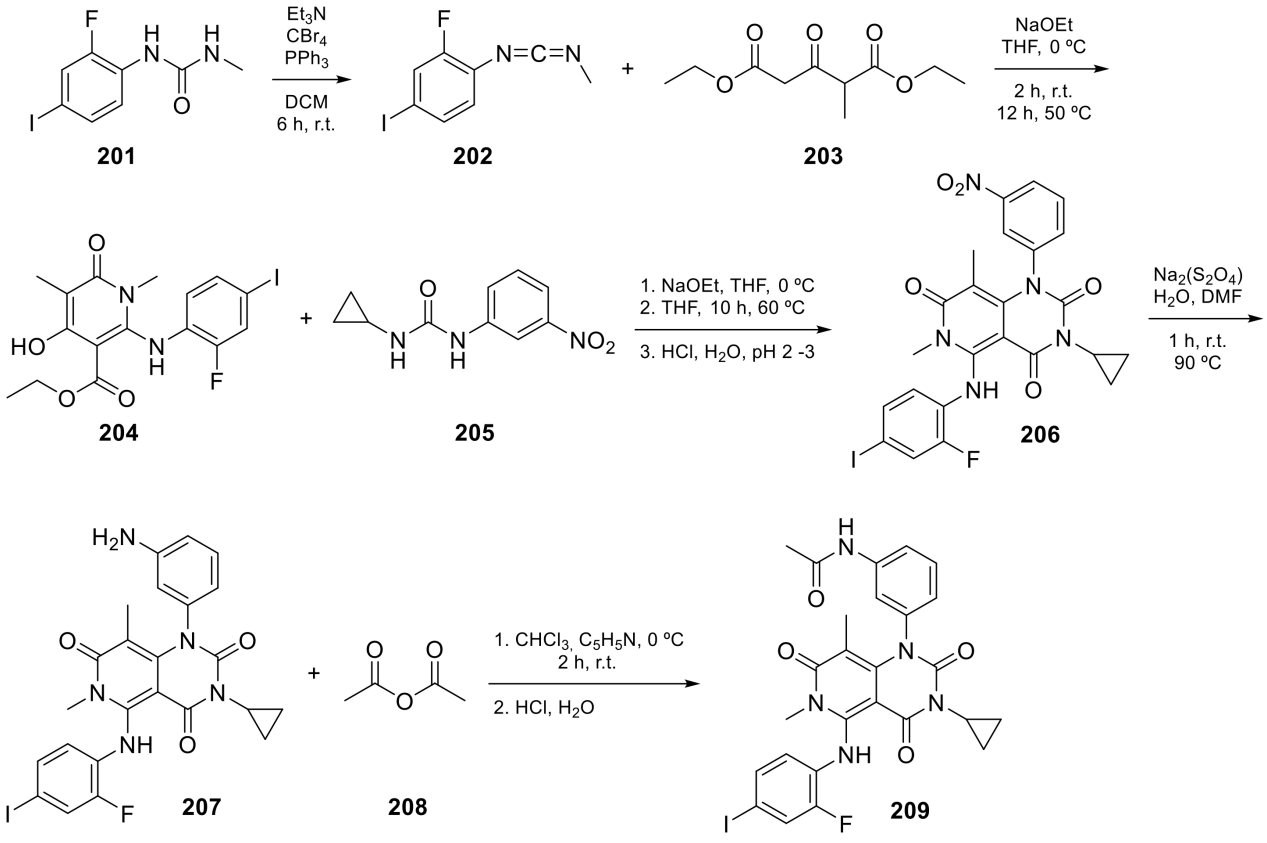
The second example is the BOS172722 derivative (**200** in Scheme 7, **Table 1**, entry 20). This compound, in combination with paclitaxel, was tested in vivo for the treatment of triple hormone receptor-negative breast cancer demonstrating a promising synergy. This selective monopolar spindle 1 (Mps1) kinase inhibitor has been identified as a potential anti-cancer agent because it is involved in the division of cancer cells. This is, therefore, an attractive target for cancer therapy [24][25]. It has the dual specificity protein kinase TTK as the target.



Scheme 7. *N*8-(2,2-dimethylpropyl)-*N*2-[2-ethoxy-4-(4-methyl-4*H*-1,2,4-triazol-3-yl)phenyl]-6-methylpyrido[3,4-*d*]pyrimidine-2,8-diamine (**200**), BOS172722 [24].

2.3. Pyrido[4,3-d]pyrimidine

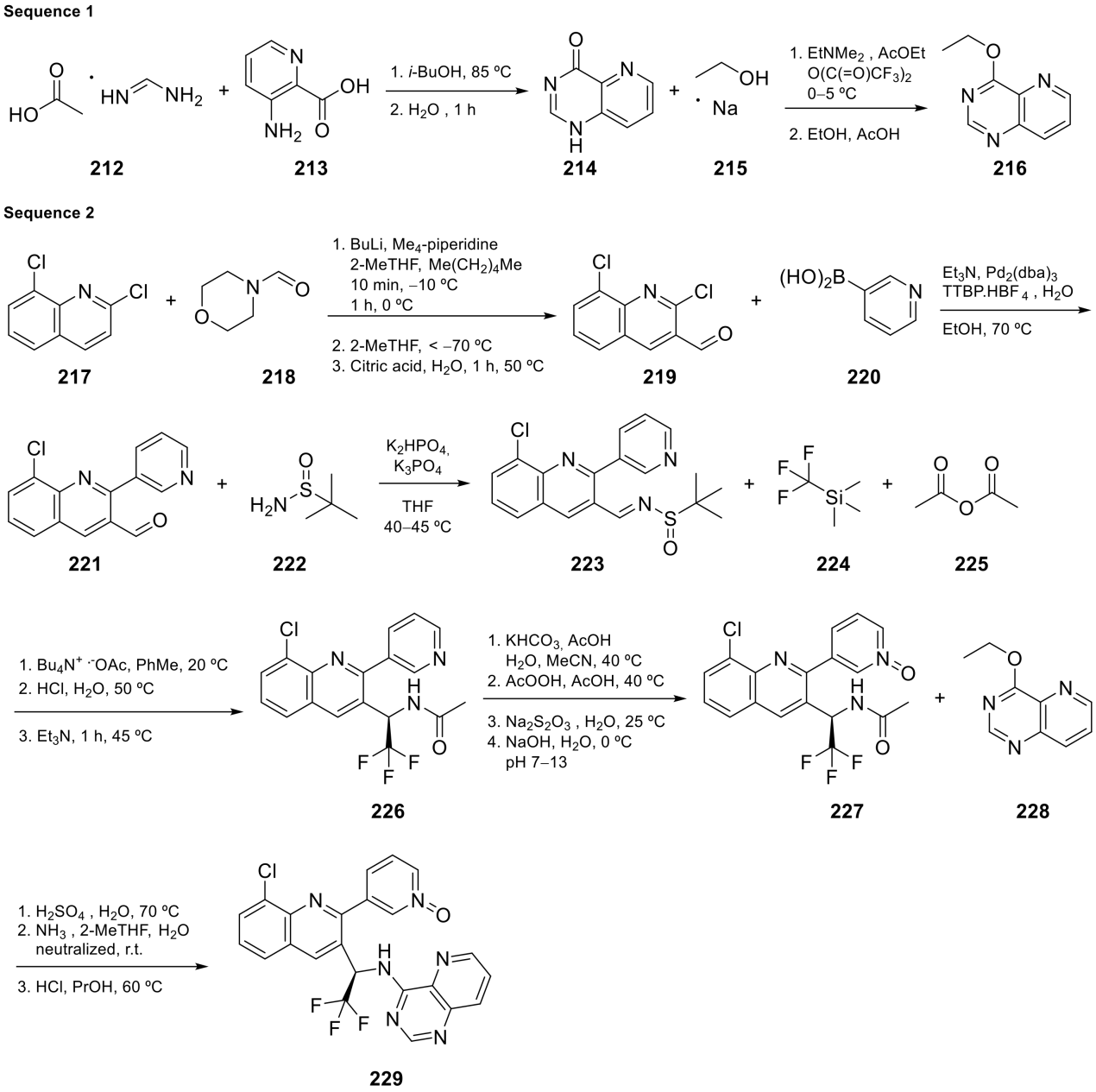
Trametinib (**209** in Scheme 8, **Table 1**, entry 21) is a kinase inhibitor used for specific types of melanoma. This compound, associated with other molecules such as Dabrafenib (Tafilnar) and/or Mekinist (trametinib), has been approved by the FDA in particular for the treatment of degenerative thyroid cancer (ATC) [26][27].



Scheme 8. Synthesis of *N*-(3-(3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*-pyrido[4,3-*d*]pyrimidin-1-yl)phenyl)acetamid, Trametinib (**209**) [28].

2.4. Pyrido[3,2-d]pyrimidine

Seletalisib (**229** in Scheme 9, **Table 1**, entry 22) is a novel small-molecule inhibitor of PI3Kδ that was evaluated in clinical assays to study the treatment and basic science of Primary Sjogren's Syndrome [29]. This molecule is an ATP-competitive and highly selective PI3Kδ inhibitor. Phosphoinositide 3-kinases (PI3K) are enzymes regulating cellular survival, development, and function. They play a key role in immune cell development and function.

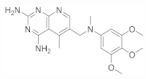
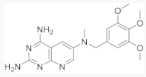
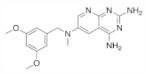
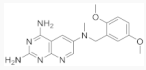
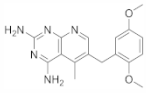
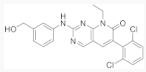
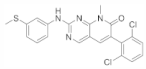
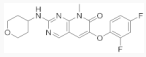
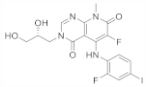
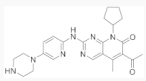


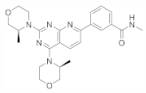
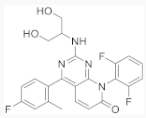
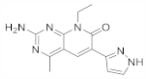
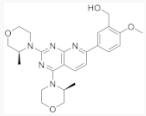
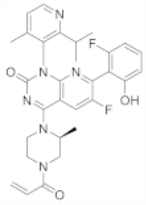
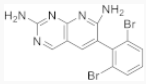
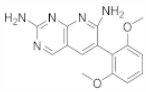
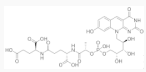
Scheme 9. Synthesis of 3-[8-chloro-3-[(1*R*)-2,2,2-trifluoro-1-([pyrido[3,2-*d*]pyrimidin-4-yl]amino)ethyl]quinolin-2-yl]pyridin-1-ium-1-olate (**229**) [30].

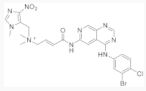
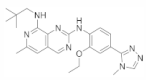
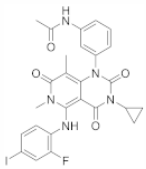
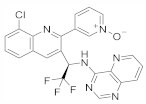
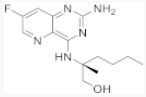
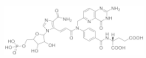
Le Meur et al. [30] patented the synthesis of Seletalisib **229** following the procedure summarized in Scheme 9, and described crystalline forms for the treatment of various pathologies.

All compounds described herein with their target were listed below (**Table 1**).

Table 1. The 24 pyridopyrimidines described here.

Entry	Structure	Name	Target	Ref.
		Pyrido[2,3-*d*]pyrimidine		
1		5-methyl-6-([methyl(3,4,5-trimethoxyphenyl)amino]methyl)pyrido[2,3-*d*]pyrimidine-2,4-diamine	DHFR Dihydrofolate reductase	[31] [32] [20]
2		*N*6-methyl-*N*6-[(3,4,5-trimethoxyphenyl)methyl]pyrido[2,3-*d*]pyrimidine-2,4,6-triamine	DHFR Dihydrofolate reductase	[15]
3		*N*6-[(3,5-dimethoxyphenyl)methyl]-*N*6-methylpyrido[2,3-*d*]pyrimidine-2,4,6-triamine,	DHFR Dihydrofolate reductase	[15]
4		*N*6-[(2,5-dimethoxyphenyl)methyl]-*N*6-methylpyrido[2,3-*d*]pyrimidine-2,4,6-triamine	DHFR Dihydrofolate reductase	[14]
5	 PIRITREXIM	6-[(2,5-dimethoxyphenyl)methyl]-5-methylpyrido[2,3-*d*]pyrimidine-2,4-diamine	DHFR Dihydrofolate reductase	[16] [17] [21]
6		6-(2,6-dichlorophenyl)-2-([3-(hydroxymethyl)phenyl]amino)-8-ethyl-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Tyrosine kinase activity	[33] [34]
7	 PD-173955	6-(2,6-dichlorophenyl)-8-methyl-2-([3-(methylsulfanyl)phenyl]amino)-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Kinase activity: Tyrosine-protein kinase transforming protein Abl	[13]
8		6-(2,4-difluorophenoxy)-8-methyl-2-[(oxan-4-yl)amino]-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Kinase activity: Mitogen-activated protein kinase 14	[35] [36] [37]
9	 TAK-733	3-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-8-methyl-3*H*,4*H*,7*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-dione	Kinase activity: Against MEK and ERK	[38] [39] [40] [41]
10	 Palbociclib	6-acetyl-8-cyclopentyl-5-methyl-2-([5-(piperazin-1-yl)pyridin-2-yl]amino)-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Kinase activity: Cyclin-dependent kinase 4/Cyclin-dependent kinase 6	[42] [43] [44] [45] [46]

Entry	Structure	Name	Target	Ref.
		Pyrido[2,3-*d*]pyrimidine		
			Breast cancer drug	
11	 Vistusertib	3-(2,4-bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl)-*N*-methylbenzamide	Kinase activity: Vistusertib (AZD2014) is a novel mTOR inhibitor	[47] [48]
12	 Dilmapimod (SB-681323)	8-(2,6-difluorophenyl)-2-[(1,3-dihydroxypropan-2-yl)amino]-4-(4-fluoro-2-methylphenyl)-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Kinase activity: P38 MAPK inhibitor, Tumor necrosis factor/Interleukin-1 beta/Interleukin-6. Potential activity against rheumatoid arthritis	[49] [50] [51] [52] [53] [54] [55]
13	 Voxtalisib	2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-7*H*,8*H*-pyrido[2,3-*d*]pyrimidin-7-one	Kinase activity: PI3K/mTOR Inhibitor	[56] [57]
14	 AZD8055	(5-(2,4-bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl)-2-methoxyphenyl)methanol	Kinase activity: Selective ATP-competitive mTOR kinase inhibitor. Induction of MEK/ERK	[58] [59]
15	 AMG-510	6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]-1*H*,2*H*-pyrido[2,3-*d*]pyrimidin-2-one	Kinase Activity: KRAS inhibitor implicated in the RAS/MAPK pathway GTPase KRas	[60] [61] [62] [63] [64]
16		6-(2,6-dibromophenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine	Biotin carboxylase	[65]
17		6-(2,6-dimethoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine	Biotin carboxylase	[33] [66]
18		(2*S*)-2-[(4*S*)-4-carboxy-4-[(2*S*)-2-([hydroxy([(2*R*,3*S*,4*S*)-2,3,4-trihydroxy-5-(8-hydroxy-2,4-dioxo-2*H*,3*H*,4*H*,10*H*-pyrimido[4,5-*b*]quinolin-10-	Methanobacterium redox coenzyme Factor 420 (F_{420})	[67]

Entry	Structure	Name	Target	Ref.
		Pyrido[2,3-*d*]pyrimidine		
		yl)pentyl]oxy))phosphoryl]oxy)propanamido]butanamido]pentanedioic acid		
		Pyrido[3,4-*d*]pyrimidine		
19	 Tarloxotinib	[(2*E*)-3-((4-[(3-bromo-4-chlorophenyl)amino]pyrido[3,4-*d*]pyrimidin-6-yl)carbamoyl)prop-2-en-1-yl]dimethyl[(1-methyl-4-nitro-1*H*-imidazol-5-yl)methyl]azanium	Kinase Activity: Pan-HER kinase inibitor	[23]
20	 BOS172722	*N*8-(2,2-dimethylpropyl)-*N*2-[2-ethoxy-4-(4-methyl-4*H*-1,2,4-triazol-3-yl)phenyl]-6-methylpyrido[3,4-*d*]pyrimidine-2,8-diamine	Kinase Activity: Dual specificity protein kinase TTK	[24] [25] [68] [69]
		Pyrido[4,3-*d*]pyrimidine		
21	 Trametinib	*N*-(3-(3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-1*H*,2*H*,3*H*,4*H*,6*H*,7*H*-pyrido[4,3-*d*]pyrimidin-1-yl)phenyl)acetamide	Dual specificity mitogen-activated protein kinase kinase 1/Dual specificity mitogen-activated protein kinase kinase 2	[26] [27] [70] [71]
		Pyrido[3,2-*d*]pyrimidine		
22	 Seletalisib	3-(8-chloro-3-[(1*R*)-2,2,2-trifluoro-1-((pyrido[3,2-*d*]pyrimidin-4-yl)amino)ethyl]quinolin-2-yl)pyridin-1-ium-1-olate	selective PI3Kδ inhibitor	[72] [30]
23		(2*S*)-2-((2-amino-7-fluoropyrido[3,2-*d*]pyrimidin-4-yl)amino)-2-methylhexan-1-ol	Chronic hepatitis B TLR8 receptor	[73] [74]
24	 β-DADF	(2*S*)-2-((4-[(2*E*)-*N*-((2-amino-4-oxo-1*H*,4*H*-pyrido[3,2-*d*]pyrimidin-6-yl)methyl)-3-(4-carbamoyl-1-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-[(phosphonooxy)methyl]oxolan-2-yl]-1*H*-imidazol-5-yl)prop-2-enamido]phenyl)formamido)pentanedioic acid	Bifunctional purine biosynthesis protein PURH	[75] [76]

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