Chapter

Synthetic Approaches for Pharmacologically Active Decorated Six-Membered Diazines

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Abstract

Diazine alkaloid (pyridazine, pyrimidine and pyrazine) scaffold, a widespread two-nitrogen containing compounds in nature (DNA, RNA, flavors, and fragrances), constitutes a central building block for wide range of pharmacological applications. Diazines are reported to exhibit antimetabolite (antifolate and), anticancer, antibacterial, antiallergic, tyrosine kinase, antimicrobial, calcium channel antagonistic, anti-inflammatory, analgesic, antihypertensive, antileishmanial, antituberculostatic, anticonvulsant, diuretic and potassium-sparing, to antiaggressive activities. Pyridazine (1,2-diazine), pyrimidine (1,3-diazine) and pyrazine (1,4-diazine) are found as mono-systems, fused or annulated in pharmaceutical, agrochemical or materials. These six-membered heterocyclic aromatic moieties defined as privileged scaffolds constitute diverse chemical structures and as such hold substantial interest for organic, medicinal and biological chemists. This chapter will focus on elaboration of the different synthetic approaches applied in preparing pharmacologically active decorated diazines with special care on pyrimidines (non-fused substituted forms) that are endowed with clinical applications. Synthetic approaches applied in preparing selected FDA approved drugs with pyrimidine as a central unit bearing different substituents will be intensively explored. Special attention will be given to novel synthetic methodologies that served molecules with improved druglikeness and ADME-Tox properties.

Keywords: diazine, pyrimidine, chemistry, synthesis, methods, substituted, medicinal, bioactive, anticancer, ADME-Tox

1. Introduction

Pyrimidine derivatives, broadly applied in therapeutic disciplines, owing to their high degree of structural diversity. This “privileged scaffold” and “derivatives” either as substituted or as fused systems gain wide interest due to plentiful biological activities reported over the years. Those versatile biological activities include (and not limited to) modulation of myeloid leukemia (for example imatinib, Dasatinib and nilotinib are pyrimidine-based drugs and well established treatments for leukemia) [1, 2], breast cancer and idiopathic pulmonary fibrosis [3], antimicrobial [4],

antifungal [5], antiparasitic [6], diuretic [7], antitumor [8–13], antifilarial [14], DNA topoisomerase II inhibitors [15], antitubercular agents [16], antimalarial [17] and antiplasmodial [18], anti-inflammatory and analgesic activities [19–21], anti-HIV [5, 22, 23], cardiovascular agents and antihypertensive [24, 25], antiulcer agents [18], hair disorders activities [26], calcium-sensing receptor antagonists, DPP-IV inhibitors [27, 28], antidiabetic [29], potent adenosine A2a receptor agonistic or antagonist action [30], TLR8 or [15] or interferon beta (IFN-β) modulators [31], vascular relaxation for ocular ciliary artery and neuroprotection on retinal ganglion cell [32], 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and coronary heart disease therapeutics [33], anticancer [8, 34–36], key intermediate for Vitamin B1 [37], pyruvate dehydrogenase kinase inhibitors [38]. In addition, many of pyrimidine derivatives are reported to possess potential central nervous system (CNS) and antidepressant properties [39], antihypnotic [40], anti-Alzheimer's Disease (AD) agents [41, 42], anticonvulsant [43], antiallergic [44] and for treatment of hypoglycemic and hypolipidemic activities [45, 46].

Over the years a large interest in fused pyrimidines compiled and exceeded in certain extent substituted pyrimidine derivatives. Though highly appealing the synthesis of fused pyrimidines- is beyond the scope of this chapter. Additionally, this chapter will not address in depth the diverse bioactivities neither in structure activity relationship (SAR), nor in detailed mechanism of actions (MOA). The main focus of this manuscript is to explore various synthetic methods employed to produce this diverse group of compounds.

Synthesis of pyrimidine and its derivatives gains a great deal of interest due to wide applications in medical and therapeutic.

The current chapter focuses on chemical process and methods to derivatize the pyrimidine heterocyclic core with di-, tri- and tetrasubstituted pyrimidines.

2. Challenges facing pyrimidine synthesis

Although widely used, the existing protocols for the synthesis of pyrimidines were labor intensive, oftentimes impractical, inefficient or incompatible with a number of functional groups, harsh reaction conditions, involvement of transition metal catalysis, multistep synthesis of the starting material, or need for inert gas protection, remain as shortcomings in known pyrimidine synthesis (**Figure 1**).

3. Synthetic methods in decorated pyrimidine core

A diverse group of drugs or drug candidates comprise pyrimidine core. The instances elaborated below belong to recently FDA approved ones or with special medical interest.

3.1 Synthesis of N-2,4-Disubstitited pyrimidines

Polyamino-pyrimidines play a very important role in biological and pharmaceutical chemistry. 2,4- diamino-pyrimidine derivatives as potential antimalarial agents [17], SNSR4 antagonists [47], antitumor agents [48] and caspase-1 inhibitors [49]. This report focused on the method development for the synthesis of the latter class of compounds.

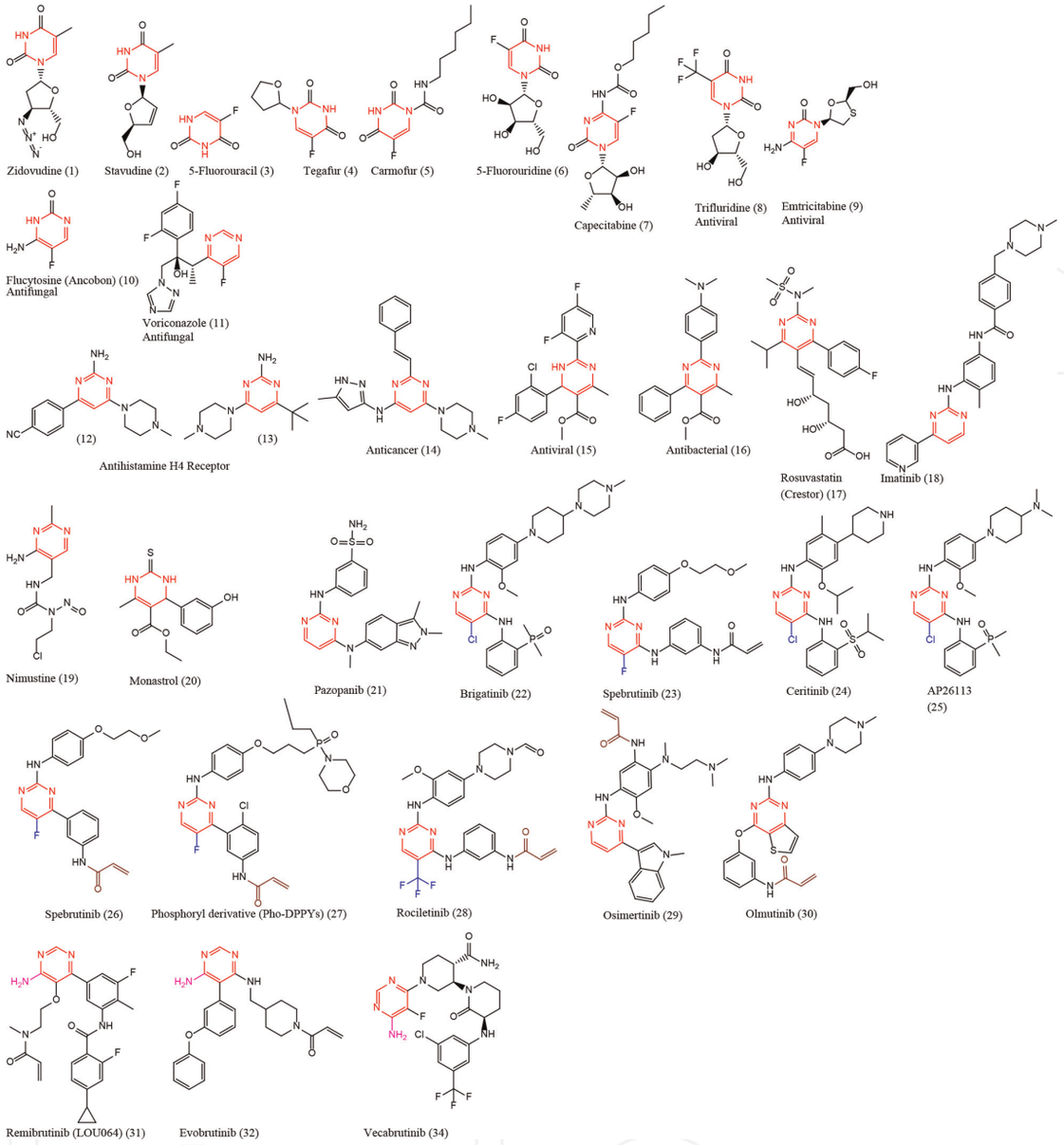


Figure 1.
Examples of chemical structures of bioactive pyrimidine-based derivatives. Pyrimidine heterocyclic rings found in potent anti-HIV agents like zidovudine (1), Stavudine (2); antiviral like Trifluridine (8), Emtricitabine (9, 15); antifungal like Voriconazole (11) Flucytosine (Ancobon) (10); antihistamine H4 receptor (12 and 13), antibacterial (16), cholesterol lowering agent Rosuvastatin (Crestor) (17); antitumor agents like fluorouracil (3), Tegafur (4), Carmofur (5), 5-Fluorouridine (6), Capecitabine (7), ENMD-2076 (14), Imatinib (18), Nimustine (19), Monastrol (20), Pazopanib (21), Brigatinib (22), Spebrutinib (23), Ceritinib (24), AP26113 (25), Spebrutinib (26), phosphoryl derivative (pho-DPPYs) (27), Rociletinib (28), Osimertinib (29), Olmutinib (30), Remibrutinib (LOU064) (31), Evobrutinib (32), Vecabrutinib (34).

Polysubstituted pyrimidines received sub- special attention due to their pronounced physiological activity.

3.1.1 Synthesis of N-2,4-Disubstituted N-2,4,5-trisubstituted pyrimidines

3.1.1.1 Approaches for synthesis of N-2,4-disubstituted pyrimidines

2,4-disubstited pyrimidines are classifies according to the type of bond linking the substituent to the core heterocycle: i) 2,4-diamminosubstituted (2,4-diN), ii) 2,4-

monoaminomonocarbon (2 N, 4C), iii) 2,4-dicarbon (2,4-diC), iv) 2,4-monoaminomonooxo (2 N, 4O), v) 2,4-monoaminomonothio (2 N, 4S), vi) 2,4-monothiomonoamino (2S, 4 N), vii) 2,4-monothiomonocarbo (2S, 4C) and so on. Substituents reported so far can be aromatic, aliphatic, heteroaromatic and heteroaliphatic.

3.1.1.2 2,4-Disubstitited pyrimidines: a heterocyclic core with privileged regioisomers

An increased number of 2,4-disubstituted pyrimidine derivatives that are endowed with bioactivities indicated high number of research articles and patent application shown in the literature (**Figure 2**). Though most of the reported activities of 2,4-disubstituted pyrimidines were related to antitumor due to ability to exert antiproliferative effect like inhibitors of KDR [50] and Aurora kinase [51], ERα/VEGFR-2 [52], T790M-EGFR [53] and L858R/T790M-EGFR double mutant [54] inhibitors, bioactivities of high significance of some 2,4-disubstituted pyrimidines such as antibacterial [55], anti-neuronal nitric oxide synthase [56], anticholinesterases [57] actions were also disclosed [58].

In the following section synthetic methods of four FDA approved drugs Pazopanib (21), Spebrutinib (51), Dabrafenib (60) and Rilpivirine (62) will be presented and discussed in details.

3.1.1.2.1 Case study—1: synthesis of Pazopanib hydrochloride [Votrient®, GW786034, 5-[[4-[(2,3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide. HCl, (21)]

Pazopanib [Votrient®, GW786034, 5-[[4-[(2,3-dimethylindazol-6-yl)-methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide (21)] is a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/b, and c-kit. The drug blocks tumor growth and inhibits angiogenesis. It was approved for renal cell carcinoma by the U.S. Food in 2009 and advanced soft tissue sarcoma [59]. The drug is marketed under the trade name Votrient by the drug's manufacturer, GlaxoSmithKline [59].

3.1.1.2.1.1 Pazopanib One drug different Synthetic Routes

In the procedure reported by Qi et al. the methylation of 3-methyl-6-nitroindazole (36) was carried in the presence of dimethyl carbonate (DMC) and 1,4-diazabicyclo [2.2.2] octane (DABCO) ending in the N2,3-dimethyl-6-nitroindazole (36) in high yield. In another report the methylation of 3-methyl-6-nitroindazole (36) was performed using trimethyl orthoformate in the presence of BF_3OEt to give rise to the N2,3-dimethyl-6-nitroindazole (37) in 65% yield.

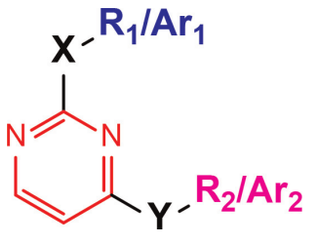


Figure 2.
Types of 2,4-disubstitited pyrimidines (X = O, S, C, NH; Y = X = O, S, C, NH).

The reduction step was carried out under hydrogenation of (36) in the presence of Pd/C and H_2 to afford the aminoindazole derivative (37) in 97% yield [60]. The subsequent condensation of aminoindazole derivative (37) with 2,4-dichloro-pyrimidine (38) to yield the pyrimidinylaminoindazole (39) and (40). A second methylation at the secondary aniline nitrogen of (40) with CH_3I and Cs_2CO_3 resulted gave (41) in 83% yield, which was afterwards condensed with aniline derivative 5-amino-2-methylbenzenesulfonamide (42) in acidic alcohol solution (HCl/isopropanol) to furnish the target compound (21) as hydrochloride salt in 81% yield.

Allowing 6-amino-2,3-dimethyl-2H-indazole (37) to react with 2,4-dichloro-pyrimidine (38) gave rise exclusively to the C4-aminated product (40) indicating regioselectivity of the reaction with 2,4-dichloropyrimidine (38). The intermediate (40) was transformed into (41) following the reaction with the sulfonamide aniline derivative i.e. 5-amino-2-methylbenzenesulfonamide (42).

The coupling of the aniline derivative like 5-amino-2-methylbenzenesulfonamide (42) to (41) was accomplished in good to high yields in refluxing ethanol.

To overcome the reduced regioselectivity in the methylation reaction of N-H indazoles, usually yielded a mixture of N-alkyl 1*H*-indazoles and N-alkyl 2*H*-indazoles regioisomers (**Figures 3** and **4**).

YiCheng Mei *et al* reported a synthetic process where the 2,3-dimethyl-6-nitro-2*H*-indazol (36) was prepared in a regioselective manner (**Figure 5**) [61].

3-Methyl-6-nitro-1*H*-indazole (35) was prepared 93.9% yield by allowing 2-ethyl-5-nitroaniline (45) to react with sodium nitrite in glacial acetic acid. The regioselective conversion of 3-methyl-6-nitro-1*H*-indazole (35) to prepare N2,3-dimethyl-6-nitro-2H-indazole (37) was accomplished using trimethyl orthoformate in toluene and DMF (10, 1 mL) at room temperature (should be kept below 35°C). These conditions

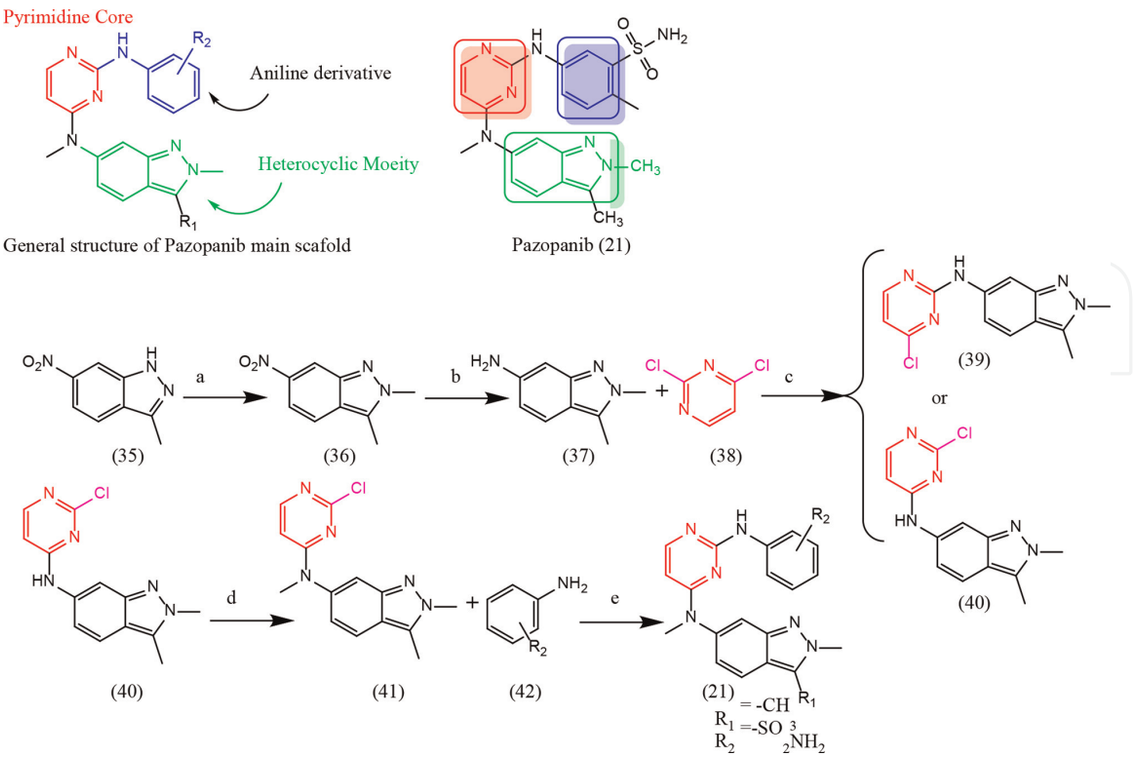


Figure 3.
Synthesis of Pazopanib (21). Reagents and conditions: a) DMC, DABCO, DMB; b) Pd/C, H_2, EtOH; c) $NaHCO_3$, EtOH; d) CH_3I, Cs_2CO_3, DMF; e) EtOH [60].

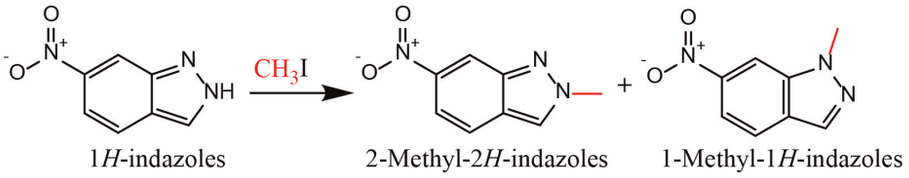


Figure 4.
Regioselective methylation of 1H-indazoles.

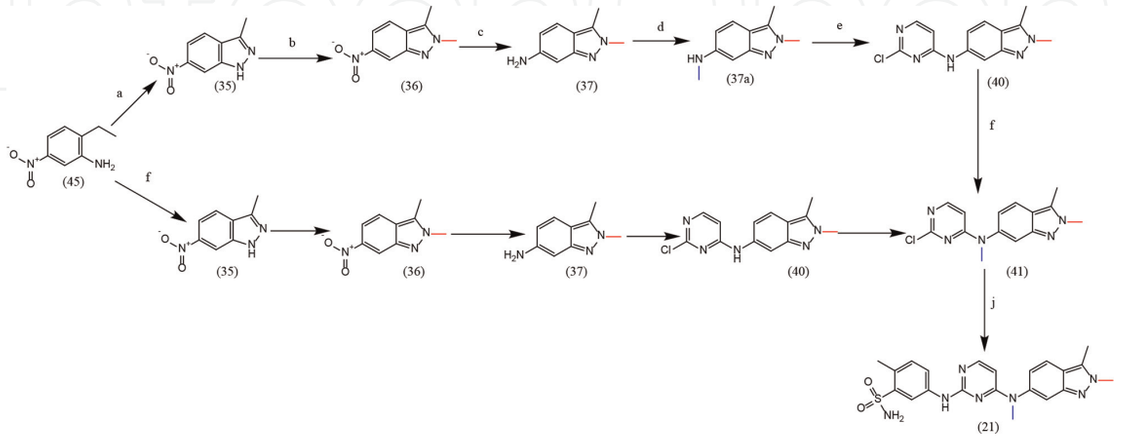


Figure 5.
Synthesis of Pazopanib (21) following YiCheng Mei et al *report. Reagents and conditions: a)* t-*BuONO, acetic acid; b) trimethyl oxonium tetraflouroborate; c) tin(II) chloride; d) 2,4-dichloropyrimidine (38); e) MeI, rt.; f) sodium nitrite, acetic acid; g) trimethyl orthoformate, DMF, sulfuric acid, toluene, reflux; h) MeOH, Pd/C, H_2, paraformaldehyde, NaH, $NaBH_4$; i) 2,4-dichloropyrimidine (38); j) 5-amino-2-methylbenzenesulfonamide, reflux.*

produce the N2-methylated isomer. The nitro-derivative was subjected to hydrogenation (Pd/C catalyst) of (36) followed by methylation using Eschweiler-Clarke methylation reaction [62], providing N-2,3-dimethyl-6-nitro-2H-indazole intermediate (37) in 63.0% yield after recrystallization from the ethanol. Worth noting that in the patent disclosed Kumar and colleagues the reduction of the N2,3-dimethyl-6-nitro-2H-indazole (36) was converted to the amino-derivative using Raney nickel in 95% yield [63].

The secondary amine in N2,3-trimethyl-2H-indazol-6-amine (37a) was reacted with 2,4-dichloropyrimidine (38) in DMF under basic conditions and elevated temperature (100°C, 3 hr) afforded N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine (41) in 88.4% yield. The final product as hydrochloric salt was prepared as a result of reacting N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2*H*-indazol-6-amine (41) with 5-amino-2-methylbenzenesulfonamide (42) in isopropanol under acidic conditions in 76.0% yield. N-(2-chloropyrimidin-4-yl)-N,2,3-dimethyl-2*H*-indazol-6-amine (40) was prepared by allowing N2,3-trimethyl-2H-indazol-6-amine (37a) to react with 2,4-dichloropyrimidine (38) in a mixture of H2O/MeOH for 24 hr. at temperature ranges between 25 and 30°C in 86.7% yield.

The N-methylation was performed using methyl iodide in DMF under basic conditions (Cesium carbonate) with N-(2-chloropyrimidin-4-yl)-N,2,3-dimethyl-2*H*-indazol-6-amine (40) to afford N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine (41) in 90% yield.

Pazopanib hydrochloride salt was prepared by allowing N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine (41) to react with 5-amino-2-

methylbenzenesulfonamide (42) in refluxing acidified (4 M HCl) isopropanol for 10–12 hr. in 97% yield. In cases the last step was performed under acidic conditions (HCl in isopropanol) then Pazopanib hydrochloride salt (21) was collected.

3.1.1.2.2 Case study −2: synthesis of pyrimidine-based Bruton's Agammaglobulinemia tyrosine kinase (BTK) [Spebrutinib, CC-292, AVL2923, (5 N-[3-[[5-fluoro-2-[4-(2-methoxyethoxy)anilino]pyrimidin-4-yl]amino]phenyl]prop-2-enamide] (51)

Spebrutinib (51), an orally bioavailable, potent and selective covalent inhibitor of Bruton's agammaglobulinemia tyrosine kinase (BTK) [59]. BTK, a cytoplasmic tyrosine kinase and member of the Tec family of kinases, plays a central role in B lymphocyte development, activation, signaling, proliferation and survival [64]. Beside it potential in autoimmune related diseases, since BTK mediates the B-cell and Fc receptor signaling pathways [64], the drug is considered with great value for neoplastic disease and particularly in hematopoietic malignancies [65–68]. Upon administration, Spebrutinib targets and covalently binds to Cys 481 in BTK, blocking the ATP-binding pocket of the enzyme BTK, thereby preventing its downstream signaling. By irreversibly inhibiting BTK, administration of this agent may lead to an inhibition of B cell receptor (BCR) signaling and may inhibit cell proliferation of B-cell malignancies. Readers interested in a wider and deeper perceptions on BTK inhibitors and embodied role in malignant and non-malignant disease are referred to excellent reviews [65–68].

Synthetically, the molecule (49) is produced starting from 2,4-dichloro-5-fluoropyrimide (45). The coupling of the two different substituents to the pyrimidine core was performed under classical conditions. The first step was accomplished by reacting the 2,4-dichloro-5-fluoropyrimide with the mono-BOCylated *meta*-diaminobenzene (46). The selective displacement of chloride at C4 by *tert*-butyl N-(3-aminophenyl) carbamate (46) renders high ratio of regioselective synthon and yielded the intermediate (47), which was reacted with the second substrate at C2 by 4-(2-methoxyethoxy)aniline (48). Due to the presence of *tert*-BOC (acid cleavable) as protecting group the two steps have be conducted under basic conditions.

Following the cleavage of the protecting group *tert*-BOC under acidic conditions, the acryloyl chloride (prop-2-enoyl chloride) was coupled to the free amine under basic conditions (**Figure 6**).

3.1.1.2.3 Case study −3: synthesis of Dabrafenib [trade name Tafinlar, N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, GSK2118436, (60)]

Rheault and his colleagues reported the synthesis of Dabrafenib (GSK2118436, (60)) (**Figure 7**). The strategy depends on synthesizing the building blocks starting from the bromobenzoic acid derivative (52) and the sulfonamide (56). The coupling to pyrimidine moiety was performed via a nucleophilic substitution of 2-chloro-4-methylpyrimidine (61) facilitated by lithiation of the 4-methyl using LiHMDS. The yield of this step was recorded as high. The synthesis of the core substituted thiozole (59) was accomplished via bromination of the benzylic/alpha carbon of (58) using NBS and reacting the intermediate with 2,2,2- trimethylthioacetamide either in polar aprotic solvent like DMF or DMA [69].

The second substitution at N2-pyrimidine was accomplished by either concentrated ammonia (7 N NH_3) in methanol in sealed tube under heating of 100°C or under acidic facilitated substitution (using HCl in 2,2,2-trifluoroethanol as solvent) when the amine

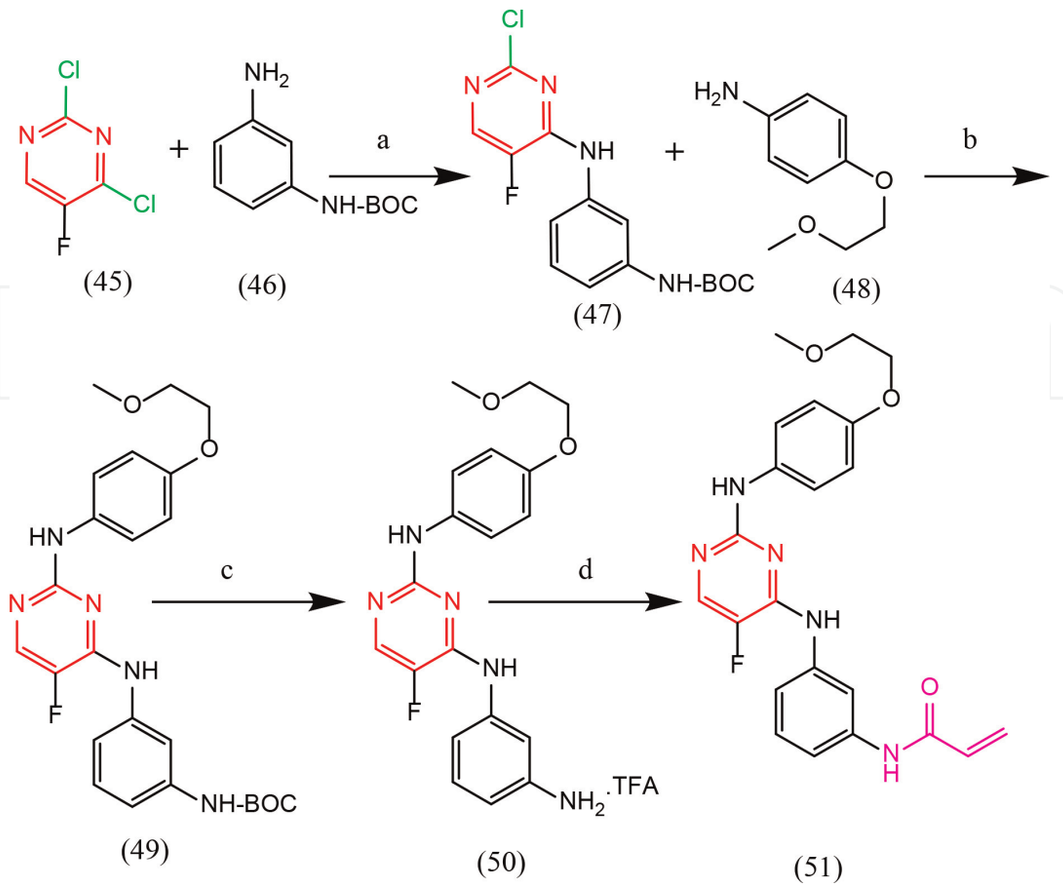


Figure 6.
Synthesis of Spebrutinib (51) [CC-292, AVL2923, (5 N-[3-[[5-fluoro-2-[4-(2-methoxyethoxy)anilino] pyrimidin-4-yl]amino]phenyl]prop-2-enamide]. Reagents and conditions: a) DMA, reflux; b) DMA, reflux; c) TFA, DCM, r.t, acyl halide, TEA, r.t.

(= R_2NH_2 amine) and microwave at elevated temperature of 180°C. This step of attaching 2-chloro-4-methylpyrimidine (61) to methyl 3-{[(2,6-difluorophenyl)sulfonyl]amino}-2-fluorobenzoate (57) was reported to proceed (71%) and afforded N-{3-[(2-chloro-4-pyrimidinyl)acetyl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide as title compound that is a mixture of keto-enol **Figures 8**, 58a ↔ 58b). The second substitution was performed following the formation of the thiazole central moiety and afforded N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)- 1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (60) in 47% yield.

The 2,4-disubstitution regioisomer selectivity around the pyrimidine core was granted by using the 2-methyl-4-chloropyrimidine substrate [65–68, 70]. Other recent report confirmed the feasibility, high yield and regio-selective coupling using 2-methyl-4-chloropyrimidine [65–68].

3.1.1.2.4 Case study —4: synthesis of the antiviral drug Rilpivirine hydrochloride [(Edurant®), 4-[[4-[4-[(E)-2-cyanoethenyl]-2,6-dimethylanilino]pyrimidin-2-yl]amino]benzonitrile; hydrochloride (62)]

The non-nucleoside reverse transcriptase inhibitor (NNRTI), Rilpivirine Hydrochloride (RPV, Edurant®) (62) got the approval both from the U.S. FDA and E.U. EMA in 2011 for the treatment of HIV-1 infection in treatment-naïve adult patients (**Figure 9**) [71, 72].

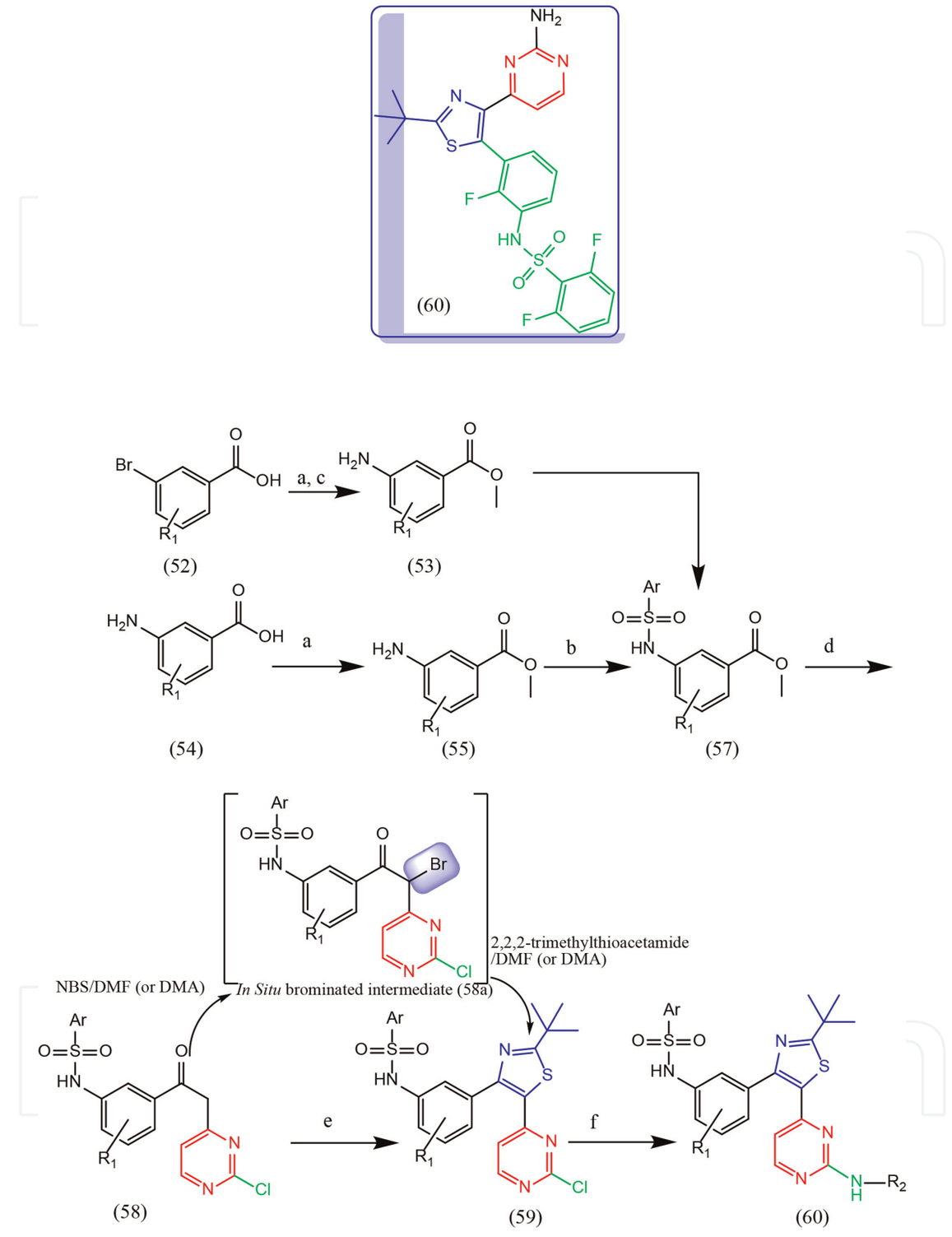


Figure 7.
Synthesis of Dabrafenib (GSK2118436, (60)). Reagents and conditions: a) H_2SO_4, MeOH; b) $ArSO_2Cl$ (43), pyridine, DCM; c) 10% Pd/C, H_2, rt., 100%, d) 2-chloro-4-methylpyrimidine (61), LiHMDS, 0°C to rt., 1 h, 92%;; e) NBS, DCM then 2-aminopyridine (61), dioxane; f) NBS, DMF (or DMA) then 2,2,2-trimethylthioacetamide, rt. → 60°C, 1 h, 30–44%; g) 7 N ammonia in methanol, sealed tube 100°C or R_2NH_2 amine, HCl, 2,2,2-trifluoroethanol, microwave, 180°C.

Structurally, the drug Rilpivirine hydrochloride (62) belongs to diarylpyrimidine (DAPY) family of compounds that re defined as the second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) targeting reverse transcriptase,

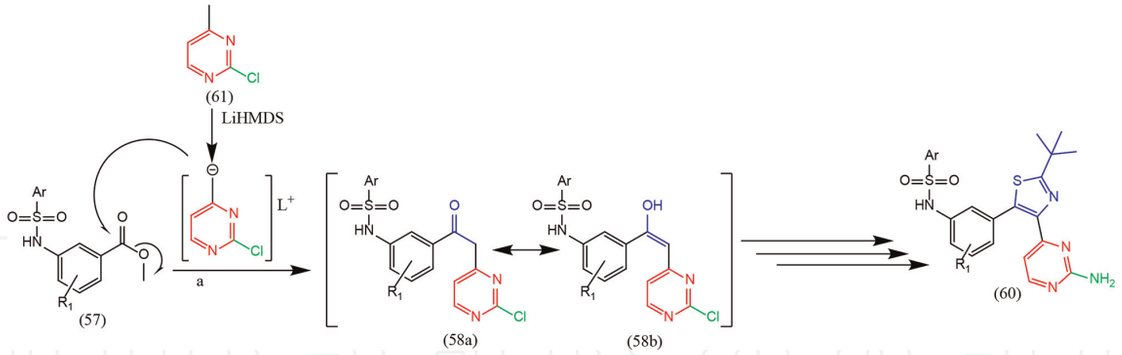


Figure 8.
Coupling of the 2,4-disubstituted pyrimidine (60) to the sulfonamide benzoic acid ester (57). Reagents and conditions: a) 2-chloro-4-methylpyrimidine (61), LiHMDS, 0°C → r.t, 1 h, 90%.

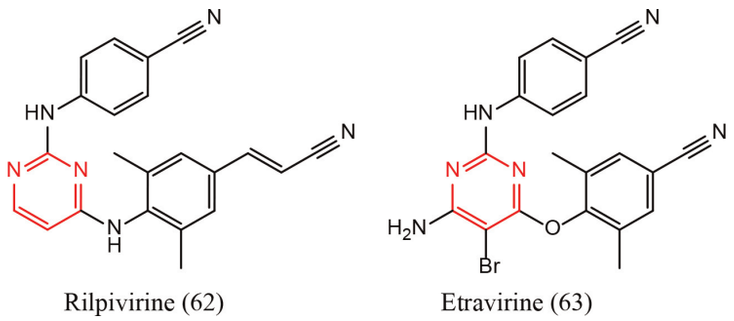


Figure 9.
Structures of FDA approved diarylpyrimidines (DAPYS) of pyrimidine-based non-nucleoside reverse transcriptase inhibitors (NNRTI) Rilpivirine (62) and Etravirine (63).

playing a great irreplaceable role in HIV transcriptional therapy [73–75]. Other antiviral agents like Etravirine (63) is also defined as DAPYs and got approved by US-FDA. Some of the DAPYs also exert anticancer action [76].

A large-scale synthetic process starting from the commercially available 2-thiouracil (65) that could be converted to 2-methylthio-4-pyrimidinone (64) following methylation using methyl iodide under basic conditions (r.t., overnight, 88%) was developed. Otherwise, 2-methylthio-4-pyrimidinone (64) could be used as a starting material. The reported synthetic process comprises from 6 steps [77].

The condensation of thioether (66) with neat 4-cyanoaniline (67) at elevated temperature to afforded the substituted pyrimidone (71) in 77% yield, which upon subsequent refluxing in $POCl_3$ provided the corresponding 4-chloropyrimidine (72) in 77% yield. 4-chloropyrimidine derivative (72) was treated with the (*E*)-cinnamonitrile aniline (72) under basic conditions (K_2CO_3) to give rilpivirine hydrochloride (62) in good yield. The final step of amination was particularly challenging and required longer time and elevated temperatures (**Figure 10**).

(*E*)-3-(4-Amino-3,5-dimethylphenyl) acrylonitrile (73) was prepared via a Heck reaction starting from the of commercially available reagents either 4-iodo- or 4-bromo-2,6-dimethyl-benzeneamine (74) or (75) and acrylamide (76) affording compound (78) as a 4:1 mixture of *E/Z* isomers. The distribution of *E/Z* olefins was increased to 98:2 by salt formation and recrystallization to ultimately provide pure (*E*)-(62) in an overall 64% yield for the two steps. The final yield was

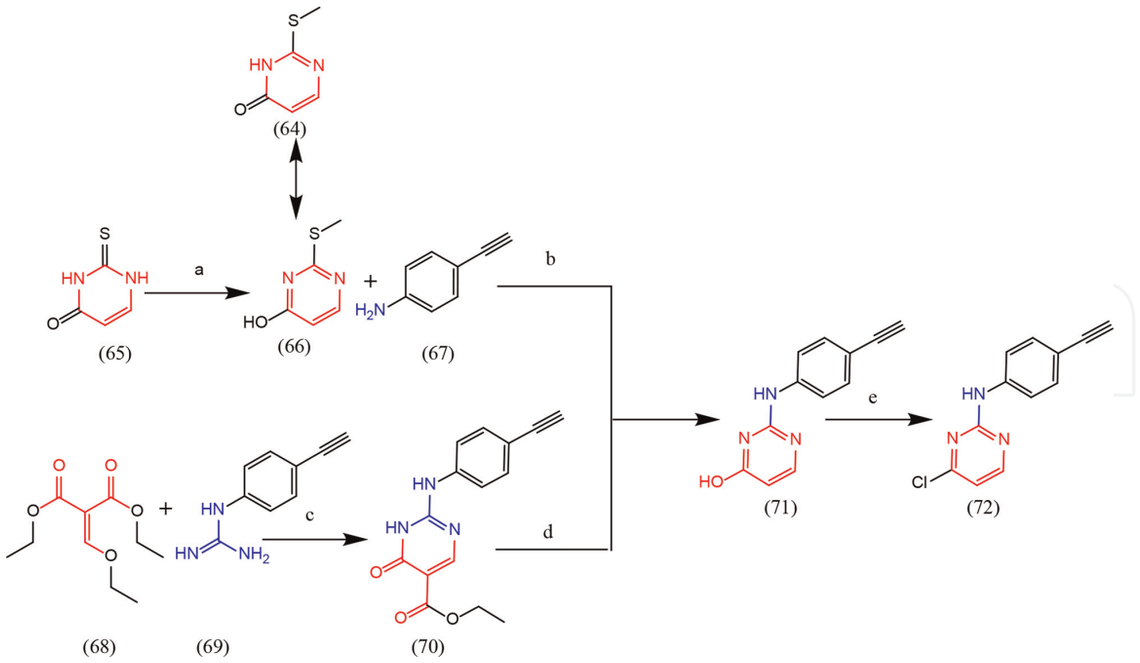


Figure 10.
Synthesis of 4-[(4-chloropyrimidin-2-yl)amino] benzonitrile intermediate (72) from 2-thioxo-2,3-dihydropyrimidin-4(1H)-one (65). Reagents and conditions: a) CH_3I, NaOH, r.t., overnight, 88%; b) DME, reflux, 18 h, 68%; c) 180–190°C, 10 h, 70–74%; d) 180°C, 8 h, 73.6%; e) $POCl_3$, reflux, 20 min, 77%.

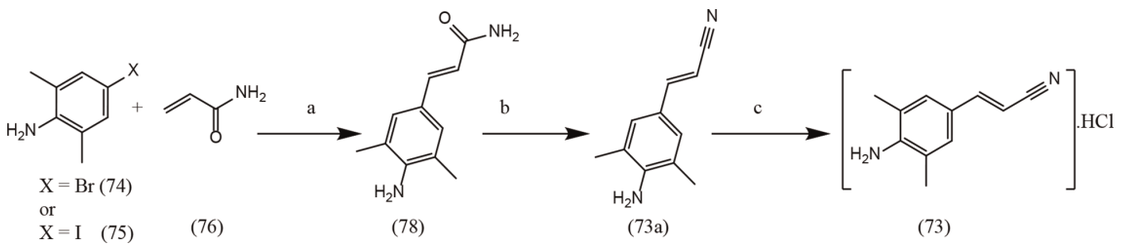


Figure 11.
Synthesis of intermediate (73) from 4-bromo-2,6-dimethylaniline (74) and acrylamide (76) as starting materials [78]. Reagents and conditions: a) $Pd(OAc)_2$, $P(C_6H_5CH_3)_3$, Et_3N, CH_3CN, N_2, 79°C, overnight, 79.5%; b) $POCl_3$, 0°C, 30 min; 20°C, overnight, 84%; c) EtOH, $((CH_3)_2CH_2)_2O$, N_2, 60°C, 30 min; HCl, 2-propanol, 60°C, 30 min, 77%. When starting from 4-iodo-2,6-dimethylaniline (75) and acrylonitrile, reagents and conditions: a) CH_3COONa, Pd/C, DMAC, N_2, 140°C, 21 h, 81%; b) EtOH, HCl, 2-propanol, 60°C, 1 h, 64.5%.

slightly improved when 4-bromo-2,6-dimethyl-benzeneamine (74) was used compared to or 4-iodo-2,6-dimethyl-benzeneamine (75) (**Figure 11**).

The conventional way to prepare the drug Rilpivirine (62) was accomplished by nucleophically displacing the 4-chloro in 4-[(4-chloropyrimidin-2-yl)amino] benzonitrile (72) with (2*E*)-3-(4-amino-3,5-dimethylphenyl)prop-2-enenitrile hydrochloride (73). The reaction was performed in acetonitrile under reflux condition for 69 h (**Figure 12**, yield: 68.6%). Connecting the two previously prepared building blocks (72) and (73) resulted in the desired products. However, the elongated refluxing of acetonitrile resulted in extended industrial process, high demand of energy, and reduced quality and purity of the final product. Using NMP at 95°C shorten the reaction time but ended in increased ration of the *cis*-(*E*)- undesired isomer byproduct. Additionally, the high boiling point of NPM renders reclaiming the solvent in industrial process unfavorable.

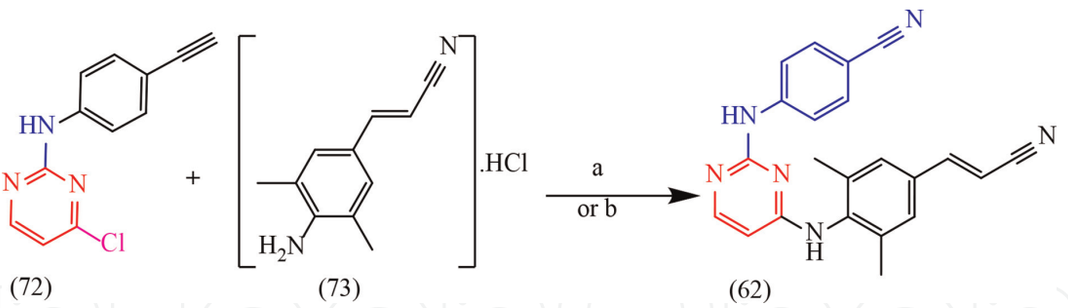


Figure 12.
Synthesis of Rilpivirine from intermediates (72) and (73). Reagents and conditions: a) CH_3CN, reflux or NMP, 95° C, or b) microwave-irradiation, CH_3CN, 140°C, 90 min, 71% [79].

Zhang *et al* Noted four drawbacks in the traditional synthetic methods: (a) the preparation of intermediate (73) via Heck reaction turned to be expensive due to the required catalyst (palladium acetate) and its ligands; (b) the preparation of intermediate (72) is also expensive and the reaction temperature is high; (c) when using uracil as a starting material instead, the reaction process and workup was rather tedious with reduced yield and (d) the final step in the synthesis of Rilpivirine, is too long (69 h) and causing energy consumption. Due to reported shortcomings of the previously reported synthesis Zhang et al. reported an optimized conditions for the synthesis of Rilpivirine and required building blocks, 4-[(4-hydropyrimidin-2-yl) amino] benzonitrile (71) and (2*E*)-3-(4-amino-3,5-dimethylphenyl)prop-2-enenitrile hydrochloride (73) employing microwave-irradiation reaction (see below more details).

Hence there is an urgent need to find more efficient and practical methods for synthesizing Rilpivirine in the pharmaceutical industry. Herein, we represent our efforts to develop an efficient synthetic route with increased overall yield and reasonable reaction time. An alternative six-step process was proposed. The improvement was primarily in preparing the intermediate (64) and in the conditions and yield on the final step. Zhang *et al* reported the solvent free fusion reaction between fusion 2-(methylthio)-4(3H)-pyrimidinone (64) and *p*-aminobenzonitrile (67) under an inert atmosphere that afforded the intermediate (72) in 70%. The intermediate 2-(methylthio)-4(3H)-pyrimidinone (64) was converted to 4-chloropyrimidine (72) form by reflux in $POCl_3$. Though the synthesis on the second building block (intermediate (73)) was still dependent of Heck reaction conditions, the final nucleophilic step was performed under microwave-assisted conditions. After trying different solvents (dioxane, acetonitrile, and NMP) and temperatures they reported a slight improvement in the yield of the final amination product (71%) for microwave-assisted in microwave-irradiation reaction with acetonitrile solvent at 140°C for 90 min compared to (69%) via traditional method [79].

Recently, it was reported by that amination of 2-chloro-4-aryloxypyrimidines using palladium catalyzed transformation (Xantphos, $Pd(AcO)_2$, Cs_2CO_3, 1.4-dioxane, reflux in N_2 atmosphere, 80°C) affording the 2,4-disubtituted product (62) in 50% yield [80]. A group of aryl-2-[(4-cyanophenyl)amino]-4-pyrimidinone hydrazones reported as potent mon-nucleoside reverse transcriptase inhibitors were prepared by Ma et al. [81]. The 2-amino-hydrazone derivatives were synthesized in a yield that ranges between 40 and 50%.

3.1.2 Synthesis of 4,5,6-Trisubstituted pyrimidines

3.1.2.1 Case study 1: synthesis of Remibrutinib [LOU064, N-[3-[6-amino-5-[2-[methyl (prop-2-enoyl)amino]ethoxy]pyrimidin-4-yl]-5-fluoro-2-methylphenyl]-4-cyclopropyl-2-fluorobenzamide, (31)]

Remibrutinib (LOU064, (31)), a highly selective and potent oral BTK inhibitor, with best-in-class profile, under investigation for a number of immune-mediated conditions [66, 68, 82]. Novartis reported rapid and effective disease activity control of Remibrutinib (31) that resulted in significant improvement in quality of life in patients with chronic spontaneous urticaria that were treated with the drug [83].

Structurally, Remibrutinib (31) belongs to a group of 4-N-5-O-6-C pyrimidine derivatives. Synthetically, the process was divided into two main parts".

i. Synthesizing the substrates (substituents) to be introduced.

ii. Step-wise substitution of the pyrimidine heterocycle core.

Three substituents are required for the construction of Remibrutinib (31):

Ammonia (NH_3, **Figure 13**, violet part), N-methyl-N-(2-hydroxyethyl) acrylamide (**Figure 13**, black and brow parts), and 5-fluoro-2-methylphenyl]-4-cyclopropyl-2-fluorobenzamide (**Figure 13**, blue and cyan parts). The three should be prepared with the proper functionalization site and reactivity for the successive substitution to work.

Starting from, 4,6-dichloro-5-methoxypyrimidine (79), the synthesis reported used the commercially available ammonium hydroxide (NH_4OH) for performing the first amination in heated 2-propanol, 70°C for 48 h. This produced the 4-amino-5-methoxy-6-chloropyrimidine (80) in high yield of 94%. Following the cleavage of 5-methoxy group the 4-amino-5-hydroxy-6-chloropyrimidine (81) was produced in 59% using conventional conditions of (BBr_3, DCM, 40°C, 3 h). The attachment of the derivatizable N-Boc-N-methyl-2- hydroxyethylamine (82) was attached to the pyrimidine core at 5-hydroxy using Mitsunobu reaction conditions (DIAD, Smopex-301, THF, 60°C, 2 hr) which afforded the intermediate (83) in 53% yield. Prior to

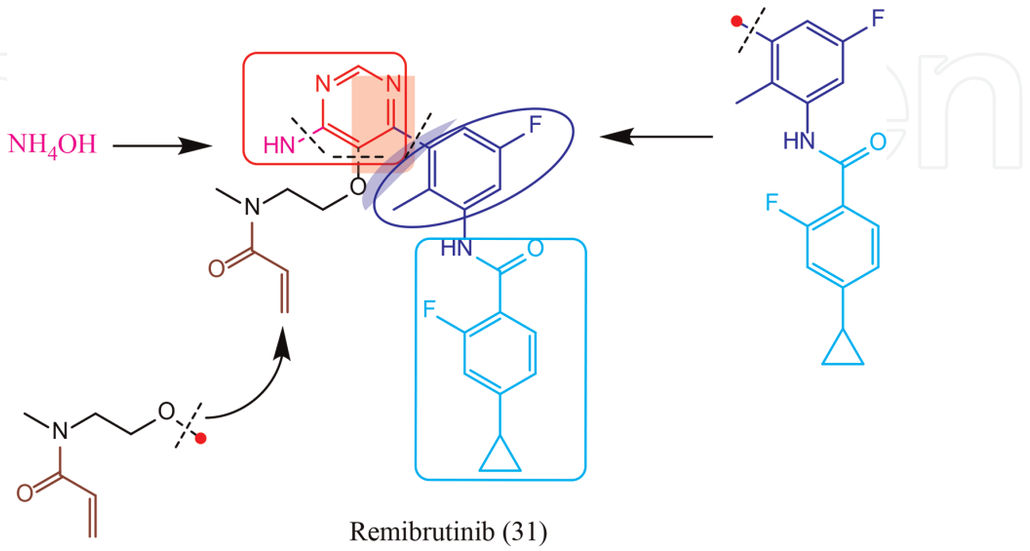


Figure 13.
Structure of Remibrutinib (LOU064, (31)) and the possible disconnections: Pyrimidine core and three different substituents.

coupling to the central pyrimidine at C6, the third substituent boronic ester intermediate (89) ought to be synthesized following the procedure depicted in the **Figure 14**.

2-Bromo-4-fluoro-6-nitrotoluene (84) was activated under Miyaura borylation reaction conditions (cross-coupling of bis (pinacolato) diboron (B_2pin_2) with aryl halides and vinyl halides using BISPIN, Pd(dppf)Cl_2·DCM, KOAc, dioxane, 100°C, 3.5 h) to afford 2-(5-fluoro-2-methyl-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (85) in 92%, which was subjected to reduction using hydrogen gas over Pd-C catalyst to produce the amino derivative (86) in 93%. In parallel, 3-fluoro-4-bromobenzoate ester (87) was coupled to cyclopropyl moiety through Suzuki reaction. The sodium bis(trimethylsilyl) amide mediated coupling with 2-(5-fluoro-2-methyl-3-minophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (86) afforded the desired boronate intermediate (89). Having the 4-cyclopropyl-2-fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) benzamide intermediate (89) in hand paved the road to the third substitution at the pyrimidine core in sequence.

To synthesize the desired intermediate *tert*-butyl N-[2-[4-amino-6-[3-[(4-cyclopropyl-2-fluorobenzoyl)amino]-5-fluoro-2-methylphenyl]pyrimidin-5-yl] oxyethyl]-N-methylcarbamate (93) (**Figure 15**), the previously synthesized 4-cyclopropyl-2-fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) benzamide (89, **Figure 14**) was coupled under Suzuki conditions to the BOC-protected *tert*-butyl-N-[2-(4-amino-6-chloropyrimidin-5-yl)-oxyethyl]-N-methylcarbamate (83) that was prepared utilizing Mitsunobu reaction (step c in **Figure 15**). The reaction proceeded under microwave and catalyst assisted ($PdCl_2(PPh_3)_2$, aq Na_2CO_3, DME, water, microwave, 110°C, 25 min) in 74% yield. The last two steps of de-BOCylation and coupling to acrylic acid undergone in feasible conditions. Worth noting the exploitation of Mitsunobu reaction (DIPEA, T_3P (50% in DMF), DMF, RT, 2 h, 45% over 2 steps).

3.1.2.2 Case study 2: synthesis of 2,4-Diamino-6-alkyl- (or 6-aryl-) pyrimidine derivatives

Wang and colleagues reported the synthesis of 2,4-diamino-6-alkyl- or 6-aryl-Pyrimidine Derivatives [84]. In attempt to develop a general method, two approaches

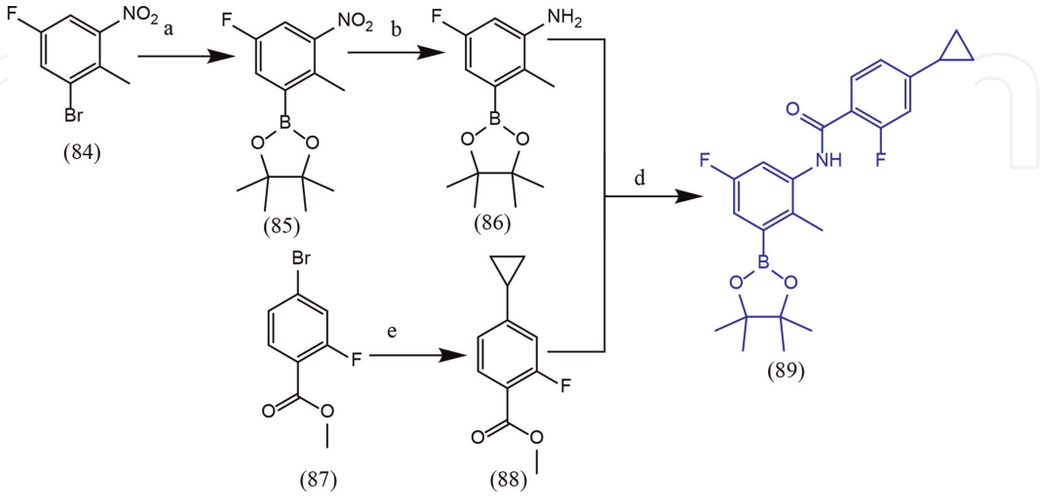


Figure 14.
Synthesis of Boronic Ester building block (89). Reagents and conditions: a) BISPIN, Pd(dppf)Cl2·DCM, KOAc, dioxane, 100°C, 3.5 h, 92%; b) H_2, Pd/C, MeOH, RT, 7 h, 93%; c) cyclopropylboronic acid, $Pd(OAc)_2$, tricyclohexylphosphine, K_3PO_4, water, toluene, 100°C, overnight, 99%; d) (86), NaHMDS (1 M in THF), THF, RT, 4 h, 76%; e) cyclopropylboronic acid, $Pd(PPh_3)4$, K_3PO_4, water, toluene, 110°C, 30 h, 96%.

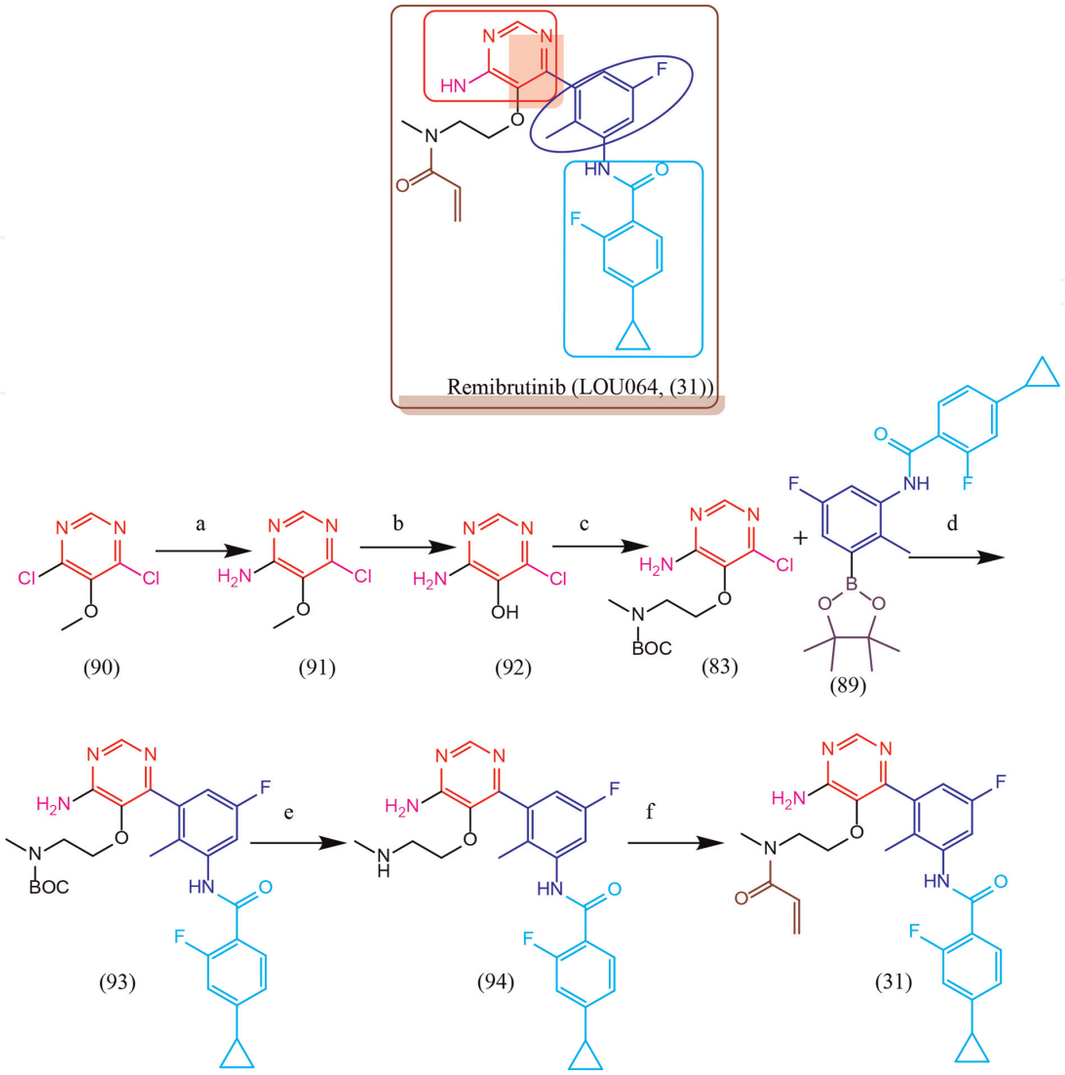


Figure 15.
Synthesis of Remibrutinib (LOU064,)31(). Reagents and conditions: a) NH_4OH, 2-propanol, 70°C, 48 h, 94%; b) BBr_3, DCM, 40°C, 3 h, 59%; c) N-Boc-N-methyl-2-hydroxyethylamine, DIAD, Smopex-301, THF, 60°C, 2 h, 53%; d) (89), $PdCl_2(PPh_3)_2$, aq Na_2CO_3, DME, water, microwave, 110°C, 25 min, 74%; e) TFA, DCM, RT, 12 h; f) acrylic acid, DIPEA, T_3P (50% in DMF), DMF, RT, 2 h, 45% over 2 steps.

were tried. First approach, the predetermined substituents were incorporated while constructing the heterocyclic pyrimidine core. This was achieved by condensing proper derivatives of 1,3-dicarbonyl with amidine or guanidine derivatives (see **Figure 16**).

The method depicted in **Figure 16** above incorporated 2-amino group (R1-NH-C2) and the 6-phenyl (R2-C6) during the assembling of the heterocyclic core. The 2-amino-6-phenylpyrimidine (101) was readily amminated at site-4 of the pyrimidine basic conditions. Relatively, mild conditions where needed for the step-wise introduction of the three substituents (**Figure 17**).

The researchers also reported the synthesis of 2,4,6-trisbustituted pyrimidines (108) using the commercially available 4,6-dichloro-2-methylthiopyrimidine (104) as a starting material for the sequential substitution under Suzuki conditions (phenylboronic acid in the presence of triphenylphosphine and palladium acetate) afforded the desired 4-chloro-2-methylthio-6-phenylpyrimidine (106a or 106b) in high yield [84] compared to the case when 2,4,6-trichloropyrimidine (109) was used

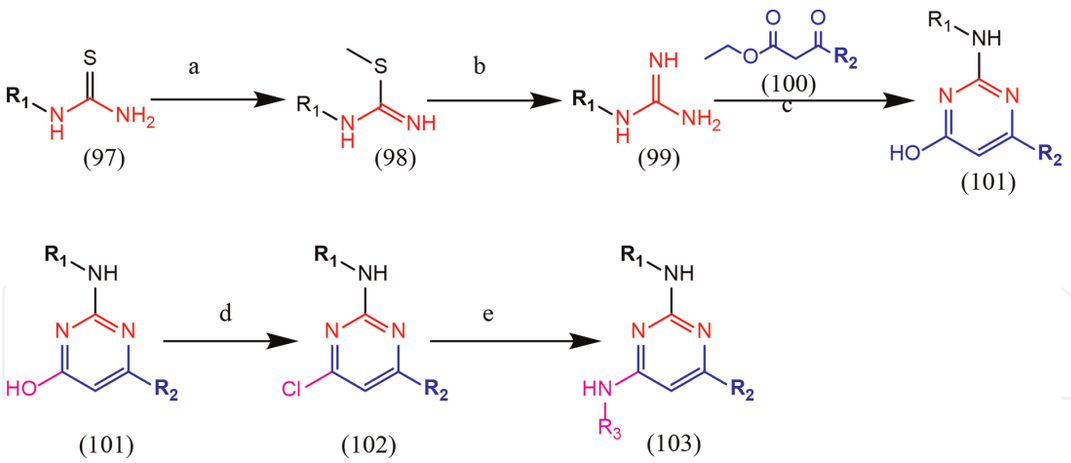


Figure 16.
Synthesis of trisubstituted pyrimidine (103) via construction of the heterocyclic core. Reagents and conditions: a) CH_3I, acetone, reflux; b) NH_3, EtOH, 100°C; c) R_2COCH_2COOEt (100), DMF, 100°C, 48 hr.; d) $POCl_3$; e) R_3NH_2, 110°C.

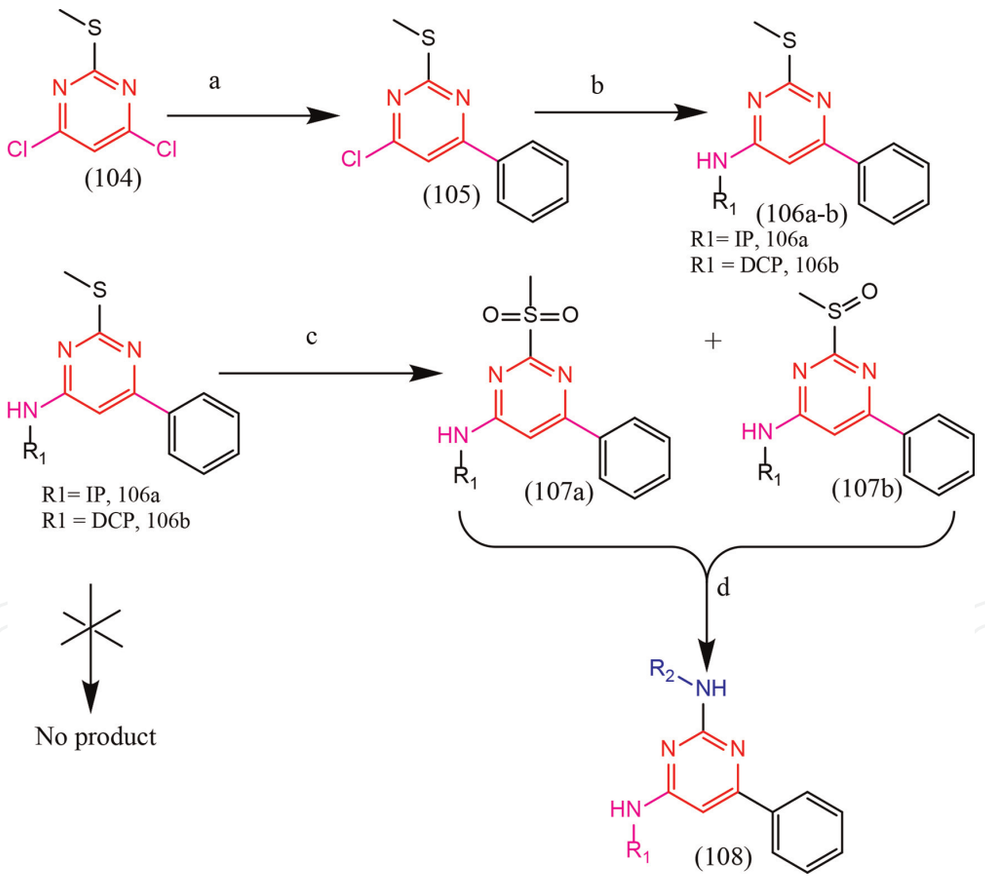


Figure 17.
Synthesis of 2,4,6-trisubstituted pyrimidines using the commercially available 4,6-dichloro-2-methylthiopyrimidine (104). Reagents and conditions: a) $C_6H_5B(OH)_2$, Pd(Oac)2II, TPP, Na_2CO_3, Glyme, reflux, 18 hr.; b) R1NH_2, 1-butanol, reflux, 6 hr.; c) 30%H_2O_2, NaWO4, EtOAc/toluene (1,1 v/v) 0°C for 30 min then RT for 2 hr.; d) R_2NH_2, neat, 140°C. DCP = 3,4-dichlorophenyl, IP = isopropyl, R1 = IP, R2 = DCP, R1 = DCP, R2 = IP.

as a starting material. Though the first substitution under Suzuki conditions afforded the 2,4-dichloro-6-phenylpyrimidine (106a or 106b) in high yield. Underlying the difference in the reactivity between 2-, 4- or 6-chloro groups toward amination

reactions the following amination proved to be challenging with almost equal amounts of 2-amino- and 4-aminopyrimidine derivatives due to reduced selectivity. Using 4,6-dichloro-2-methylthiopyrimidine (104) as a starting material proved to be efficient in facilitating the first amination while the second amination was not accomplished in high yield.

3.1.2.3 Case study 3: synthesis of Buparlisib [NVP-BKM120; BKM120; 1,202,777: 78-3, 5-(2,6-Dimorpholinopyrimidin-4-Yl)-4-(trifluoromethyl)pyridin-2-amine (115)]

Buparlisib (BKM120, NVP-BKM120), belongs to a family of 2-morpholino, 4-substituted, 6-heterocyclic pyrimidine derivatives, that was developed by Novartis as a pan-PI3K inhibitor [85]. Recent studies indicated that it also targets tubulin [86] and it is a brain penetrable [87].

Burger *et al*. reported the synthesis of Buparlisib (BKM120; NVP-BKM120, 115) as a pan-class I PI3K inhibitor [88]. The synthesis was accomplished in a four-step process starting from 2,4,6-trichloropyrimidine (109). The first step encompasses a nucleophilic substitution reactions to form two C-N bonds of morpholine substituents with the pyrimidine core [4,6-dimorpholino-2-chloropyrimidine (110) and 2,4-dimorpholino-6-chloropyrimidine or 4,4′-(6-chloropyrimidine-2,4-diyl) dimorpholine (111), **Figure 18**]. Reacting (109) with 2.5 equivalent of morpholine ended in producing the 2,4-disubtituted intermediate 4,4′-(6-chloropyrimidine-2,4-diyl) dimorpholine (111) in a 80% yield. The reaction was highly regioselective, however, a minor amount (8%) of the 4,6-regioiomer (110) was also detected. In parallel, 2-amino-4-trifluoromethyl pyrimidine (112) was converted to 5-bromo-4-(trifluoromethyl)-2-pyrimidylamine (113) using N-bromosuccinimide (NBS) via an oxidative radical electrophilic brominating reaction [89]. The functionalized 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (114) was prepared by reacting 5-bromo-4-(trifluoromethyl)-2-pyridylamine (113) with bis (pinacolato) diboron under conventional conditions (potassium acetate, bis (pinacolato) diboron and bis (diphenylphosphino) ferrocene palladium (II) chloride) in a 5:1 mixture with the starting material. The dioxaborolanated intermediate (114) was introduced to the pyrimidine core via palladium-mediated C-C cross-coupling

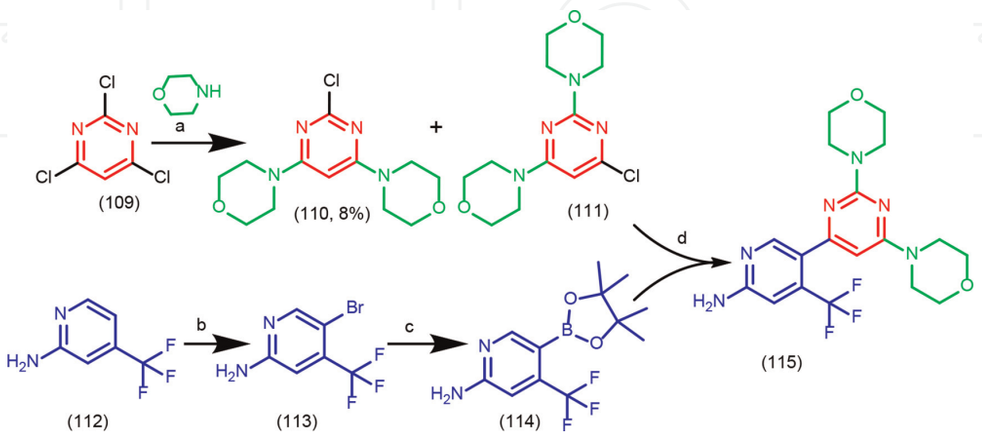


Figure 18.
Synthesis of Buparlisib (BKM120; NVP-BKM120) (115). Reagents and conditions: a) morpholine, DIEA, EtOH, 80%; b) NBS, CH_2Cl_2, 80%; c) bispiacolatodoron (1,1'-Bis(diphenylphosphino) ferrocene palladium (II) chloride, Pd(dppd)$_2$CleDCM), DME, 2 N Na_2CO_3, 95°C, 15 h, 48%; d) bispiacolatodoron, Pd (dppd)$_2$CleDCM, DME, KOAc, (potassium acetate, bis(pinacolato) diboron (Bis(diphenylphosphino) ferrocene palladium (II) chloride), 95°C, 15 h, 95%.

(step d in **Figure 18**) applying Suzuki reaction conditions affording the final product (115) in 95% yield [88].

The synthesis of Buparlisib (115) was also disclosed by Xu et al. employing similar conditions. A high yield and purity cross-coupling was reported (yield >94% and HPLC purity: >99%) [90].

3.1.3 Synthetic methods in preparing 2,4,6-Trisubstituted pyrimidines

Step-wise replacement of chloride groups employing nucleophilic substitution conditions, Suzuki coupling, Ulman coupling or Grignard reaction was reported to afford di-, tri- and tetra-substituted derivatives of pyrimidine (114) (**Figure 19**). The conditions used depend in many cases on the order and type of the linkage emerging between the substituents and the heterocyclic pyrimidine. It has also to consider the physicochemical properties of the substituent.

The final 2,4,6-trisubstituted product (115) can vary according to the type of linkage with the core heterocyclic pyrimidine. There are various versions of linkages (see **Figure 20**, for possible combination of linking moieties with the pyrimidine heterocyclic core) (**Figure 21**).

3.1.3.1 Methods to synthesized N*-2,4,6-trisubstituted (at C2, C4 and C6 respectively) pyrimidine derivatives*

One of the early identified S-2-*N*-4,6-trisubstituted pyrimidine aurora kinase inhibitor is the compound VX-680 (**Figure 22**). Luo et al. reported the synthesis of a group of N-2,4,6-trisubstituted pyrimidine derivatives and evaluated their action as

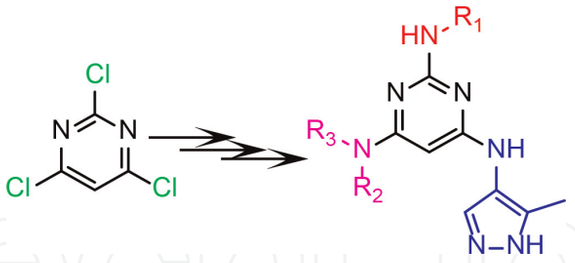
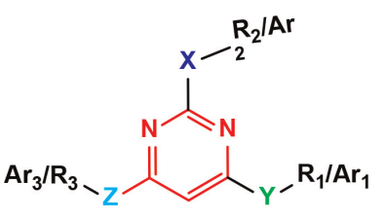


Figure 19.
Synthesis of unsymmetrical trisubstituted pyrimidines.



X = N, O, C, S
Y = N, O, C, S
Z = N, O, C, S

Figure 20.
Possible linkages between the substituents and pyrimidine heterocyclic core.

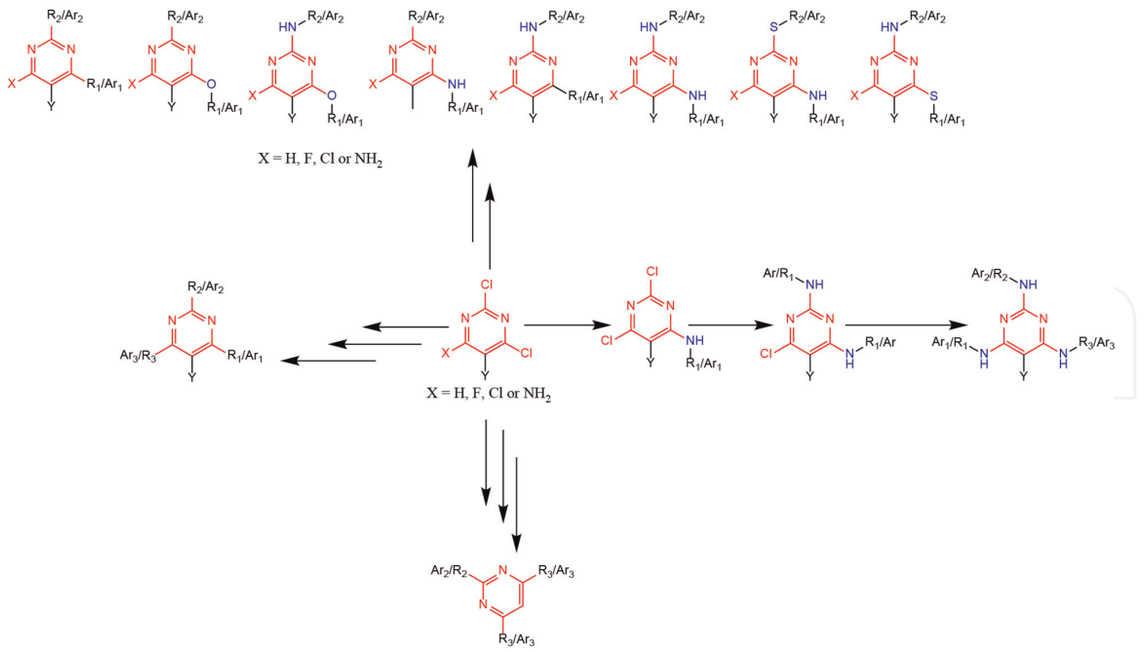


Figure 21.
Possible derivatives of trisubstituted pyrimidine heterocyclic core.

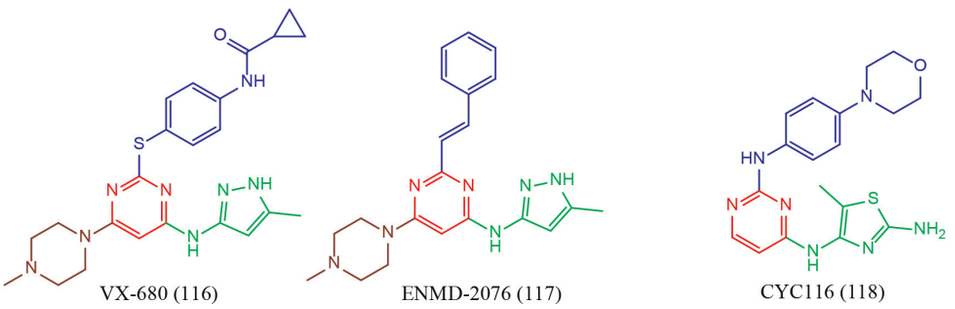


Figure 22.
Examples of bioactive trisubstituted pyrimidine.

selective aurora A kinase inhibitors [91]. Luo et al. reported synthesis of N-trisubstituted pyrmidines starting from 2,4,6-trichloropyrimidine (109).

Starting from 2,4,6-trichloropyrimidine (109), and in a sequential nucleophilic substitution the three substrates were introduced at sites 4-, 2- and 6- of the pyrimidine core. Aminopirazole 5-methyl-1H-pyrazol-3-amine (119) was allowed to react with 2,4,6-trichloropyrimidine (109) under basic conditions at cold temperature and afforded the 4-substitited pyrimidine (120) in high yield. The acid facilitated second amination was performed under elevated temperature afforded the 2,4-diaminated intermediate (121). The third amination afforded the final 2,4,6-trisubstituted product (122) took place under microwave assisted and elevated temperatures (1,4-dioxane, under microwave, 150–180°C) (**Figure 23**) [91].

3.1.4 Synthetic methods in preparing 2,4,5,6-Tera-substituted pyrimidines

One main strategic approach employs the step-wise replacement of leaving groups that exist on the already constructed pyrimidine (like 2,4,6-trichloropyrimidine (109)). The selection of the substituted pyrimidine as starting material depends on the

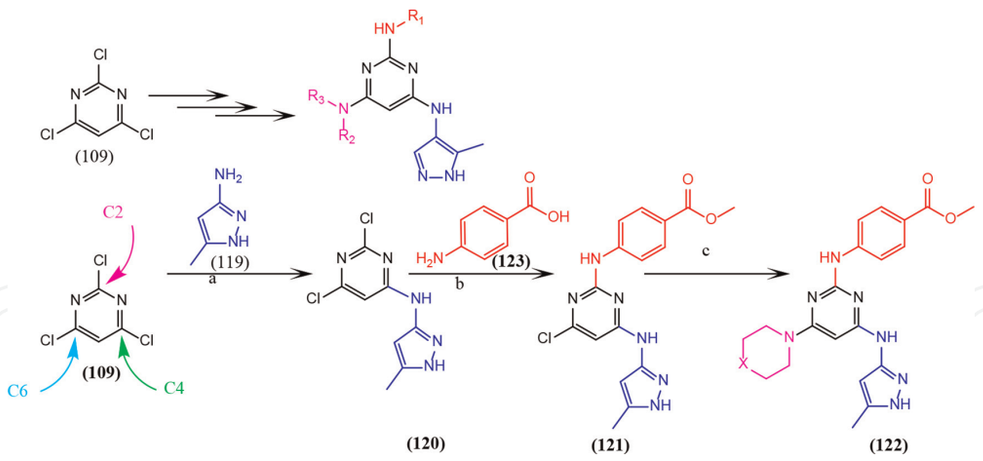
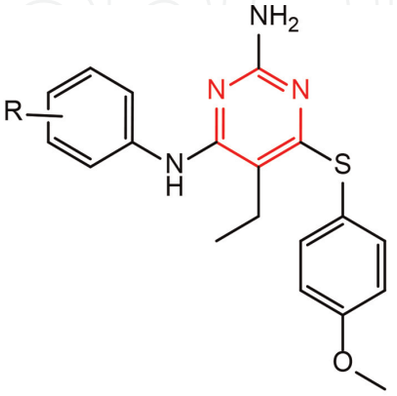


Figure 23.
Synthesis of N-*2,4,6-trisubstituted pyrimidine derivatives as potent aurora a kinase inhibitor. Reagents and conditions: a) Et_3N, EtOH, 0°C; b) $TsOH.H_2O$, n-BuOH or 1,4-dioxane, 100–140°C; c) 1,4-dioxane, under microwave, 150–180°C.*

desired product i.e. in case of 2,4-disbustitited pyrimidine the synthesis starts with 2,4-dihalopyrimidine and in case of 2,4,6-trisubstitutedpyrimidine the 2,4,6-trichloropyrimidine (109) is picked. Additionally, the reaction conditions and reagents used in the chemical process is by virtue reliant on the type of chemical bond formed or the type reaction employed. The order of applying the sequential displacement of the leaving groups is contingent on the type and properties of the functional group and conditions that ensure better purity and higher yield of the intermediates, building blocks or the final products. A special attention will be devoted to recent reports related to synthesis of FDA approved drugs or in few cases such derivatives with high potential bio-activities.

Regioselectivity is mostly guaranteed by picking the proper starting material and the fitting sequence of substitution (**Figure 24**).

In a recent study Zhang and colleagues reported the synthesis of anisole containing 2,4,5,6-tetrasubstituted pyrimidines [92]. The team exploited the commercially available reagents like properly substituted malonic acid diesters (124) and guanidine hydrochloride (125) that were condensated in anhydrous methanol under slightly



R = H, Methyl-, Ethyl-, Propyl-, Isopropyl-, Propargyl-
R = Allyl-, Butyl-, *Sec*-Butyl-, Phenyl-, Benzyl-, Fluoro-

Figure 24.
Examples of 2,4,5,6-tetrasubstituted pyrimidines. R = H, methyl-, ethyl-, propyl-, isopropyl-, Propargyl-., R = allyl-, butyl-, sec*-butyl-, phenyl-, benzyl-, Fluoro-.*

basic conditions (sodium methoxide) to produce the 5-substituted 4,6-dihydroxy-2-aminopyrimidine intermediate (126). (126) was converted to the 5-substituted 4,6-dichloro-2-aminopyrimidine derivative (127) upon treatment with Vilsmeier–Haack–Arnold (VHA) reagent [93]. Cations should be taken prior to treating 5-substituted 4,6-dichloro-2-aminopyrimidine derivatives with (chloromethylene) dimethyliminium chloride (VHA, 130) (**Figure 26**).

Using VHA reagent, drying of the starting materials and conducting the reaction under inert conditions helped in affording the final products in higher yields and purity compared to the previously reported reaction conditions (such as chloride donating mineral acids such as $POCl_3$, PCl_5, $SOCl_2$, or $COCl_2$ with diverse additives like DMF, pyridine, 2-methylpyridine, diphenylamine, or triethylamine) reported to end in less than 30% yields and complicated purification procedures [94]. Following the deprotection of the 2-(dimethylamino) methylene protecting group using hydrochloric acid the desired 4,6-dichloro-5-substituted-2-aminopyrimidines were isolated and purified. The 4,6-dichlorides were sequentially displaced under nucleophilic substitution conditions. The first 4-chloro was substituted by aniline derivatives in refluxing ethanol (see step c in **Figure 25**) while the second chloride was exchanged for anisole (4-methoxythiophenol) employing sodium tert-butoxide (1.33 mmol), under heating at 82°C (see step d in **Figure 25**, [92].

3.1.4.1 Synthesis of bay 41–4109 racemate [methyl 4-(2-chloro-4-fluorophenyl)-2-(3,5-difluoropyridin-2-yl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (135)]

The synthesis of Bay 41–4109 (135) (**Figures 27**) was initiated by allowing β-ketoacetate (133) to react with pyridine-2-carboximidamide salt and phenylacetaldehydes (134) via Biginelli cyclocondensation [95]. The reaction proceeded in isopropanol under microwave irradiation to produce the corresponding products (135) (**Figures 28** and **29**). On note, Bay 41–4109 (135) can be used for further derivatization. For example, the bromination of (140) using *N*-bromosuccinimide (NBS) can lead to the brominated intermediate (141), which can be easily substituted with nucleophiles like morpholine, *N*-methylpiperazine, methoxyethanol or thiobenzene producing the corresponding derivatives (142a-d). Oxidation of these

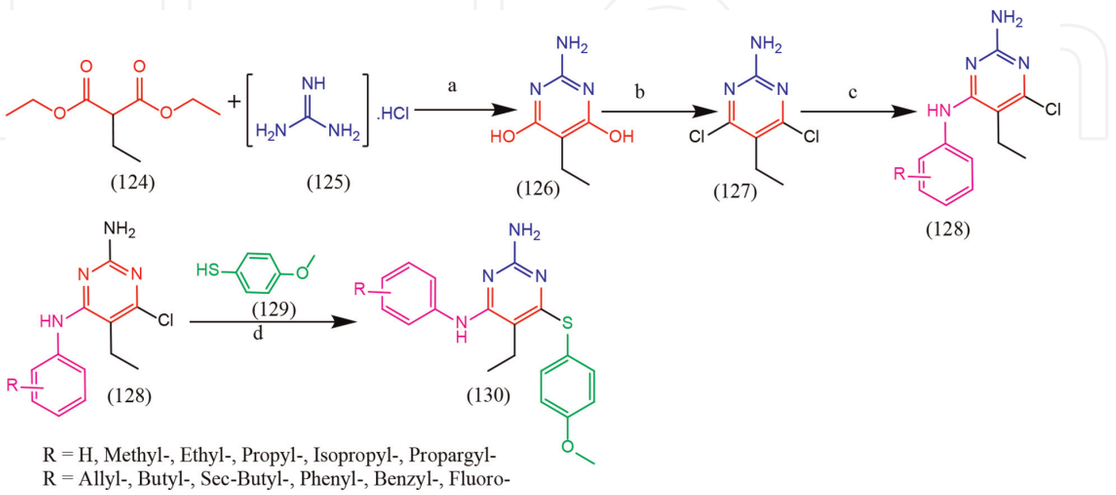


Figure 25.
Conversion of 5-substituted-2-amino-4,6-dihydroxypyrimidines (126) to 5-substituted 2-amino-4,6-dichloropyrimidines (127) using (chloromethylene) dimethyliminium chloride (130).

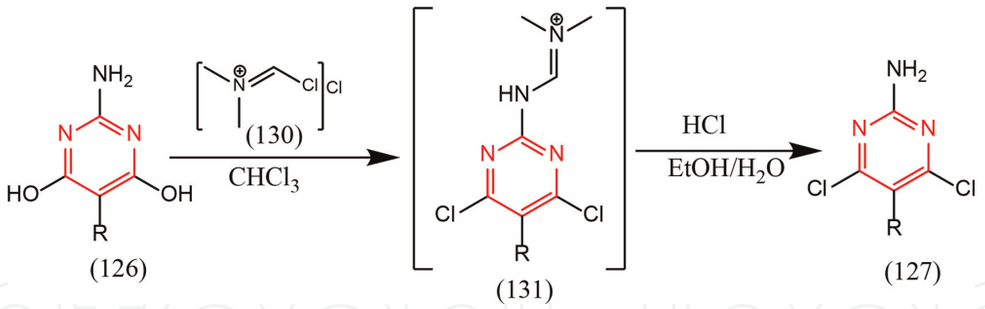


Figure 26.
Synthesis of 2,4,5,6-tetrasubstituted pyrimidine derivatives. Reagents and conditions: a) EtONa/EtOH; b) (chloromethylene) dimethyliminium chloride/$CHCl_3$; c) different anilines, ethanol, 100°C, 4 h; d) isopropanol, sodium tert*-butoxide, 82°C, 6 h.*

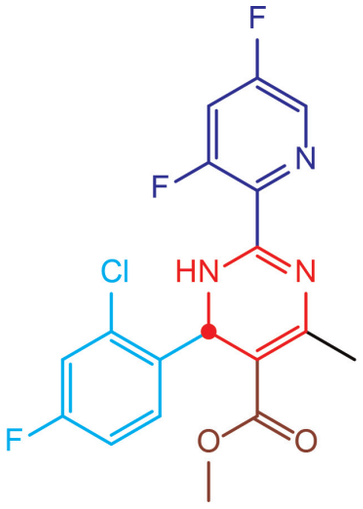


Figure 27.
Bay 41–4109 racemate (135).

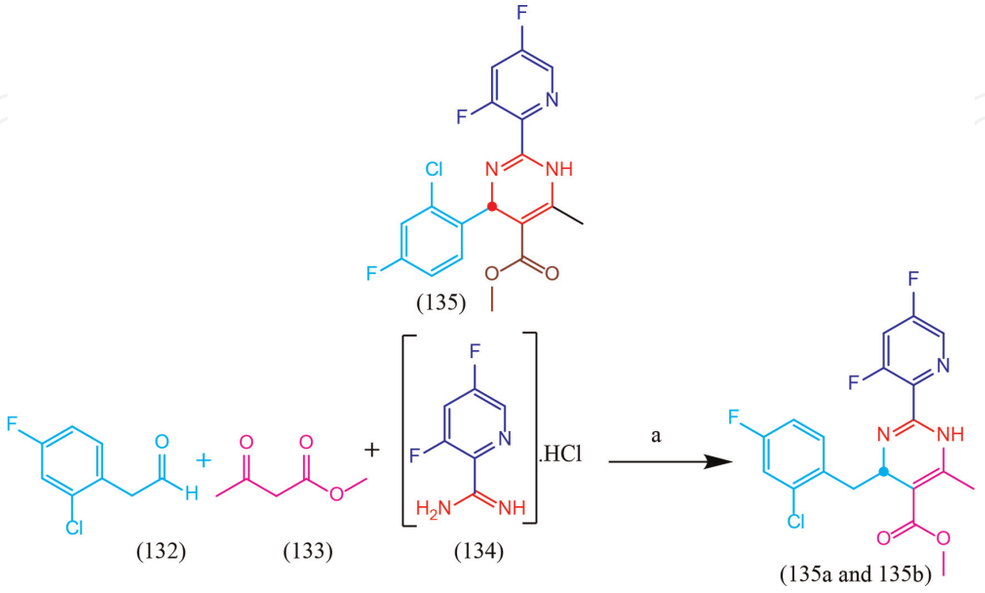


Figure 28.
Synthesis of bay 41–4109 (135). Method-1: One-pot three-component Biginelli condensation using aldehyde, β-ketoester and amidine. Reagents and conditions: a) piperidine, AcOH, i*PrOH, 12 h, 11–36%.*

dihydropyrimidines using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) easily led to the desired pyrimidines (144).

3.1.5 Synthesis of 2-amino-4,6-disubstituted pyrimidine

Altenbach et al. initiated the synthesis of a group of 4-*tert*-butyl-6-substituted pyrimidin-2-ylamine derivatives (**Figure 30**) starting 2,4-dichloropyrimidine (38) that was alkylated with pivalic acid (151) via nucleophilic substitution of 4-chloro- using silver nitrate $AgNO_3$ and ammonium persulfate. The 4-*tert*-butyl-6-chloropyrimidin-2-ylamine intermediate (151) was subjected to sequential nucleophilic amination to end in the desired group of compounds (154a-e). At the first step the displacement of the 2-chloro with N-Me-piperazine (155) afforded 4-*tert*-butyl-2-chloro-6-(4-methylpiperazin-1-yl) pyrimidine (152) as a mixture with second regioisomer 4-*tert*-butyl-6-chloro-2-(4-methylpiperazin-1-yl) pyrimidine (153). Following chromatography, (152) was treated with the second nucleophile to result in the desired group of compounds (154a-e) [94].

The same group also reported the synthesis of a group of 2-amino-4,5,6-trisubstituted pyrimidines (160a-m and 161a-o) starting from 2-amino-4,6-dichloro-5-substituted intermediate (156) (**Figure 31**). Evidently, 2-amino-4,6-dichoro-5-substituted intermediate (156) was treated with 1-methylpiperazine (155) under basic conditions (TEA or DIEA) while refluxed for 16 hours [94]. The second substitution was dependent on the type of connecting bond. In case of forming a C-C bond at C6 of the pyrimidine core, Suzuki conditions boronic acid derivatives (4-cyanophenylboronic acid or 4-methylphenylboronic acid), tetrakis (triphenylphosphine)-palladium (0) ($Pd(PPh_3)_4$) in 2-dimethoxyethane under basic (2 M Na_2CO_3) and inert conditions. In the case of forming C-N bond at C6, Ullmann nucleophilic substitution

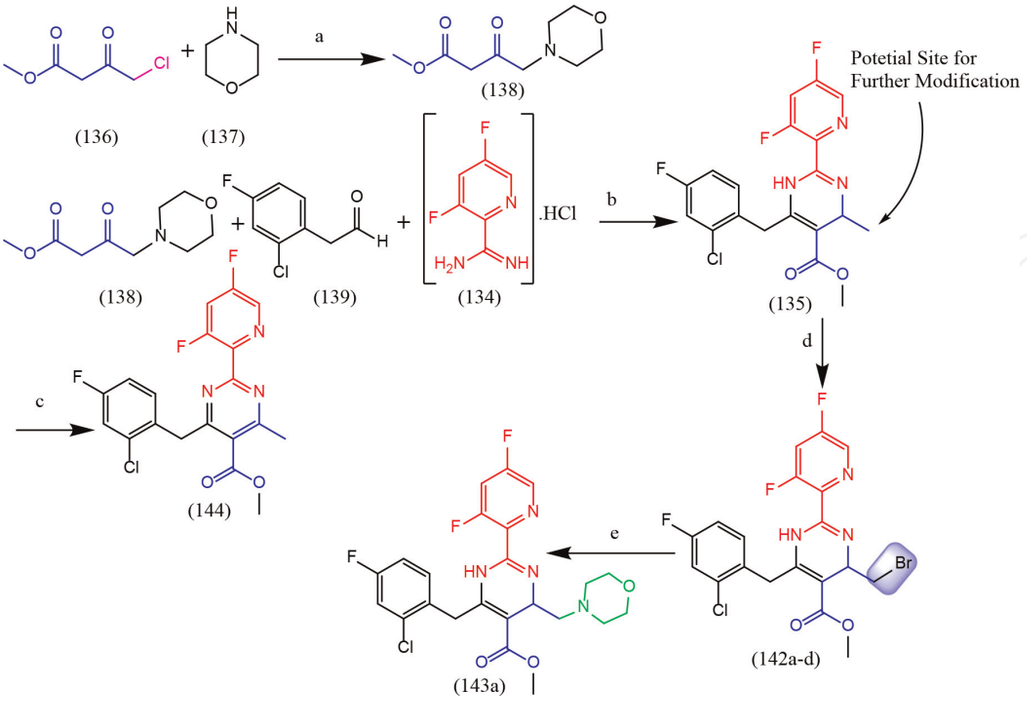


Figure 29.
Synthesis of bay 41–4109 (135). Method-2: Reagents and conditions: a) NaH, DMF, 0°C → rt., 1 h, 41–60%, b) pyridine-2-carboximidamide, Et_3N, μW, 10 min, 14%; c) DDQ, toluene, rt., 1 h, 42–68%; d) NBS, 1,2-DCE, 50°C, 30 min, 80%; e) morpholine, Et_3N, DMF, 0°C, 1 h, 29–72%.

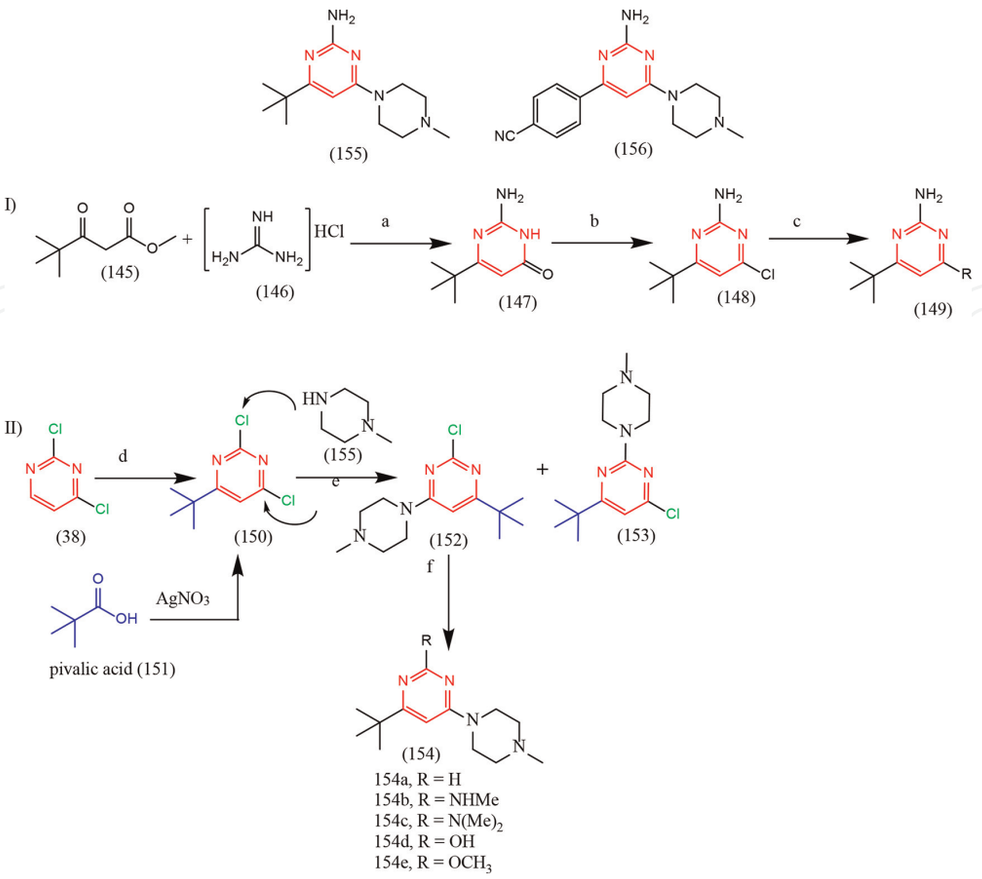


Figure 30.
Synthesis of 2-amino-4,6-disubstituted pyrimidine derivative. Reagents and conditions: I): a) guanidine hydrochloride, EtONa, EtOH, Δ; b) $POCl_3$, Δ; water; and c) amine, Δ, EtOH, Et_3N; II) reagents and conditions: d) pivalic acid, $AgNO_3$, ammonium persulfate, CH_3CN/H_2O; e) N-me-piperazine, Et_3N, EtOH, Δ, chromatography; (154a): R = H): H_2, Pd/C, MeOH; (154b): R = NHMe) 40% aqueous $MeNH_2$, 2-MeOEtOH, Δ; (154c): R = NMe_2): 40% aqueous Me_2NH, 2-MeOEtOH, Δ; (154d): R = OH): 1 M HCl, 16 h, Δ; (154e): R = OMe): Excess NaOMe, MeOH, Δ.

conditions were applied. For example for synthesizing 4-(4-methylpiperazin-1-yl)- 6-(4-phenylimidazol-1-yl)pyrimidin-2-ylamine (160). The corresponding substituent 4-phenylimidazole (87 mg, 0.6 mmol) (159) was added to 4-(4-methylpiperazin-1-yl)- 6-chloropyrimidin-2-ylamine (157) in presence of catalytic copper iodide (CuI, 0.13 mmol ratio) under basic condition (K_2CO_3) in DMF that was heated to 135°C overnight. Generally, the yields reported for Suzuki conditions (C-C bond) were higher than those reported under Ullmann conditions.

2-Amino-4,6-dichloropyrimidines (156) were also used as starting materials for preparing 2-amino-4,5,6-trisubstituted derivatives (160a-m and 161a-o) (see **Figure 31**).

3.1.6 Synthesis of etravirine; (TMC 125); 2,4-[[6-amino-5-bromo-2-[(4-cyanophenyl) amino]-4-pyrimidinyl] oxy]-3,5-dimethylbenzonitrile (63)]

Etravirine is a novel diarylpyrimidine, second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of human immunodeficiency virus type 1 infection, which has been approved by the U.S. Federal Drug Administration for the treatment of AIDS in the year 2008 [80, 96, 98].

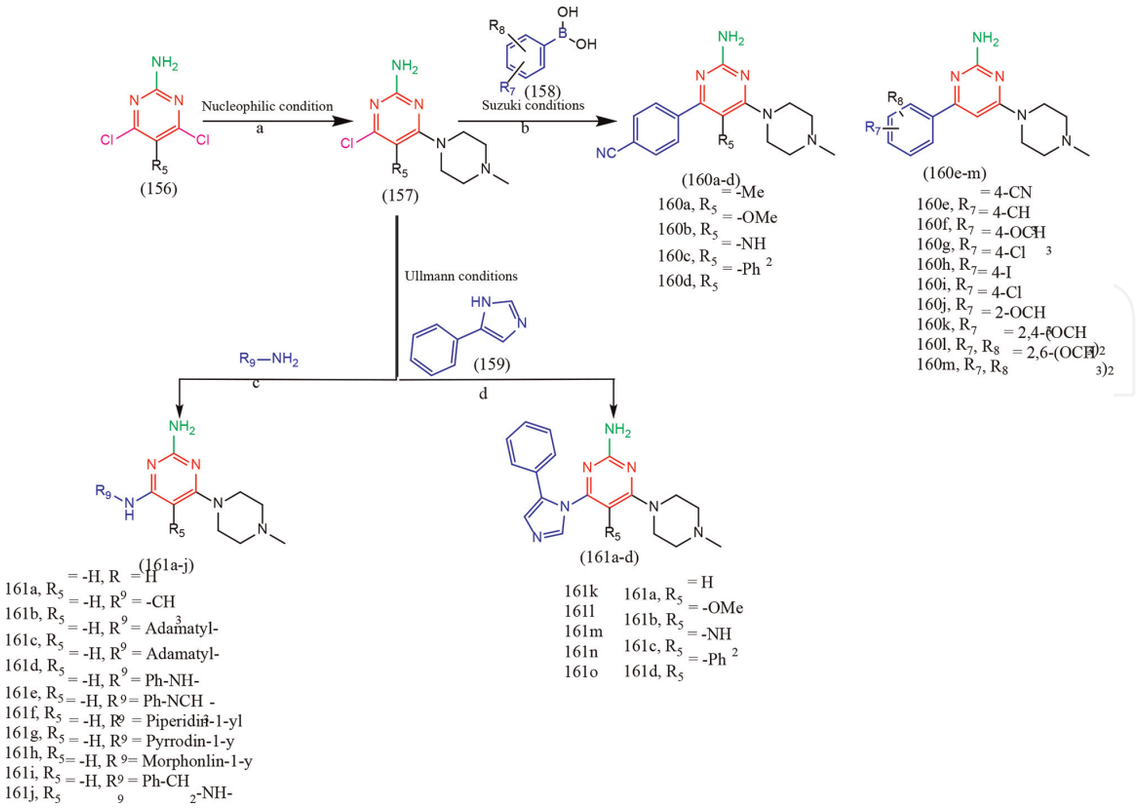


Figure 31.
Synthesis of 2-Amino-4,5,6-Trisubstituted pyrimidine derivatives. Reagents and conditions: a) N-me-piperazine, Et_3N, EtOH, Δ; b) compounds (160a-160 m): Intermediate (157), R7/R8-Ph-B(OH)2, $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, Δ; c) compounds (161a-1600): Intermediate (157), the corresponding amine, 2-ethoxyethanol, Hunig's base, 110–140°C; d) Ullmann conditions: Intermediate (157), corresponding heterocycle, CuI, K_2CO_3, DMF, 130°C; and (iii) NaI, 47% aqueous HI, 80°C, 98% [94].

It is a potent inhibitor of HIV reverse transcriptase [98], and active against NNRTI-Resistant Strains of HIV, by its ability to adapt its binding orientation and overcome common NNRTI resistance associated mutations (RAMs) such as K103N and achieving viral suppression and improving the immune function in treatment-experienced HIV-infected patients [99].

The synthesis of Etravirine (63) is fraught with many difficulties, the foremost being the poor yield and long reaction time required at the aminolysis stage [100].

The most efficient approach to overcome the mentioned disadvantages is four linear steps where the microwave promoted amination is the most critical one of these routes, as it shortens the amination reaction time from 12 h to 15 min, and improve the overall yield of the synthetic route from 30.4 to 38.5% (**Figure 32**) [100].

2,4,6-trichloropyrimidine (109) was first reacted with 4-hydroxy-3,5-dimethyl-benzonitrile (162) in the presence of diisopropylethylamine in refluxing dioxane and heated at 70°C for 2 hours, to give the biaryl ether derivative: 4-[(2,6-dichloro)-4-pyrimidinyloxy]-3,5-dimethylbenzonitrile (163) [96].

The second substitution reaction with aniline derivative 4- aminobenzonitrile (164) using potassium tert-butoxide as a base and N-methylpyrrolidone as a solvent over a period of 30 min and stirred for another 2 h at 0–5°C, to give compound 4-[[6-Chloro-2-[(4-cyanophenyl) amino]-4-pyrimidinyl] oxy]3,5-dimethylbenzonitrile (165) with a yield of 60.6%. The aminolysis of (165) went smoothly using 25% aq ammonia (15 mL), and N-methylpyrrolidone (20 mL) at temp 130°C, for 15 min in a microwave reactor, then the reaction mixture was brought to 5–10°C, 100 mL water

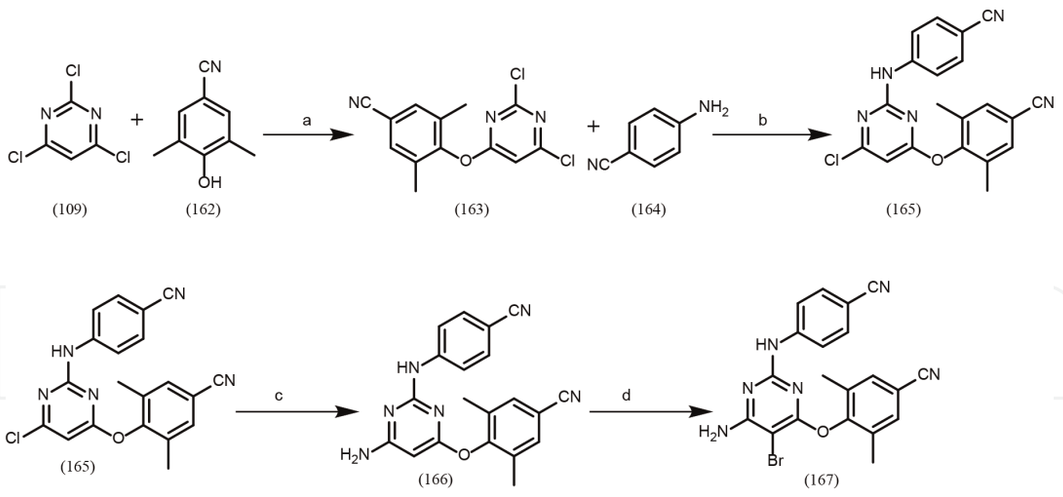


Figure 32.
Synthesis of Etravirine (63). Reagents and conditions: a) DIEA in refluxing dioxane, 70°C, 2 hours, 92.5%; b) potassium tert-butoxide, N-methylpyrrolidone, 30 min and stirred for another 2 h at 0–5°C, 60.6%; c) 25% aq NH_3, N-methylpyrrolidone, 130°C, 15 min in a microwave reactor, 5–10°C, 100 mL water, stir 30 min. Filter, wash with 100 mL H_2O, dry at 45–50°C, 85.6%; d) Br_2, DCM, 0–5°C, stirring 5 h, 80.2%.

was added to this solution followed stirring another 30 min. The generated solid was filtered, washed with 100 mL of water and dried at 45–50°C to give the amine: 4-[[6-amino-2-[(4-cyanophenyl) amino]-4-pyrimidinyl] oxy]3,5-dimethylbenzonitrile (166) in good yield (85.6%).

Finally, bromination of (166) was conducted in the presence of liquid bromine in DCM at 0–5°C, the reaction was stirred at this temperature for 5 h to give etravirine (63) in 80.2% yield [96].

3.1.7 Synthesis of Minoxidil; (MNX); [(2,4-diamino-6-piperidinopyrimidine 3-oxide) (171)]

Minoxidil (MNX) is a direct vasodilator introduced in the early 1970s for the treatment of hypertension [101]. Its first literature appearance was in 1968 and preliminary trials were first described in man in 1969 [102].

Coincidentally, physicians observed hair regrowth and generalized hypertrichosis in balding patients, which led to the development of a topical minoxidil formulation for treating androgenetic alopecia (AGA) first in male and then in female individuals [26, 103, 104].

An easy protocol for the synthesis of minoxidil drug in a two-step procedure is done, using magnetic nanoparticles of ferrites, which have been widely used as green and efficient heterogeneous catalysts in the synthesis of organic compounds, where these nano catalysts provide prominent advantages such as simple synthetic procedure, high catalytic activity, chemical reactivity and perfect reusability.

Magnetic nanoparticles (MNPs) of $CoFe_2O_4$ were prepared through a solid-state grinding procedure, in an agate mortar, where a mixture of $CoCl_2$, Fe $(NO_3)_3{\cdot}9H_2O$, NaOH, and NaCl in a molar ratio of 1:2:8:2 was mixed, ground for 45 min at room temperature, then the excess amount of salt was removed from the reaction mixture, the obtained residue was dried in an oven at 80°C for 60 min, calcinated at 300, 500, 700, and 900°C within 80 min (20 min at each temperature) (**Figure 33**) [105].

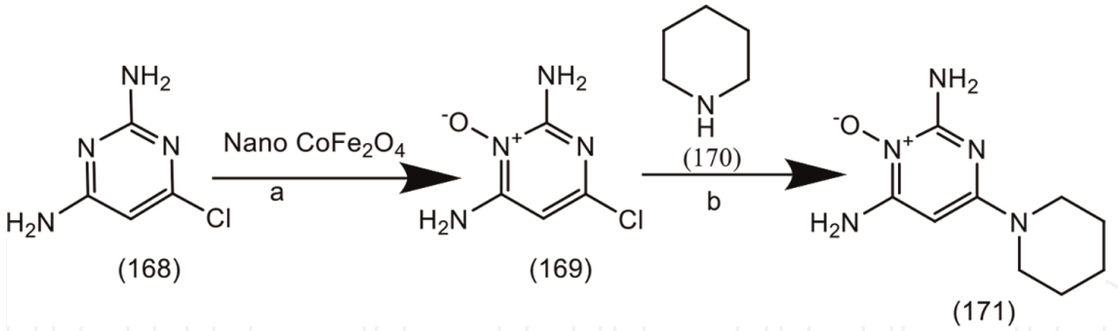


Figure 33.
Synthesis of Minoxidil (171). Reagents and conditions: a) Nano $CoFe_2O_4$ (5 Mol%), H_2O_2 (0.5 ml), ETOH, reflux, 60 min, 95%; b) Piperidine, reflux, 120 min, 80%.

First step was carried out by N-oxidation of 6-chloro-2,4-diaminopyrimidine (168) using (30%, 0.5 mL) H_2O_2 in the presence of $CoFe_2O_4$ magnetic nanocatalyst (5 mol %) in 5 ml ethanol under reflux conditions for 60 min to get 2,6-diamino-4-chloro-pyrimidine N-oxide (169) in yield (95%).

A nucleophilic substitution reaction using boiling piperidine (106°C) under neat conditions with 2,6-diamino-4-chloro-pyrimidine N -oxide (169), for 120 min was then carried as step two, affording 2,4-diamino-6-piperidinopyrimidine 3-oxide (minoxidil, (171)) product in high yield (80%) and purity without requiring any further purification.

4. Conclusion

This manuscript brings a focused perspective of synthetic methods employed in producing bioactive pyrimidine-based derivatives. A special consideration is given to the FDA approved pyrimidine-based drugs, however, approaches to synthesize bioactive synthons endowed with in interesting bioactivities are also included.

Synthetic approaches used for preparing pyrimidine-cored structures varied from nucleophilic substitution to C-C, C-N cross-coupling or heterocyclization of complementary dielectrophilic (+)C–C–C(+) and dinucleophilic (−)N-C-N(−) fragments. Converting the carbonyl/or hydroxyl group to chloride using $POCl_3$ was often employed in facilitating the substitution reaction at the desired site. In other cases, oxidizing methyl thioether to sulfone offers a convenient option for substitution reactions.

It was noted that reactivity of the four possible sites (C2, C4, C4 and C6) is affected by a prior existence of substitutes or the type of the linkages (C-C, C-N, C-S or C-O).

4.1 Decorated pyrimidines: privileged scaffolds meeting the Mission

The 2,3-diazine (pyrimidine) is found in the core of wide range of bioactive drugs and drug candidates. That includes natural products (from bacteria all along until mammalians) sources and synthetic pharmaceuticals. A wide-range of activities were associated with pyrimidine and derivatives (antibacterial, antitumor, antiviral, analgesic, antiarrhythmic, antifungal [106], antimalarial, anticonvulsant, sought be. Thus,

the structure is considered by medicinal chemists, drug discovery researchers and pharmacologist as medicinally privileged scaffold.

4.2 Two strategies to afford diverse derivatives

4.2.1 Post Heterocyclization

One main strategy in derivatizing pyrimidine get advantage of the availability of halogenated core synthons [mono-, di- or trichloro-pyrimidines]. An approach defines as "post- heterocyclization modification. In such cases, halogenated pyrimidine (frequently 2,4-dichloropyrimidine (38) or 2,4,6-trichloropyrimidine (109)) proved to be highly treasured when subjected to modifying reaction conditions and reagents and afforded the desired products. 2,4-dichloropyrimidine (38), 2,4,6-trichloropyrimidine (109) or similar analogues are made use of in preparing long list of modified pyrimidines. In such case, synthetic methods used in decorating pyrimidine-cored analogues were diverse and include nucleophilic substitution, C-C, C-N, C-O and C-S cross-coupling employing Suzuki or Ullmann conditions or amide coupling.

4.2.2 Constructing while Heterocyclization

In the cases where the desired product is not feasible via coupling or substitution, cross-coupling to reactive form of the heterocyclic core, alternative approaches were implemented. Constructing of the substituted pyrimidines via heterocyclization of predetermined "designed" components i.e. starting from derivatized parts that upon applying matching reaction conditions a "merged" modified core is amalgamated. For example, the syntheses of 2,4,5,6-terasubstituted pyrimidines were made possible by "fusion" of ß-ketoester derivatives with the corresponding amidine or guanidine elements. All should be conducted under carefully designed and appropriate implemented reaction conditions.

4.3 Cases elaborated

Four examples of FDA approved 2,4-disubstitited pyrimidine drugs Pazopanib (21), Remibrutinib (31), Dabrafenib (60) and Rilpivirine (62) were discussed in particular. Examples 4,5,6-trisubstituted pyrimidines like Remibrutinib (31), 2,4-diamino-6-alkyl- or 6-aryl-pyrimidine derivatives were also presented. The approach starting from 2,4,6-trichloropyrimidine (109), giving rise to N-trisubstituted pyrimidine derivatives like Buparlisib [NVP-BKM120] (115) were discussed. A light was shed on 2,4,5,6-tetrasubstituted pyrimidines like Bay 41–4109 (135) and 2-amino-4,6-disubstituted pyrimidines, Etravirine (TMC 125) (63), 2,4-diamino-6-piperidino-pyrimidine 3-oxide Minoxidil (171).

4.4 No means to delineate all

This manuscript aimed at briefing the reader, in an elaborative manner, with some instances and show-case of chemical process affording selected examples of FDA-approved therapeutics. The focus is on approaches employed the "post-heterocyclization" modification methods.

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Conflict of interest

The authors declare that no conflict of interest exists.

Notes/thanks/other declarations

Yousef Najajreh would like to express his special thanks, gratitude and truthful appreciation to my dearest family: my wife Muna, my two daughters Aseel and Layan and my two sons Mulham and Majd for all the love, compassion, and support received from them all along.

This chapter is dedicated to the respectable memories of my mother Jaleelah and my father Salem who passed a way of old age and to the reminiscence of my dearest brothers Mohammed, Iqab and my sister Zahra who left us to a better world. Peace Be Upon Them All.

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Abbreviations

PI3K	phosphoinositide-3-kinase
DNAPK	DNA dependent protein kinase
PI4K	1-phosphatidylinositol-4-kinase
mTOR	mammalian target of rapamycin
PTEN	phosphatase and tensin homolog
NBS	N-bromosuccinimide
DIEA	diisopropylethylamine
Pd(dppf)Cl2-DCM	dichloro [1,1′-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct
DIEA	diisopropylethylamine
DME	dimethoxyethane
CYP	cytochrome P450
CL	clearance
PK	pharmacokinetics
ABCB1	ATP-binding cassette sub-family B member 1
ABCG2	ATP-binding cassette sub-family G member 2
Ac	Acetyl
ALK	anaplastic lymphoma kinase
BMS	Bristol–Myers Squibb

Bn	benzyl
Boc	*N-tert*-butoxycarbonyl
CbzCl	benzyl chloroformate
CDI	*N*,*N*′-carbonyldiimidazole
CFDA	Chinese Food and Drug Administration
CNS	central nervous system
COD	1,5-cyclooctadiene
Cy	cyclohexyl
Dba	dibenzylideneacetone
DBU	1,8-diazabicycolo [5.4.0] undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCHA	dicyclohexylamine
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
3,4-DHP	3,4-dihydropyran
$(DHQ)_2PHAL$	hydroquinine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	dimethylacetamide
DMAC	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMD	Duchenne's muscular dystrophy
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMM	maleic acid dimethyl ester
DMPU	1,3-dimethyl tetrahydropyrimidin-2(1*H*)-one
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
EMA	European Medicine Agency
Et	ethyl
EU	European Union
EtOAc	ethyl acetate
GD1	Gaucher disease 1
GT1	genotype 1
HATU	*o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HBTU	*N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HCV	hepatitis C virus
HDAC	histone deacetylase
HOAc	acetic acid
HOBt	1-hydroxybenzotriazole hydrate
HONB	*N*-hydroxy-5-norbornene-2,3-dicarboximide
HPLC	High performance liquid chromatography
i-Pac	isopropyl acetate

IPF	idiophathic pulmonary fibrosis
i-Pr	isopropyl
LiHMDS	lithium hexamethyldisilazide
LDA	lithium diisopropylamide
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEK	methyl ethyl ketone
MEMCl	2-methoxyethoxymethyl chloride
2-MeTHF	2-methyltetrahydrofuran
MIBK	methyl isobutyl ketone
Moc	methoxycarbonyl
MsCl	methanesulfonyl chloride
MsOH	methanesulfonic acid
MSRA	methicillin-resistant *Staphylococcus aureus*
MTBE	methyl *tert*-butyl ether
MVK	methyl vinyl ketone
MW	microwave
N-Ac-Leu	*N*-acetyl leucine
n-BuLi	*n*-butyllithium
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHS	*N*-hydroxysuccinimide
NK_1	Neurokinin-1
NMP	*N*-methyl-2-pyrrolidone
NMM	*N*-methyl morpholine
NMMO	4-methylmorpholine *N*-oxide
NS5A/B	nonstructural 5A/B
NsCl	2-nitrobenezenesulfonyl chloride
NSCLC	non-small cell lung cancer
$(o\text{-tol})_3P$	tris(2-methylphenyl)phosphine
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane
PDE-4	phosphodiesterase IV
$Pd(OAc)_2$	palladium acetate
Ph	phenyl
PhMe	toluene
PI3K	phosphatidylinositol 3-kinase
PMDA	Pharmaceuticals and Medical Devices Agency
PPAR	peroxisome proliferator-activated receptor
PPTS	pyridinium *p*-toluenesulfonate
PSA	psoriatic arthritis
PTCL	peripheral T-cell lymphoma
p-TsOH	*p*-toluenesulfonic acid
PTSA	*p*-toluenesulfonamide
Py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
$[Rh(COD)_2]$ OTf	bis (1,5-cyclooctadiene)rhodium(I)trifluoromethane-sulfonate

Rt	room temperature
SGLT2	sodium-glucose co-transporter 2
TB	tuberculosis
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrogen sulfide
TBME	*tert*-butylmethyl ether
t-Bu	*tert*-butyl
TEA	triethylamine
TEPA	triethylphosphonoacetate
TIPS	triisopropylsilyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMDS	1,1,3,3-tetramethyldisiloxane
TMS	trimethylsilyl
TNF	tumor necrosis factors
THP	tetrahydropyranyl
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TNF	tumor necrosis factor alpha
T_3P	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide
TPAP	tetrapropylammonium perruthenate
Ts	4-toluenesulfonyl
USA	United States of America
US FDA	United States Food and Drug Administration
VEGFR2	vascular endothelial growth factor 2
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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