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Review

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Recent advances in the reactions of pyrrolo[2,3-*d*]pyrimidines

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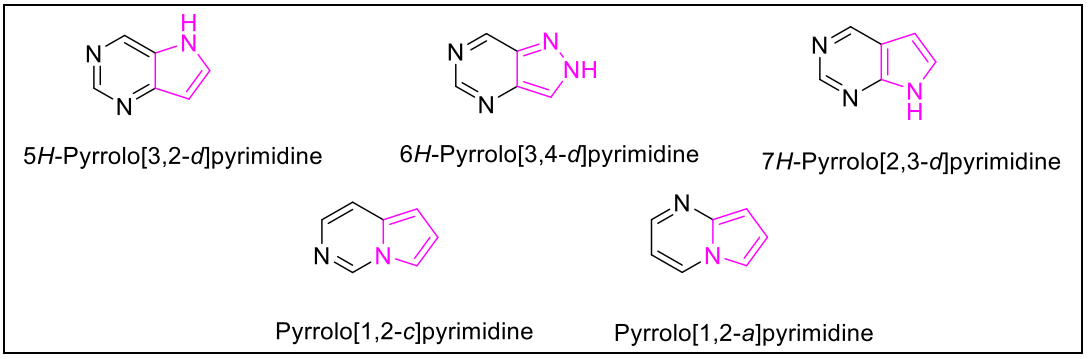
Abstract

Pyrrolo[2,3-*d*]pyrimidine is one of the important biogenic purine nucleoside analogues with a variety of biological uses. By replacing the N7 atom with a carbon atom, the five-membered ring gains electrons, which makes it possible to add extra substituents at the C7 position. This usually leads to derivatives with higher base pairing in DNA or RNA or more efficient binding to enzymes. It has been discovered that a wide range of 7-deazapurine nucleosides have potent cytotoxic or cytostatic qualities. Most promising are 7-hetaryl-7-deazaadenosines, which are phosphorylated in cancer cells and integrated into RNA (which inhibits proteosynthesis) and DNA (which damages DNA). This review discusses the modern reactions and their different conditions that were carried out on the pyrrolo[2,3-*d*]pyrimidine, whether they occurred in the pyrrole nucleus or the pyrimidine nucleus.



Keywords: Pyrrolo[2,3-*d*]pyrimidine, nucleophilic substitution reaction, Buchwald-Hartwig coupling reaction

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1. Introduction

Pyrrole is one of the most common heterocycles found in both plant and animal kingdoms, primarily due to its role as a component of chlorophyll in plants and hemin and vitamin B12 in animals. Pyrrole and its derivatives have demonstrated a range of biological activities, including antibacterial and antifungal properties,[1,2] antitumor effects,[3,4] analgesic capabilities,[5] antitubercular activity,[6-9] anti-inflammatory effects,[10] and significant applications in pharmaceutical research.[11-15] Pyrrolo[2,3-*d*]pyrimidines represent a significant class of heterocyclic compounds, gaining considerable attention due to their wide-ranging biological activities.[16] These fused bicyclic systems are known for their versatility in medicinal chemistry, particularly in the development of novel therapeutic agents,[17] and also referred to as 7-deazapurine, is present in a variety of natural or synthesized compounds that showcase intriguing biological properties.[16] The rigid structure of the pyrrolo[2,3-*d*]pyrimidine scaffold features two hydrogen bond acceptors and one hydrogen bond donor, with five positions (C2, C4, C5, C6, and N7) available for modification. Derivatives of pyrrolo[2,3-*d*]pyrimidine are recognized for their diverse biological activities and potential inhibitors such as tyrosine kinase inhibitors,[17-19] anticancer agents,[20-22] anti-proliferative agents,[23] anti-tubercular agent,[24,25] antimicrobial,[26,27] antiviral,[26] antioxidant,[28] inflammatory activities,[29] and anti-antiviral agent.[30]

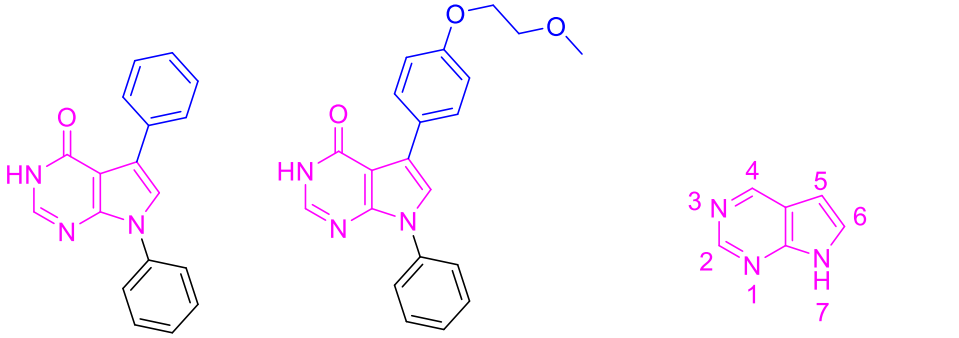


Figure 1. Selective pyrrolo[2,3-*d*]pyrimidine derivatives as inhibitors of MAP4K4.

Mitogen-activated protein kinase kinase kinase kinase-4 (MAP4K4), also referred to as HGK (hematopoietic progenitor kinase/germinal center kinase-like kinase), it has recently gained recognition for its

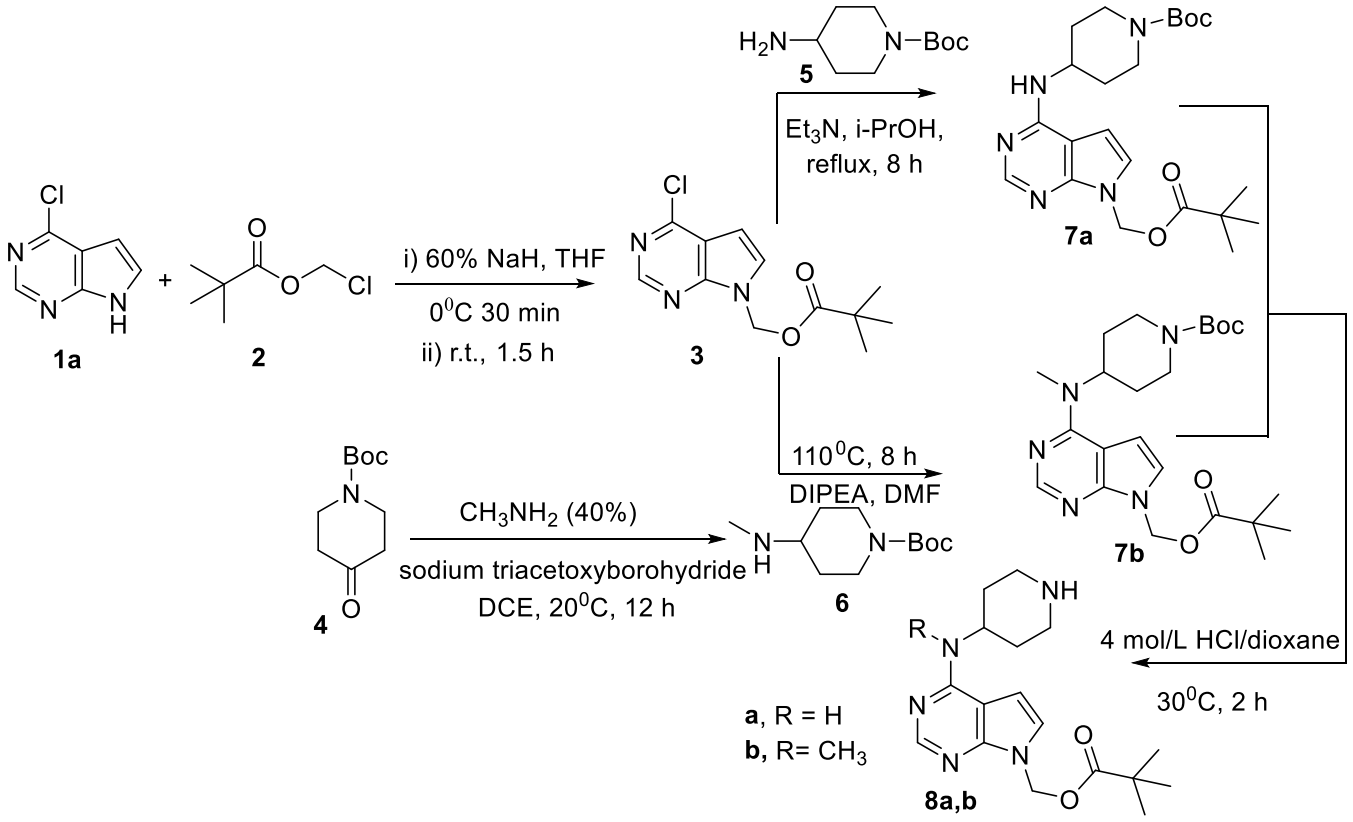
regulatory function in myocardial injury and tissue recovery. Two effective inhibitors of MAP4K4, namely 5,7-diphenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (F1386-0303, IC50 34 nm) and 5-(4-(2-methoxyethoxy) phenyl)-7-phenyl-3,4a,7,7a-tetrahydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (DMX-5804, IC50 3 nm), have been identified as potent selective inhibitors of MAP4K4. Notably, DMX-5804 demonstrated superior bioavailability *in vivo* compared to F1386-0303.[31] This review emphasizes recent developments in the chemistry of pyrrolo[2,3-*d*]pyrimidine from 2012 to 2024, and is based on searches conducted in SciFinder, Reaxys, and Web of Knowledge.

2. Reactions of Pyrrolo[2,3-*d*]pyrimidine

The skeleton of 7-*H*-Pyrrolo[2,3-*d*]pyrimidine (7-deazapurine, 7-DAP) is acknowledged as a significant privileged scaffold that is widely found in various bioactive natural products and drug compounds.[18] This structure has demonstrated remarkable pharmacological properties.

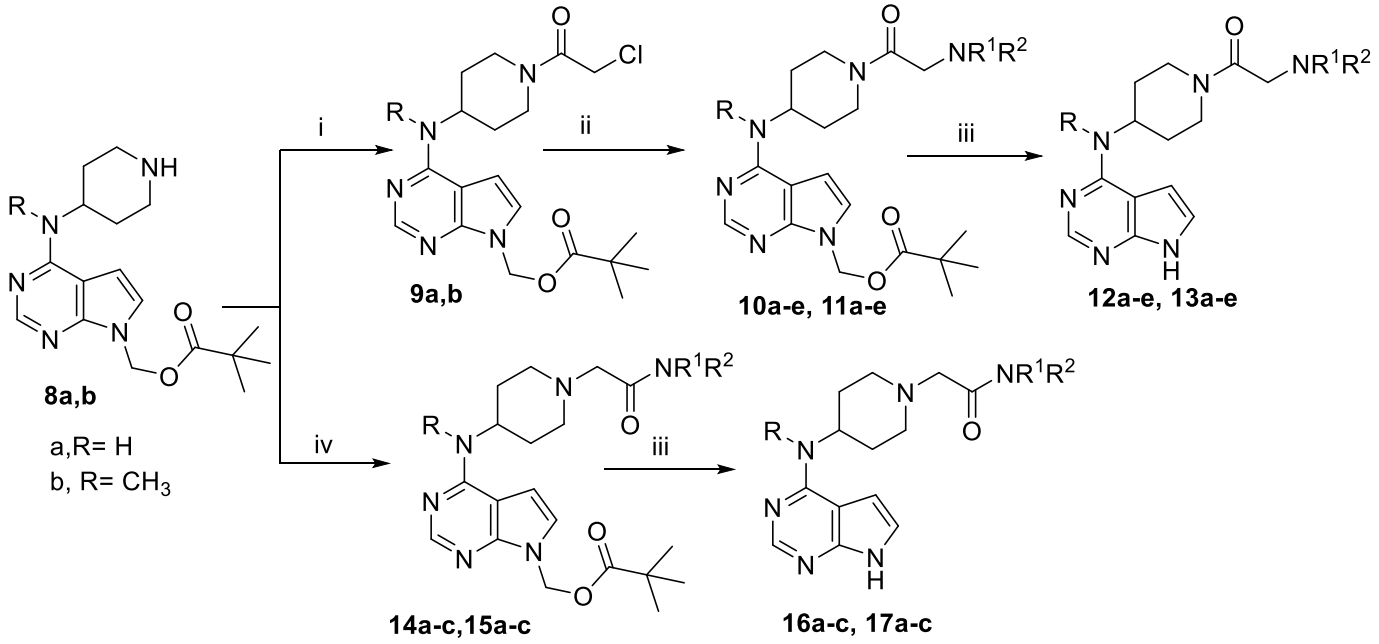
2.1. Nucleophilic substitution reactions of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine

Recently,[33] it was reported that the reaction between chloro derivative **1a** and chloromethyl pivalate **2** was performed in the presence of 60% NaH/THF, yielding the corresponding compound **3**. The reductive amination reaction of *tert*-butyl 4-oxopiperidine-1-carboxylate **4** with 40% methylamine gave compound **6** in satisfactory yield. Nucleophilic substitution reaction of intermediate **3** with *tert*-butyl 4-aminopiperidine-1-carboxylate **5** or **6**, using Et_3N or DIPEA subsequently afforded the corresponding compounds **7a,b**. Reaction of **7a,b** with HCl/dioxane, N-Boc group was removed and the compounds **8a,b** were obtained (Scheme 1).



Scheme 1. Protection of *N*-7 of pyrrolo[2,3-*d*]pyrimidine **1a** with chloromethyl pivalate **2**

Reaction[33] of compound **8a,b** with chloroacetyl chloride led to formation of the corresponding compound **9a,b**. The latter Intermediate **9a,b** was subjected to further reaction with various amines at r.t to give the corresponding compounds **10a-e** and **11a-e**. Hydrolysis of latter compound with NaOH/H_2O solution in methanol gave the compounds **12a-e** and **13a-e**. The key intermediate **8a,b** underwent alkylation reaction with various 2-chloroacetamids at 60°C to afford the intermediates **14a-c** and **15a-c**. Also, hydrolysis of compounds **14a-c** and **15a-c** with NaOH/H_2O solution in methanol afforded the corresponding derivatives **16a-c** and **17a-c** (Scheme 2).

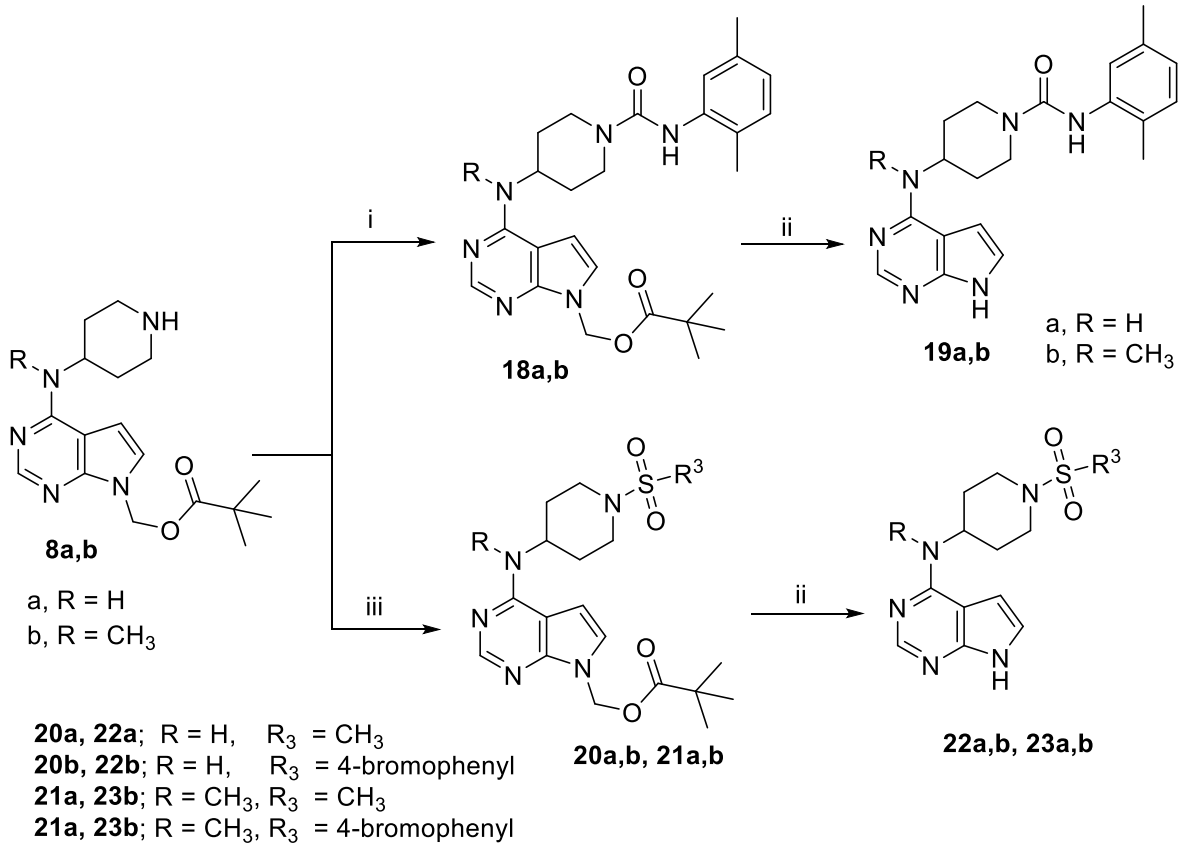


(i) Et_3N, chloroacetyl chloride, THF, r.t., 30 min, (ii) amine, K_2CO_3, MeCN, r.t., 30 h.
(iii) 1 mol/L NaOH/H_2O, methanol, r.t., 2 h, (iv) various 2-chloroacetamids, K_2CO_3, MeCN. 60°C, 1 h; 1 mol/L NaOH/H_2O, methanol, r.t., 2 h.

10b,12b,14b,16b	R = H, NR_1R_2 = morphilin-1-yl	**11c, 13c**	R = CH_3, NR_1R_2 = pyrrolidin-1-yl
10c,12c	R = H, NR_1R_2 = pyrrolidin-1-yl	**11d, 13d**	R = CH_3, NR_1R_2 = 4-methylpiprazin-1-yl
10d,12d	R = H, NR_1R_2 = 4-methylpiprazin-1-yl	**11e, 13e**	R = CH_3, NR_1R_2 = piperidin-1-yl
10e, 12e	R = H, NR_1R_2 = piperidin-1-yl	**14c, 16c**	R = H, NR_1R_2 = 2,5-dimethylphenylamino
11b, 13b,15b,17b	R = CH_3, NR_1R_2 = morphilin-1-yl	**15c, 17c**	R = CH_3, NR_1R_2 = 2,5-dimethylphenylamino

Scheme 2. N-Alkylation reactions of pyrrolo[2,3-*d*]pyrimidine derivative **8a,b.**

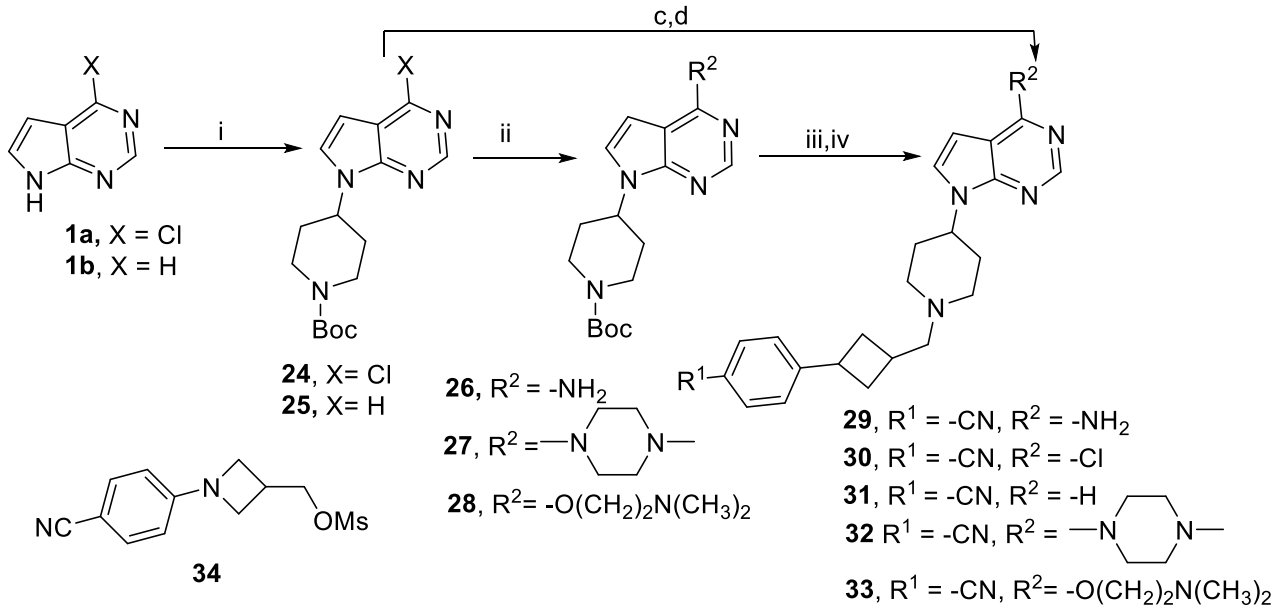
The acylation[33] of compounds **8a,b** with phenyl (2,5-dimethylphenyl)carbamate or various sulfonyl chlorides afforded the corresponding compounds **18a,b, 20a,b** and **21a,b** respectively (Scheme 3). Finally, deprotection of the methyl pivalate (POM) from the latter compounds **18a,b, 20a,b** and **21a,b** gave successfully the corresponding compounds **19a,b, 22a,b**, and **23a,b** as previously described in procedures shown in Scheme 3.



(i) phenyl (2,5-dimethylphenyl)carbamate, Et_3N,THF, 60^0C, 4 h (ii) 1 mol/L NaOH/H_2O, methanol, r.t., 2 h
(iii) various sulfonyl chlorides, Et_3N, MeCN, 60^0C, 1 h

Scheme 3. Synthesis of *N*-(1-hydrosulfonylpiperidin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine **22a,b** and **23a,b**.

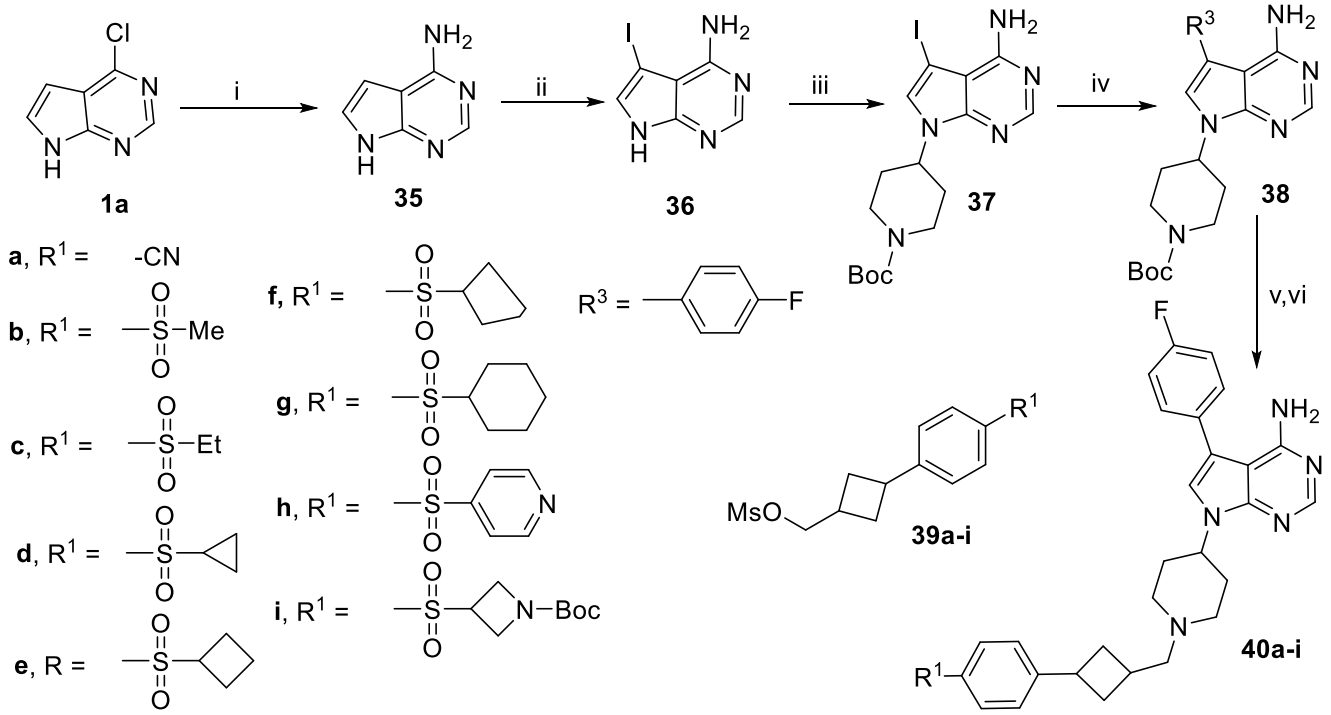
Bai, H. *et al* mentioned that,[34] the Mitsunobu reaction of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1a** (X = Cl) or 7*H*-pyrrolo[2,3-*d*]pyrimidine **1b** (X = H) with *N*-Boc-4-piperidinol yielded the corresponding pyrrolo[2,3-*d*] pyrimidine derivatives **24, 25.** Treatment of compound **24** was with ammonia or *N*-methylpiperazine gave the compounds **26** and **27.** Interaction of **24** with *N*,*N*-dimethylaminoethanol afforded the compound **28.** The Boc group was Deprotected using trifluoroacetic acid (TFA). Nucleophilic substitution reaction of compounds **24-28** gave the corresponding pyrrolo[2,3-*d*]pyrimidine derivatives **29-33** (Scheme 4).



(i)anhydrous THF, N-Boc-4-piperidinol, PPh_3, DIAD, rt, overnight.
(ii) for **31**, $NH_3 \cdot H_2O$/dioxane = 2/1 (v/v), 110 ^{0}C, 8 h; for **32**, EtOH, DIPEA, 70 .C, reflux, 16 h;
for **33**, THF, NaH, rt, overnight; (iii) DCM, TFA, rt, 1–3 h; (iv) intermediate **34**, K_2CO_3, KI, CH_3CN, 80 ^{0}C, overnight.

Scheme 4. Synthetic pathways of compounds **29-33.**

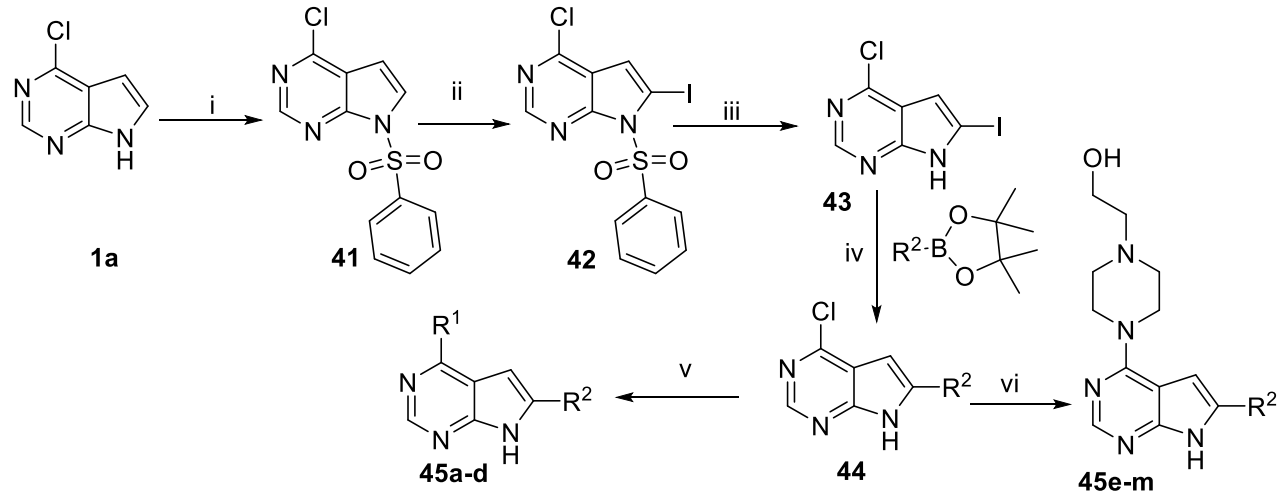
In continuation to what was mentioned above,[34] the reaction of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1a** with ammonia provided the compound **35**. The Iodination reaction of the latter compound **35** with *N*-iodosuccinimide (NIS) led to formation of the derivative **36**. Treatment of compound **36** with *N*-Boc-4-piperidinol through Mitsunobu reaction afforded **37**. Coupling of **37** with boronic acid or ester afforded the corresponding intermediate **38**. Removing of the Boc group from compound **38** was performed in presence of TFA followed by nucleophilic substitution with the intermediates **39a-i** gave the corresponding compounds **40a-l** (Scheme 5).



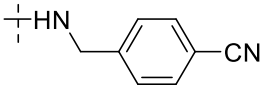
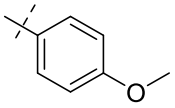
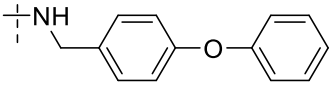
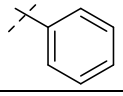
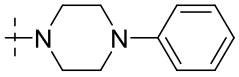
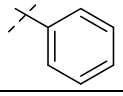
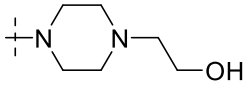
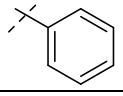
(i) $NH_3 \cdot H_2O$, 130 .C, 6 h; (ii) NIS, THF, rt, 1 h; (iii) anhydrous THF, *N*-Boc-4-piperidinol, PPh_3, DIAD, rt, overnight; (iv) corresponding boric acid or boric acid ester, (dppf)$PdCl_2$, K_2CO_3, 1,4-dioxane/EtOH/H_2O = 7/3/4 (v/v/v), 80 ^{0}C, overnight; (v) DCM, TFA, rt, 1–3 h; (vi) intermediates **39a-i,** K_2CO_3, KI, CH_3CN, 80 ^{0}C, overnight.

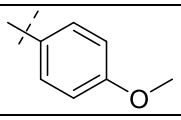
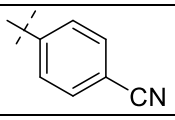
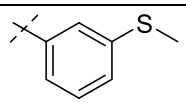
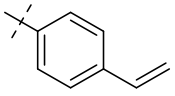
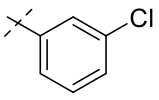
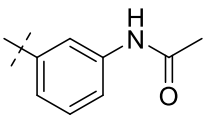
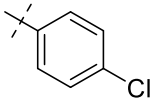
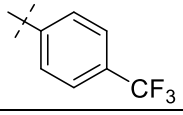
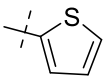
Scheme 5. The synthetic routes of pyrrolo[2,3-*d*]pyrimidine derivatives **40a-i.**

Wang L. *et al* suggested that,[35] Reaction of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1a** with *N,N*-diisopropylethylamine (DIPEA), followed by reaction with $PhSO_2Cl$ resulted the corresponding compound **41.** Iodination of the latter compound **41** with iodine (I_2) in the presence of lithium diisopropylamide (LDA) yielded **42**. Furthermore, interaction of the latter derivative **42** with sodium hydroxide removes the -SO_2Ph and leads to the formation of 4-chloro-6-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (**43**). Compound **43** underwent a Suzuki-Miyaura coupling reaction giving the corresponding pyrrolo[2,3-*d*]pyrimidine derivatives **44**. Compound **44** was activated with DIPEA, followed by reaction with benzylamine or piperazine to obtain the compounds **45a-d**. Whereas, refluxing the compound **44** with DIPEA, followed by the addition of *N*-(2-hydroxyethyl) piperazine resulted to the formation the corresponding derivatives **45e-m** (Scheme 6).



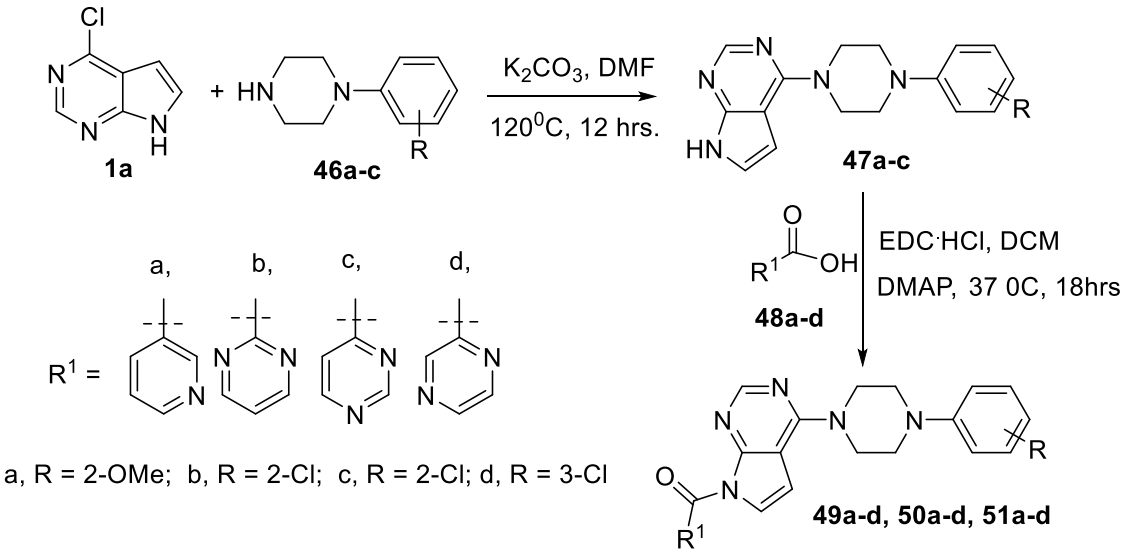
(i) $PhSO_2Cl$, DIPEA, THF, 60 ^{0}C reflux; (ii) I_2, LDA, THF, -78 0^C; (iii) NaOH(aq), MeOH, rt; (iv) $Pd(dppf)Cl_2$, K_2CO_3, N_2, 1,4-Dioxane, 80 ^{0}C; (v) Benzylamine derivatives, piperazine derivatives, DIPEA, *N*-butanol, 100 ^{0}C, reflux; (vi) N-(2-hydroxyethyl)piprazine, DIPEA, *N*-butanol, 100 ^{0}C, reflux

Comd. No	R^1	R^2
45a		
45b		
45c		
45d		

Comd. No	R^2	Comd. No	R^2	Comd. No	R^2
45e		**45h**		**45k**	
45f		**45i**		**45l**	
45g		**45j**		**45m**	

Scheme 6. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **45a-m.**

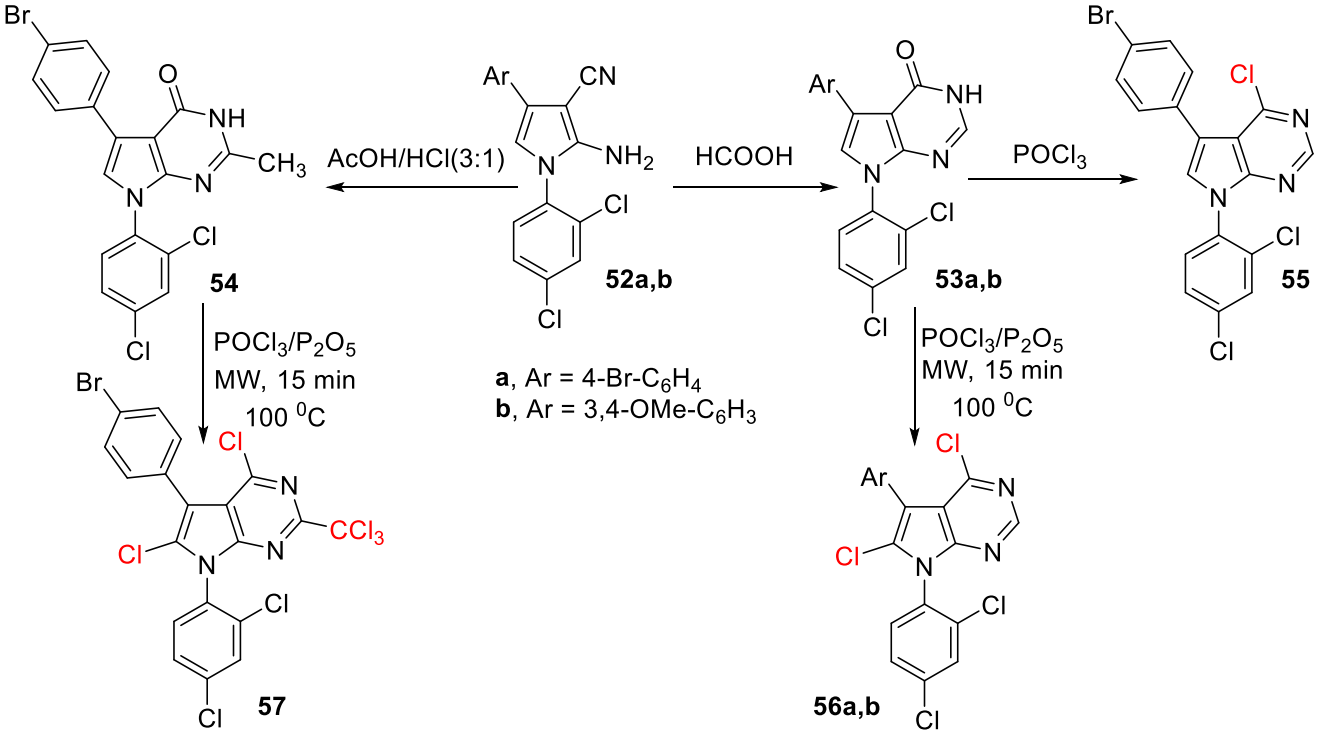
It was found that,[36] Reaction of the choro derivative **1a** and substituted piperazine **46a–c** in the presence of potassium carbonate and DMF gave the corresponding pyrrolo[2,3-*d*]pyrimidine derivatives **47a–*c***. Furthermore, treatment of compounds **47a–c** with substituted acids **48a–d** using EDC.HCl in DMAP and DCM afforded the corresponding compounds **49-50(a–d)** (Scheme 7).



Scheme 7. Synthesis of substituted pyrrolo[2,3-*d*]pyrimidine derivatives **49-51(a-d)**.

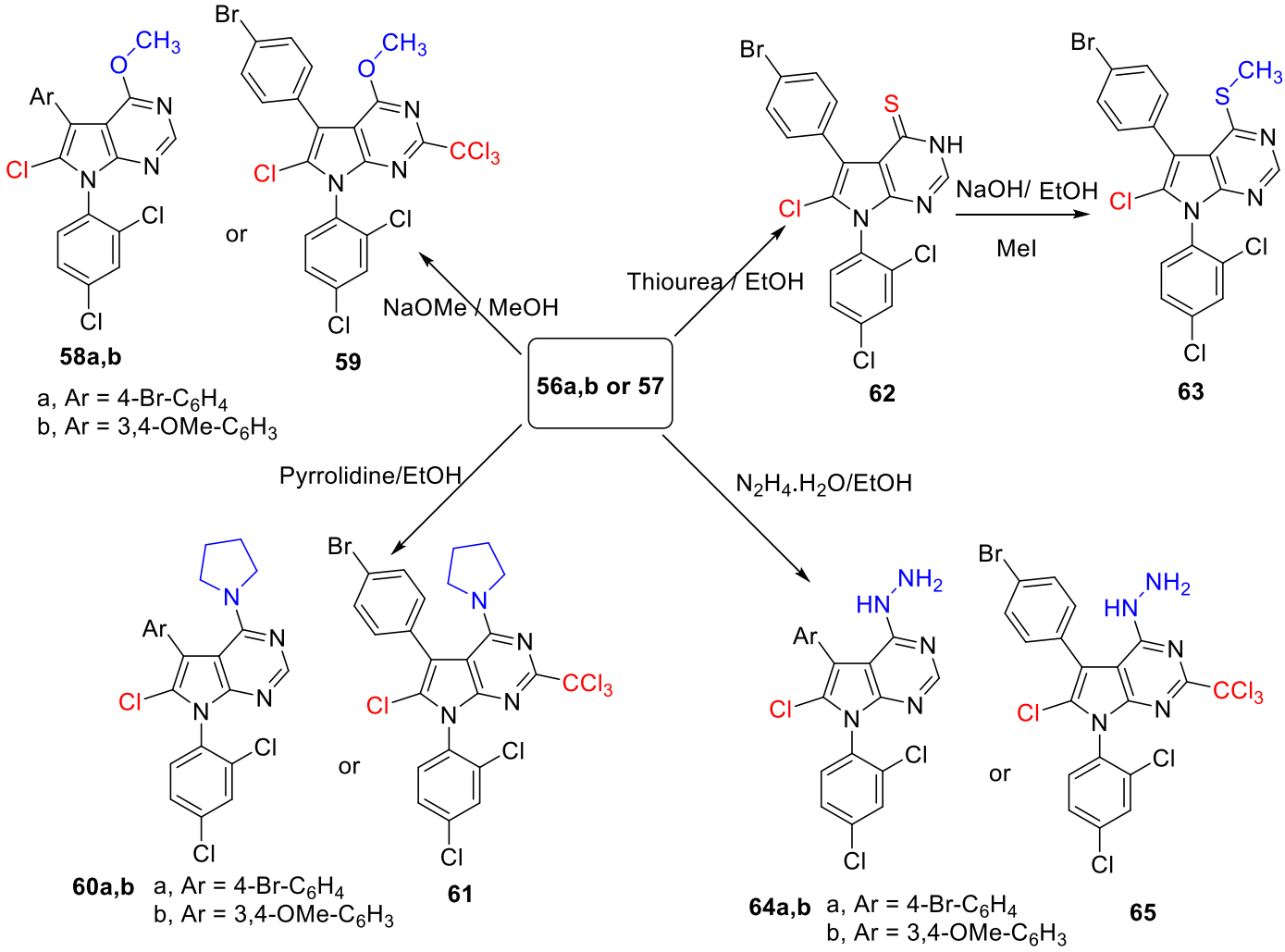
2.2. Reactions on C-6 of pyrrolo[2,3-*d*]pyrimidine

In 2023, it was found that,[37] Treatment of aminonitrile derivative **52a,b** with formic acid afforded the corresponding pyrrolo[2,3-*d*]pyrimidin-4-ones **53a,b.** whereas, the reaction of **52a,b** with acetic acid and hydrochloric acid mixture gave compound **54**. Treatment of compound **53a,b** with an excess of $POCl_3$ afforded the derivative **55**. While the chlorination of compound **53a,b** using a mixture of $POCl_3/P_2O_5$ under the microwave technique (MW) gave the corresponding compound **56a,b**. Similarly, treatment of **54** with $POCl_3/P_2O_5$ under the same conditions yielded compound **57**. It is noteworthy that the chlorination by $POCl_3$ occurred on C-4 only. Whereas the chlorination using a mixture of $POCl_3/P_2O_5$ under the microwave technique occurred in the methyl group, C-6 in addition to C-4 (Scheme 8).



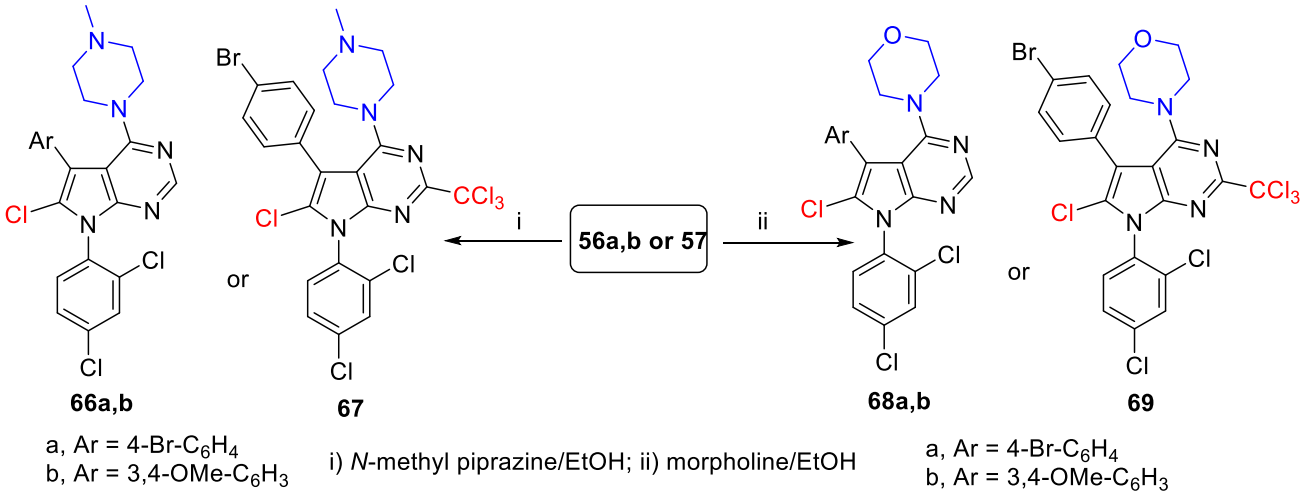
Scheme 8. Chlorination of pyrrolo[2,3-*d*]pyrimidine derivatives **53a,b** and/or **54.**

The same authors mentioned that[37] treatment of compounds **56a,b** and **57** with sodium methoxide in methanol gave **58a,b** and **59** respectively**.** Also, the reaction of pyrrolo[2,3-*d*] pyrimidine **56a,b** and **57** with pyrrolidine in ethanol afforded the corresponding derivatives **60a,b** and **61** respectively. Whereas interaction of **56a** with thiourea in boiling ethanol afforded **62**. Methylation of the latter compound with MeI in ethanol in the presence of NaOH gave the corresponding methylthio derivative **63**. Interaction of **56a,b** and **57** with hydrazine hydrate in boiling ethanol gave the corresponding the hydrazino derivatives **64a,b** and **65** (Scheme 9).



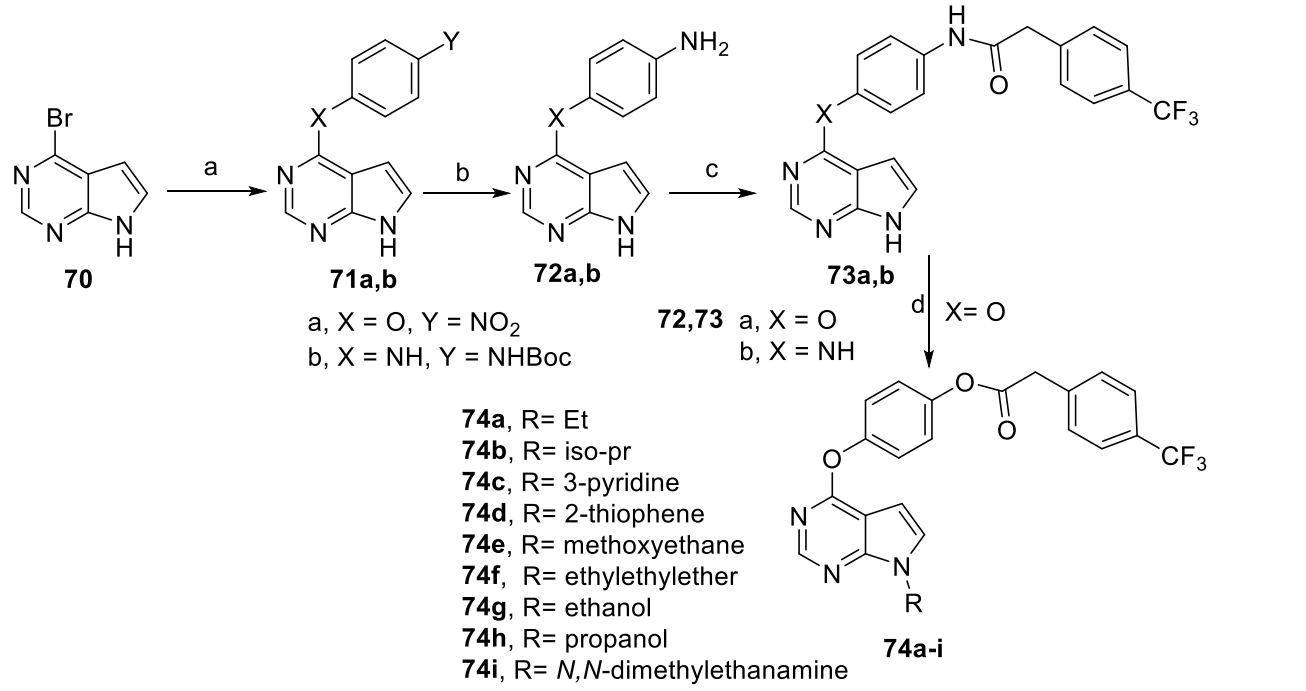
Scheme 9. Nucleophilic substitution reactions of chloro derivatives **56** or **57.**

Similarly, reaction of chloro derivatives **56a,b** and/or **57** with *N*-methyl piperazine or morpholine gave a series of substituted pyrrolo[2,3-*d*]pyrimidine **67** and **69** (Scheme 10)[37].



Scheme 10. Nucleophilic substitution reactions of chloro derivatives **56a,b** or **57.**

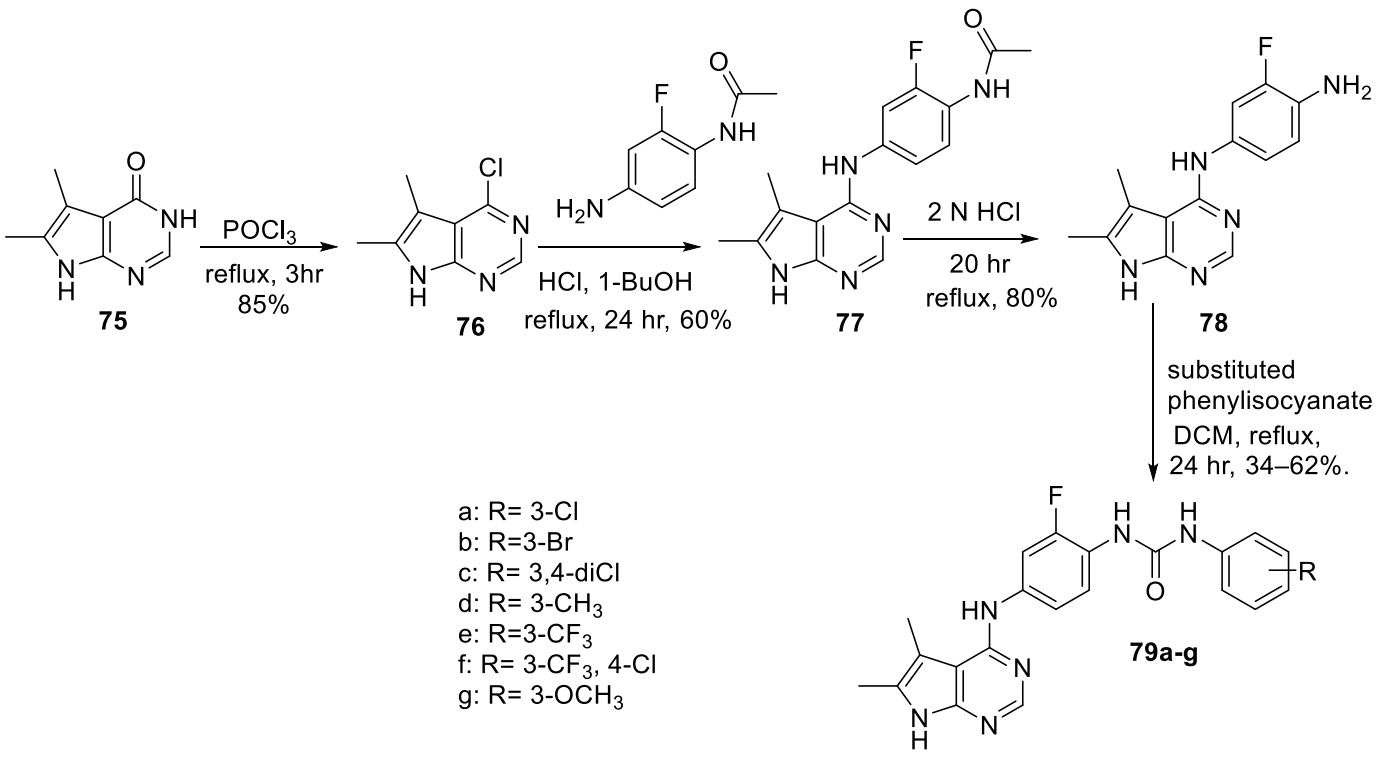
Treatment[38] of bromo derivative **70** with 4-nitrophenol using DIPEA gave the corresponding compound **71a**. Reduction of the nitro compound **71a** with Fe yielded the amino derivative **72a**. Coupling of the latter compound **72a** with 4-(trifluoromethyl)phenylacetic acid afforded the corresponding acetamide derivative **73a**. Reaction of compound **73a** with different alkyl halides resulted the corresponding pyrrolo[2,3-*d*] pyrimidine derivatives **74a-i**. Compound **71b** was prepared by nucleophilic substitution reaction of compound **70**. Treatment of **71a** with TFA afforded compound **72b.** Coupling of compound **72b** with 4-(trifluoromethyl)phenylacetic acid afforded the corresponding derivative **73b** (Scheme 11).



Reagents and conditions: (a) 4-nitrophenol, DIPEA, NMP, 140 ^{0}C, 24 h, 81% (**71a**); t-butyl(4-amino-phenyl)carbamate, DIPEA, NMP, 140 ^{0}C, 24 h, 40% (**71b**); (b) Fe, NH_4Cl, DMF/EtOH/H_2O, 100 ^{0}C, 20 min, 95% (**72a**); TFA/DCM, rt, 1 h, 96% (**72b**); (c) 4- (trifluoromethyl)phenylacetic acid, HATU, DIPEA, THF, rt, 6 h; (d) RI or RBr, Cs_2CO_3, DMF, rt, 10 h, 8%–40%.

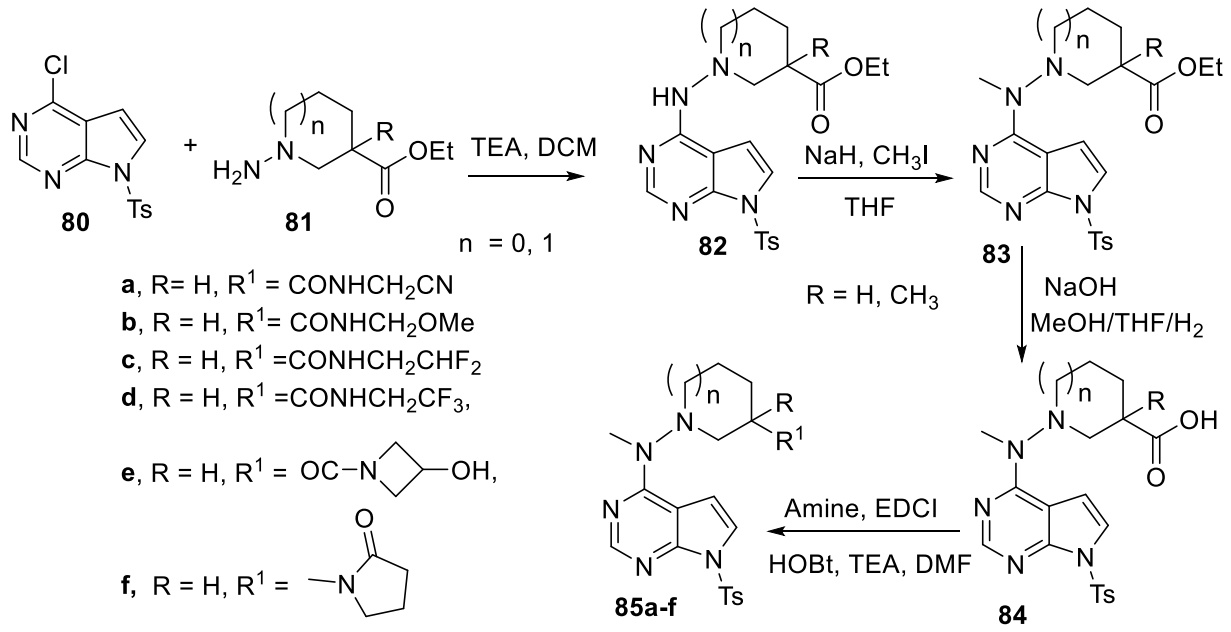
Scheme 11. Synthesis of compounds **73a,b** and **74a-i.**

Adel, M. *et al* suggested that,[39] the synthesis of 4-chloropyrrolopyrimidine derivative **76** was performed by chlorination of compound **75** with $POCl_3$. Reaction of The chloro derivative **76** with 2-fluro-4-amino acetanilide in 1-butanol and drops of conc. HCl gave the amide derivative **77**. Treatment of **77** with 2N HCl provided the amine derivative **78.** When the amine derivative **78** was refluxed with isocyanates, the urea-based pyrrolo[2,3-*d*]pyrimidine derivatives **79a-g** were obtained (Scheme 12).



Scheme 12. Treatment of amine compound **78** with isocyanates to afford the compounds **79a-g.**

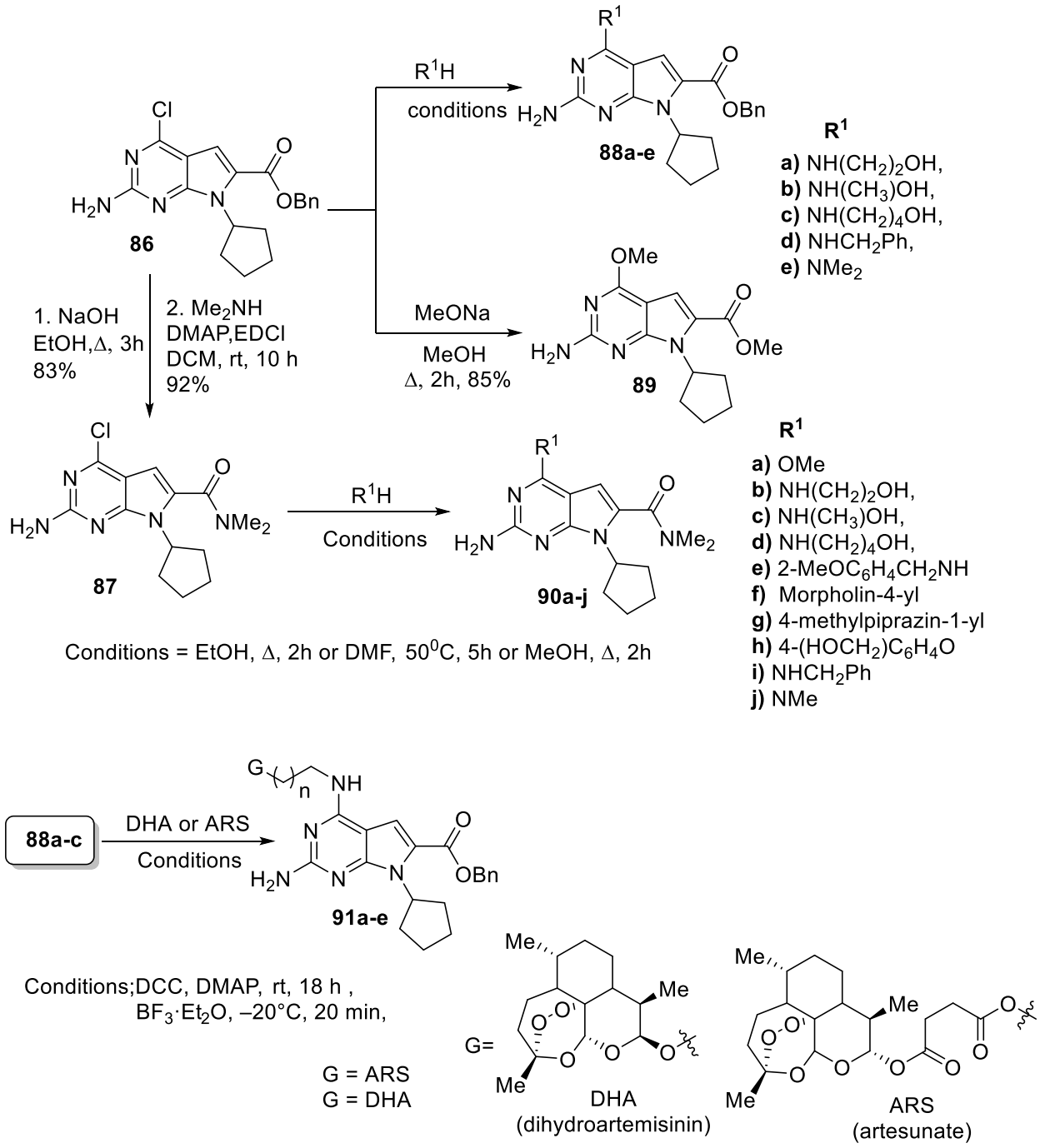
Treatment[40] of compound **80** with hydrazino derivative **81** afforded the corresponding product **82**. Methylation of compound **82** with CH_3I and NaH provided the N-methyl derivative **83**. Hydrolysis of **83** afford the corresponding acid **84**. Reaction of **84** with different substituted amines gave the corresponding compounds **85a-f** (Scheme 13).



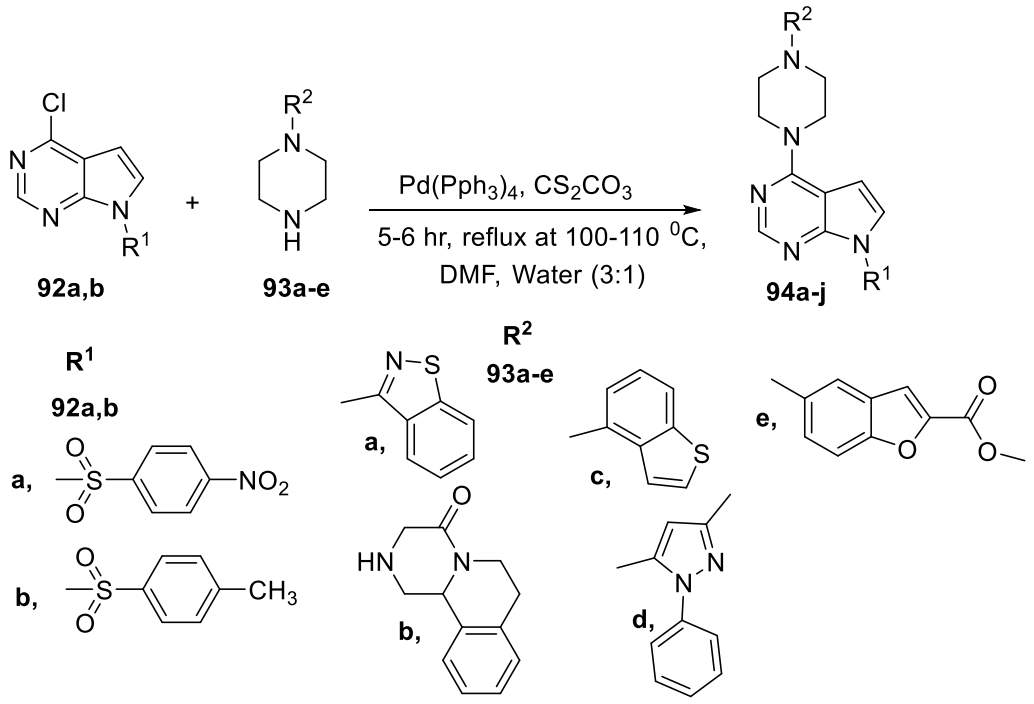
Scheme 13. Synthesis of hydrazinyl compound contained pyrrolo[2,3-*d*]pyrimidine moiety **85a-f**.

The authors mentioned that,[41] reaction of **86** with different amino alcohols, amines, or MeOH gave the corresponding compounds **88a–e, 89**. Hydrolysis of benzyl ester **86** followed by the amidation in the presence of Me_2NH and EDCI afforded compound **87**. Nucleophilic substitution reaction of **87** gave compounds **90a–j.** Treatment of compounds **88a–c** with ARS (artesunate) and/or DHA (dihydroartemisinin) gave the corresponding pyrrolo[2,3-*d*]pyrimidine derivatives **91a-e** (Scheme 14).

It was found that,[42] Buchwald Hartwig coupling reaction occurred through the interaction of chloro derivatives of pyrrolo[2,3-*d*]pyrimidine **92a,b** with piperazine derivatives **93a-e** using cesium carbonate and tetrakis (triphenylphosphine) palladium in DMF:H_2O mixture (3:1) affording the corresponding substituted pyrrolo[2,3-*d*] pyrimidine derivatives **(94a-j)** (Scheme 15).

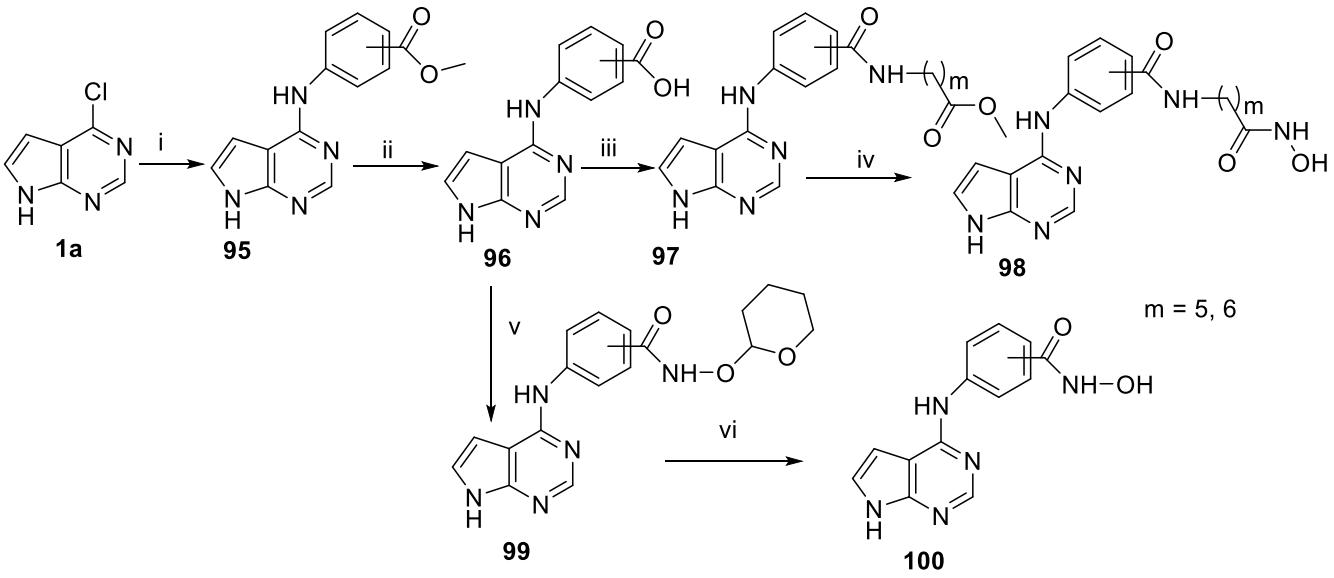


Scheme 14. Reactions on the 6-benzyl carboxylate of pyrrolo[2,3-*d*]pyrimidine **86.**

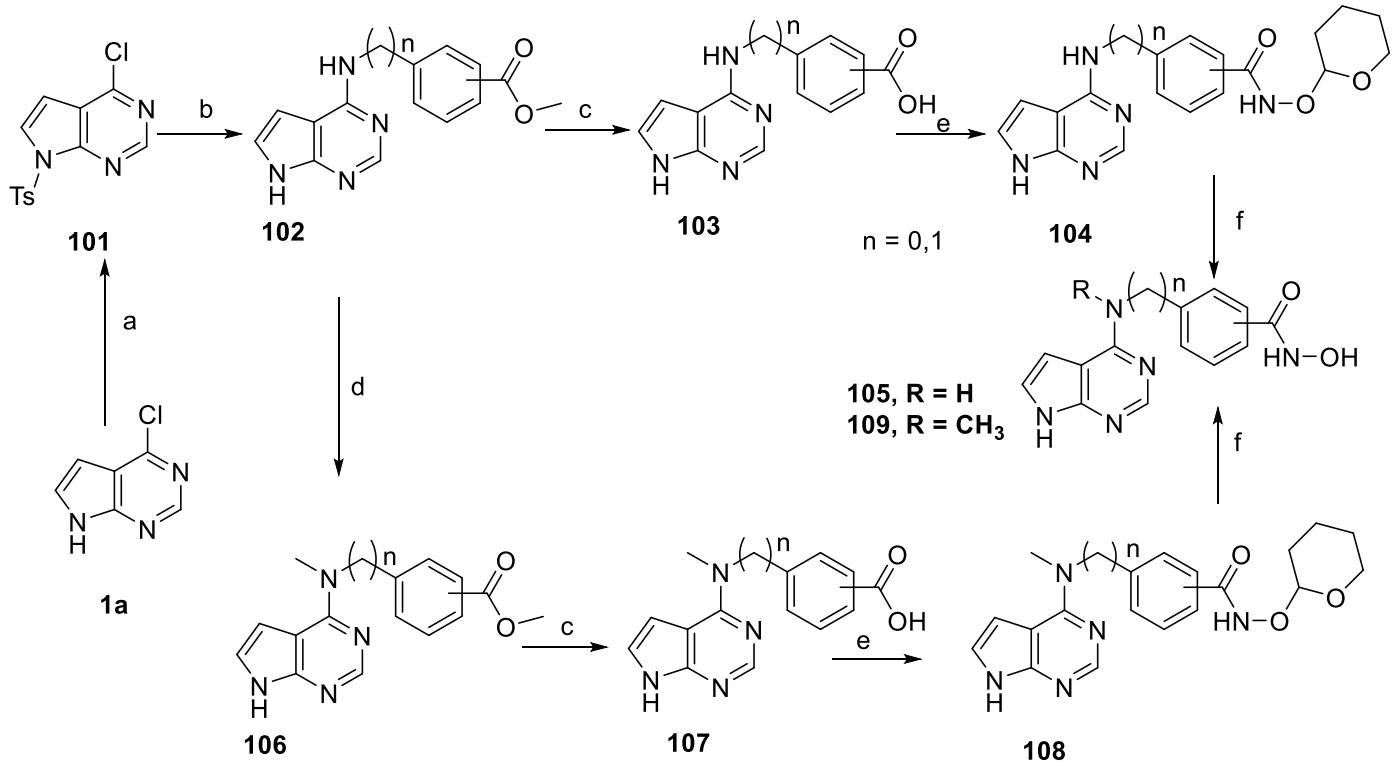


Scheme 15. Buchwald Hartwig coupling reaction of **92a-j.**

Li, S. *et al* found that,[43] Reaction of compound **1a** with methyl aminobenzoates afforded **95a,b.** Hydrolysis of the latter compounds with NaOH led to formation of the corresponding carboxylic acids **96a,b**. Condensation of **96a,b** with different methyl aminoalkanoates produced **97.** Reaction of the latter compound with hydroxyl amine gave the corresponding hydroxamic acid **98**. Furthermore, reaction of **96** with NH_2OTHP yielded the corresponding **99**. Also, reaction of the compound **99** with hydroxyl amine gave hydroxamic acid **100**. On the other hand, reaction of **1a** with tosyl chloride resulted the compound **101.** Treatment of the latter compound **101** with various methyl aminobenzoates afforded **102**. Hydroxamic acids **105** were achieved from compound **102** using the similar methods of synthesizing **100** from **95**. Interaction of intermediates **102** with CH_3I led to formation of **106**. Similarly, hydroxamic acids **109** could be obtained using the similar procedure described above in the synthesis of compound **100** from **95** (Scheme 16).



i) various methyl aminobenzoate, isopropanol, conc HCl, reflux; (ii) MeOH, 2.5 N NaOH, reflux; (iii) various methyl aminoalkanoates,TBTU, TEA, anhydrous DMF; (iv) $NH_2OH{\cdot}HCl$, KOH, anhydrous CH_3OH; (v) NH_2OTHP, EDCI, HOBt, TEA, DMF; (vi) HCl, anhydrous EtOAc

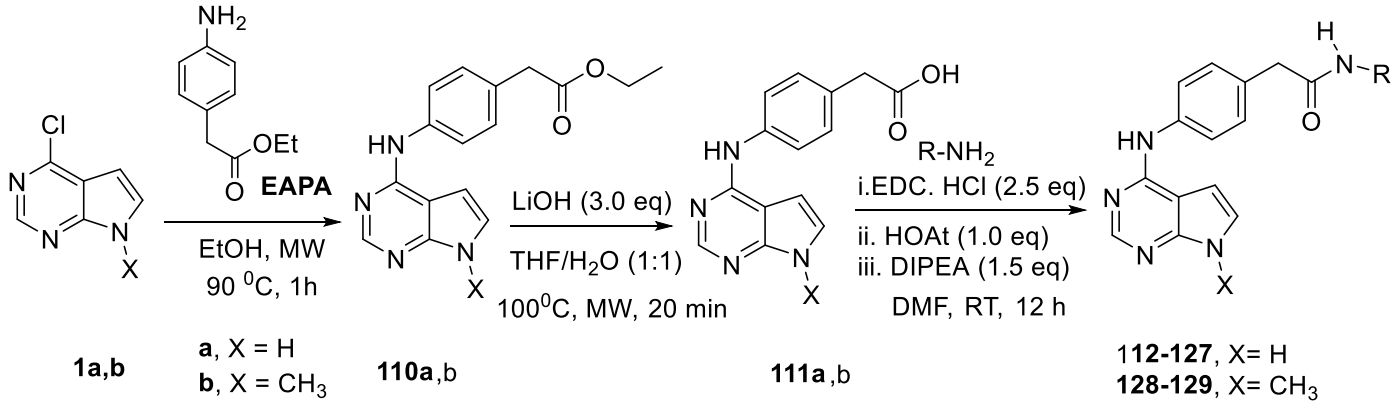


a)TsCl, TEA, DMAP, DCM; b) various methyl aminobenzoate, isopropanol, conc HCl, reflux; c) MeOH, 2.5 N NaOH, reflux; d) Cs_2CO_3, CH_3I, DMF; e) NH_2OTHP, EDCI, HOBt, TEA, DMF; f) HCl, anhydrous EtOAc

Scheme 16. Synthesis of Hydroxamic acids-based pyrrolo[2,3-*d*]pyrimidine **105** and **109**.

Lakkaniga, N. R *et al* reported that,[44] the nucleophilic substitution reaction of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **1a,b** with ethyl-2-(4-aminophenyl)acetate (EAPA) gives the ester derivatives **110a,b**. Treatment of the ester **110a,b** with LiOH in THF/H_2O led to formation of corresponding carboxylic acid derivative **111a,b**.

Reaction of **111a,b** with different substituted anilines in the presence of (EDC) afforded the corresponding acetamide derivatives **112-129** (Scheme 17).



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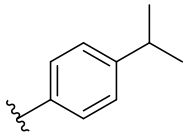
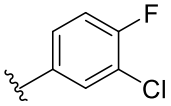
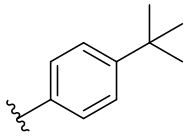
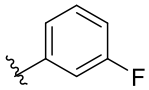
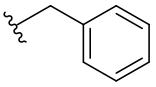
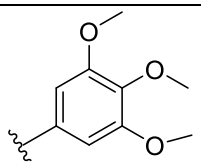
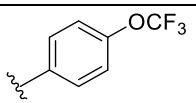
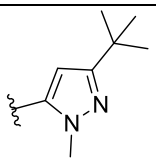
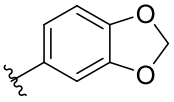
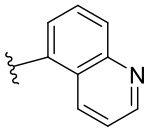
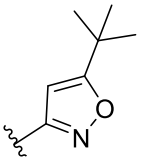
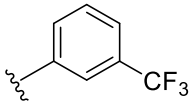
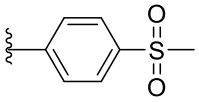
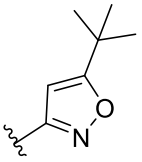
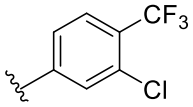
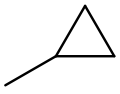
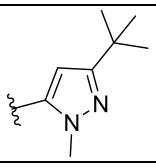
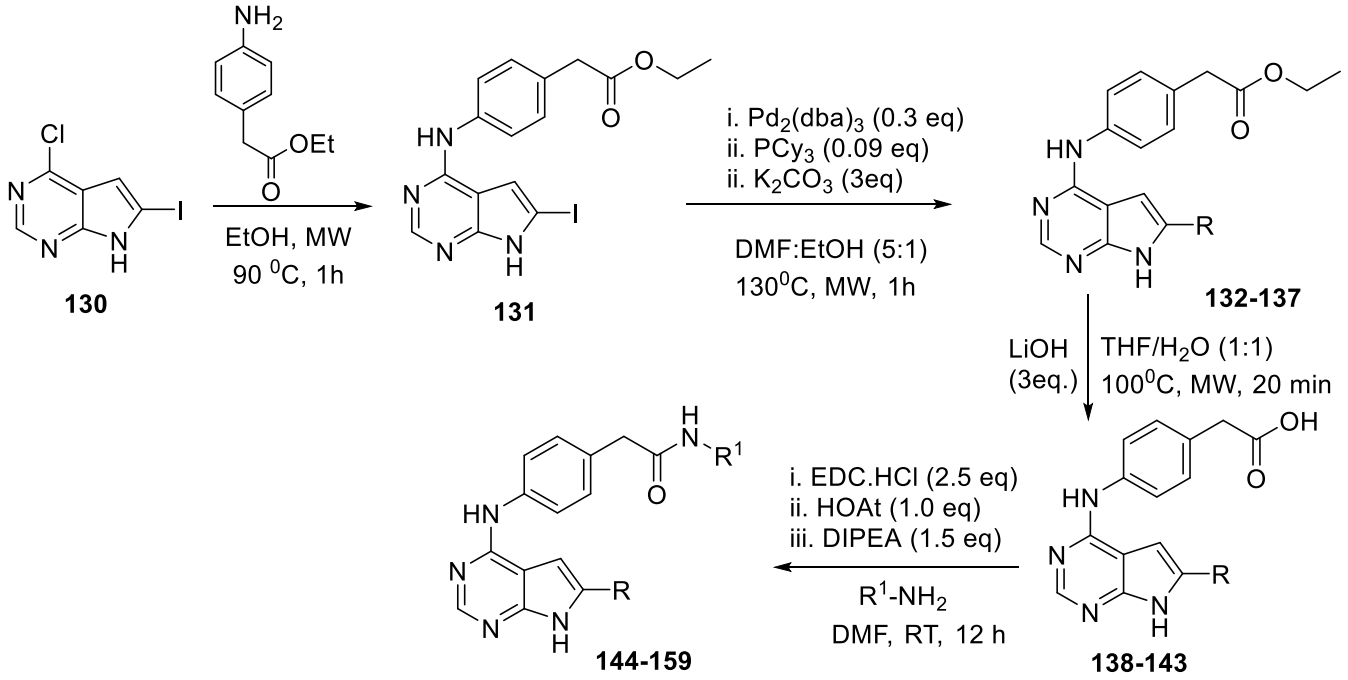
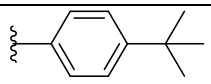
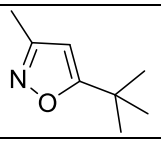
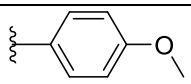
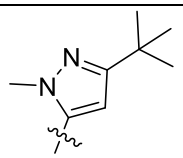
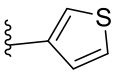
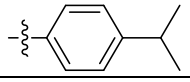
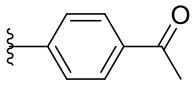
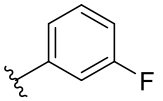
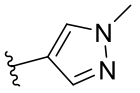
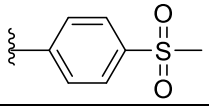
112		118		124	
113		119		125	
114		120		126	
115		121		127	
116		122		128	
117		123		129	

Scheme 17. Synthesis of pyrrolo[2,3-*d*]pyrimidine substituted-N-phenylacetamide derivatives **112-129.**

Furthermore, in continuation to what mentioned above by the same authours,[44] 4-chloro-6-iodo-7H-pyrrolo[2,3-*d*]pyrimidine **130** was prepared as described previously,[45] similarly treatment of compound **130** with ethyl 2-(4-aminophenyl)acetate gave the corresponding ester **131**. Suzuki Miyaura coupling[46] of this intermediate **131** with several boronic acid using Suzuki Miyaura coupling reaction[46] afforded the

corresponding compounds **132-137.** Hydrolysis of latter compounds with LiO in THF/H_2O resulted in the formation of corresponding acids **138-143**. Reaction of acids **138-143** with EDC gave the derivatives **144-159** as shown in scheme 18.



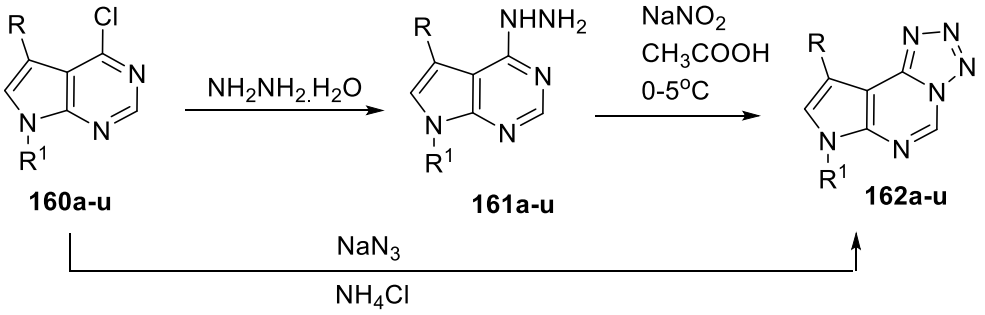
No	R	No	R^1
132, 138		144, 146, 150, 151, 153, 155, 159	
133, 139		145, 149, 152, 154, 158	
134, 140		148, 157	
135, 141		147, 156	
136, 142			
137, 143			

Scheme 18. Nucleophilic substitution reaction of 4-chloro-6-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine **130**.

2.3. Synthesis of tricyclic systems containing pyrrolo[2,3-*d*]pyrimidine

It was found that the reaction of chloro derivative **160a-u** with hydrazine hydrate afforded the corresponding hydrazine derivative **161a-u**, which was allowed to react with sodium nitrite in glacial acetic acid to obtain the

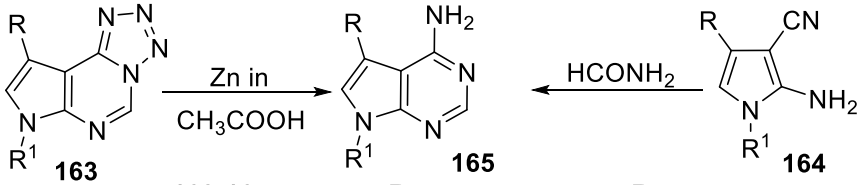
tetrazolopyrrolopyrimidines **162a-u**. Alternatively, treatment of chloro derivative **160a-u** with sodium azide in the presence of the ammonium chloride afforded the tetrazolopyrrolopyrimidines **162a-u** (Scheme19).[47,48]



160-162	R	R_1	160-162	R	R_1
a	C_6H_5	4-$OCH_3C_6H_4$	**l**	C_6H_5	4-FC_6H_4
b	C_6H_5	4-BrC_6H_4	**m**	C_6H_5	3-Cl-4-FC_6H_3
c	C_6H_5	4-IC_6H_4	**n**	4-$OCH_3C_6H_4$	C_6H_5
d	4-$OCH_3C_6H_4$	4-BrC_6H_4	**o**	4-$OCH_3C_6H_4$	4-$OCH_3C_6H_4$
e	4-$OCH_3C_6H_4$	4-IC_6H_4	**p**	4-$OCH_3C_6H_4$	4-FC_6H_4
f	4-ClC_6H_4	4-$CH_3C_6H_4$	**q**	4-$OCH_3C_6H_4$	3-Cl-4-FC_6H_3
g	4-ClC_6H_4	4-$OCH_3C_6H_4$	**r**	4-ClC_6H_4	C_6H_5
h	4-ClC_6H_4	4-BrC_6H_4	**s**	4-ClC_6H_4	4-ClC_6H_4
i	4-ClC_6H_4	4-IC_6H_4	**t**	4-ClC_6H_4	4-FC_6H_4
j	C_6H_5	C_6H_5	**u**	4-ClC_6H_4	3-Cl-4-FC_6H_3
k	C_6H_5	4-ClC_6H_4			

Scheme 19. Synthesis of tetrazolopyrrolopyrimidines **162a-u.**

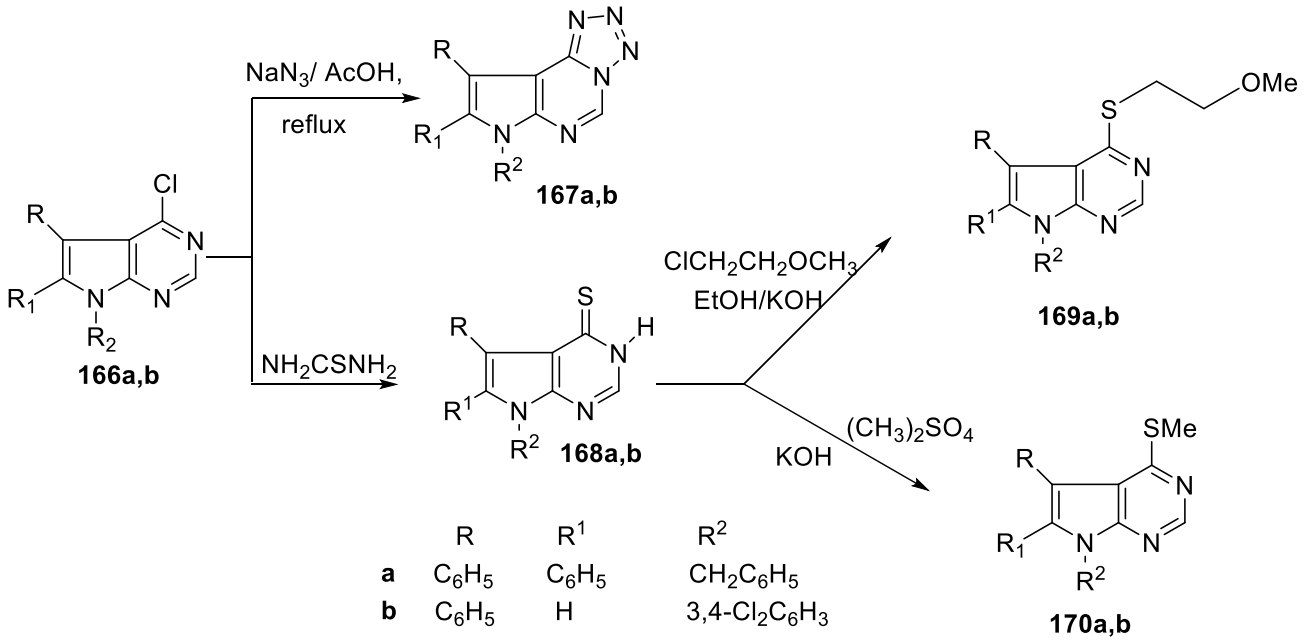
Interaction[49] of tetrazolopyrrolopyrimidines **163** with zinc in acetic acid obtained the corresponding amino derivative of pyrrolo[2,3-*d*]pyrimidines **165**, which could be prepared by another route by reaction of amino nitrile **164** with formamide (Scheme 20).



163-165	R	R_1
a	C_6H_5	4-$OCH_3C_6H_4$
b	C_6H_5	4-BrC_6H_4
c	C_6H_5	4-IC_6H_4
d	4-$OCH_3C_6H_4$	4-BrC_6H_4
e	4-$OCH_3C_6H_4$	4-IC_6H_4
f	4-ClC_6H_4	4-$CH_3C_6H_4$
g	4-ClC_6H_4	4-$OCH_3C_6H_4$
h	4-ClC_6H_4	4-BrC_6H_4
i	4-ClC_6H_4	4-IC_6H_4

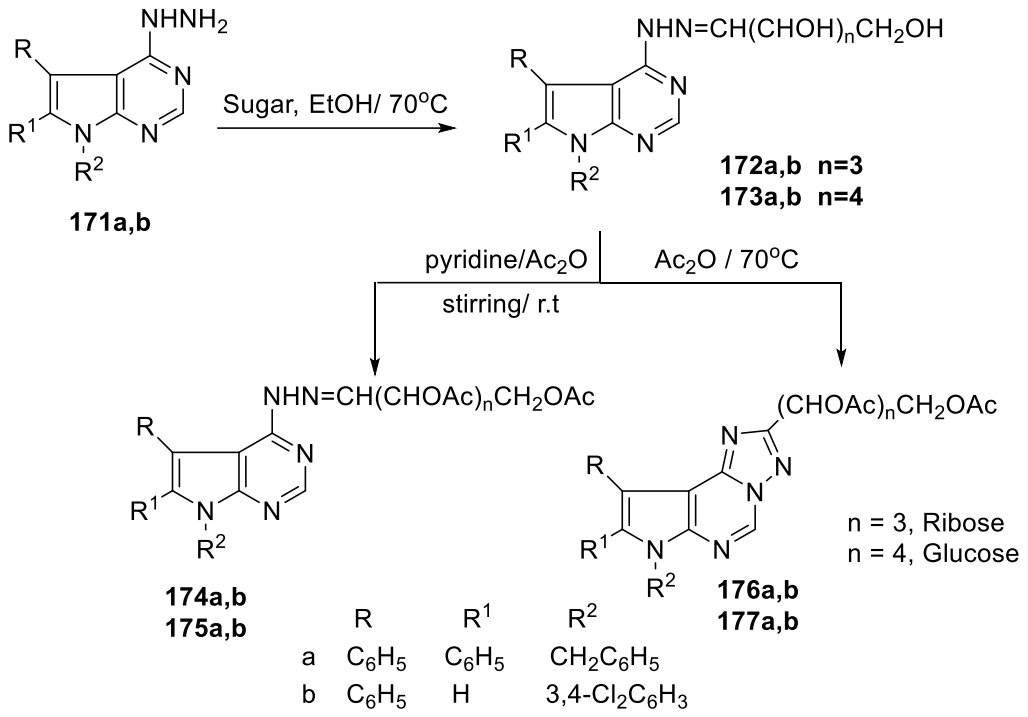
Scheme 20. Synthesis of amino derivative of pyrrolo[2,3-*d*]pyrimidines **165**.

Rashad *et al*.[50] reported that, Treatment of compounds **166a,b** with sodium azide or thiourea gave the corresponding tetrazole **167a,b** or thione derivative **168a,b** respectively. Reaction of compounds **168a,b** with dimethylsulfate afforded **170a,b** whereas, its reaction with 2-chloroethyl methyl ether gave the corresponding derivatives **169a,b** (Scheme 21).



Scheme 21. Some reactions of chloropyrrolo[2,3-*d*]pyrimidine derivative **166a,b**.

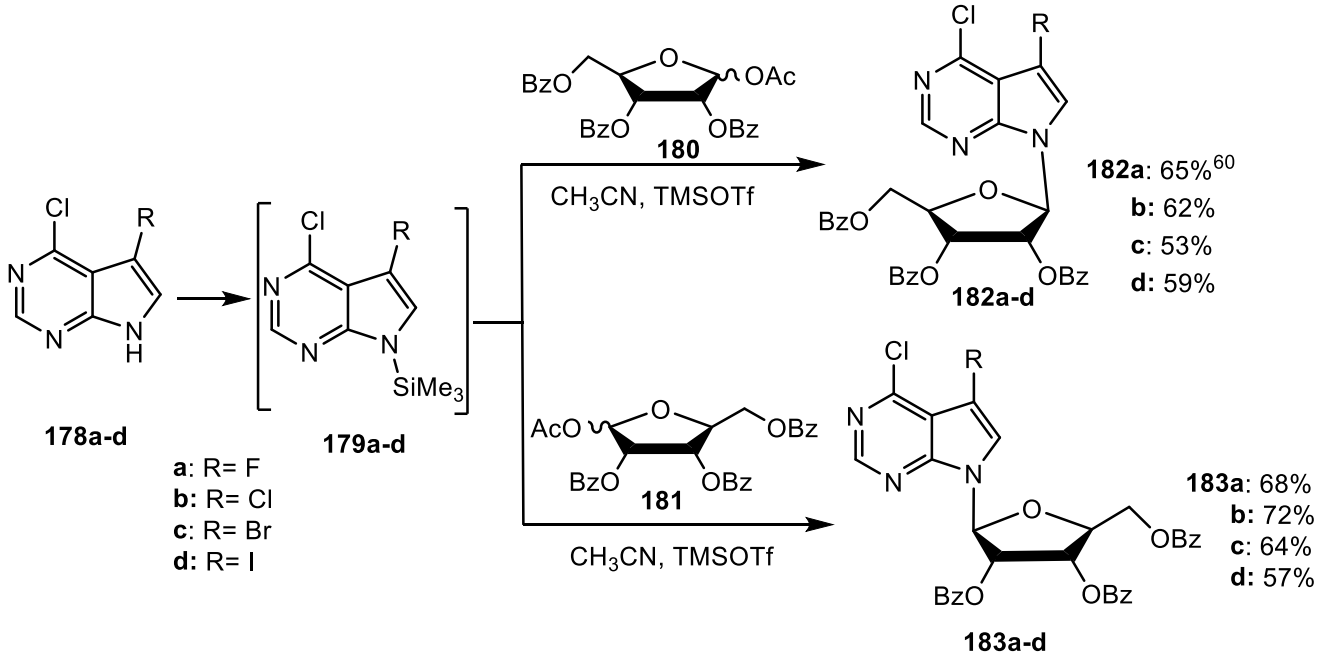
Also,[50] Reaction of the hydrazine derivative **171a,b** with some monosacharides: namely D-ribose or D-glucose in the presence of glacial acetic acid as a catalyst yielded the corresponding hydrazone derivatives **172a,b** and **173a,b**. Heating of **172a,b** and **173a,b** with Ac_2O at 70 ^{0}C afforded products **176a,b** and **177a,b** whereas, when the acetylation reaction was carried out in dry pyridine at room temperature, the products were identified as **174a,b** and **175a,b** (Scheme 22).



Scheme 22. Synthetic routes of compounds **174-177.**

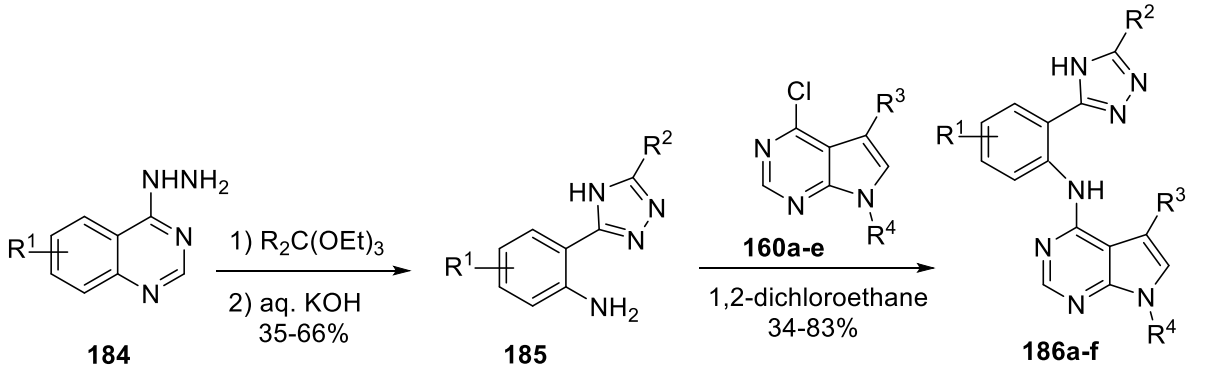
2.4. Nucleophilic substitution reactions on N-7

The nucleobases **178a–d** were silylated with BSA in dry MeCN at r.t to obtain the corresponding derivative **179a-d** and then reacted with D-ribofuranose **180** or L-ribofuranose **181** using TMSOTf (trimethylsilyl trifluoromethanesulfonate) to give the glycosylated intermediates **182a–d** and **183a–d** (Scheme 23).[51]



Scheme 23. Synthesis of glycosylated intermediates **182a–d** and **183a–d.**

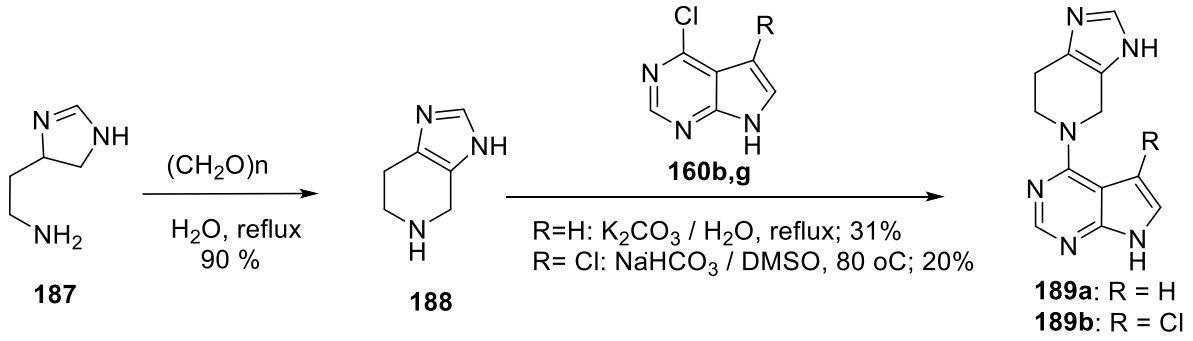
Lippa *et al*.[52] Reaction of hydrazino derivative **184a-f** with orthoformates afforded the corresponding triazole derivatives **185a-f** which were reacted with chloropyrrolopyrimidine derivatives **160a-e** yielding the compound **186a-e** (Scheme 24).



Comd.	R^1	R^2	R^3	R^4	Comd.	R^1	R^2	R^3	R^4
186a	H	H	C l	H	186d	H	Me	H	H
186b	H	H	H	Me	186e	4-Cl	Me	H	H
186c	H	H	Me	H	186f	5-Cl	Me	H	H

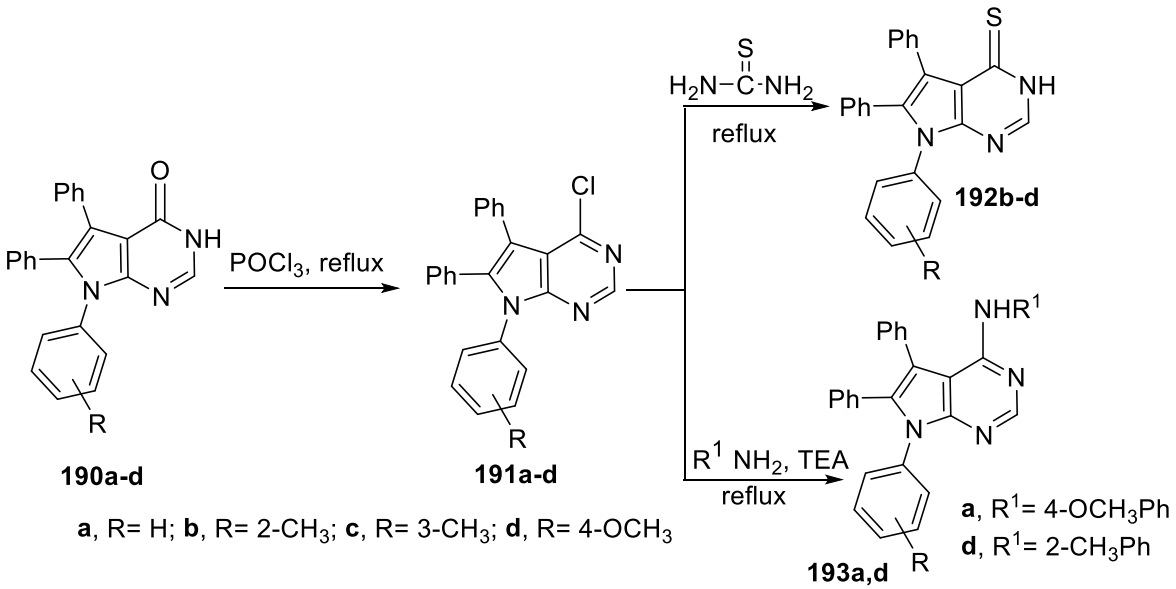
Scheme 24. Synthesis of substituted pyrrolopyrimidine derivatives **186a-e.**

The synthesis of imidazopiperidines **189a,b** were performed[52] by the condensation of histamine **187** with aldehyde in boiling water to give compound **188**. Reaction of chloropyrrolopyrimidine **160a,b** with amine afforded the final analogs **189a,b** (Scheme 25).



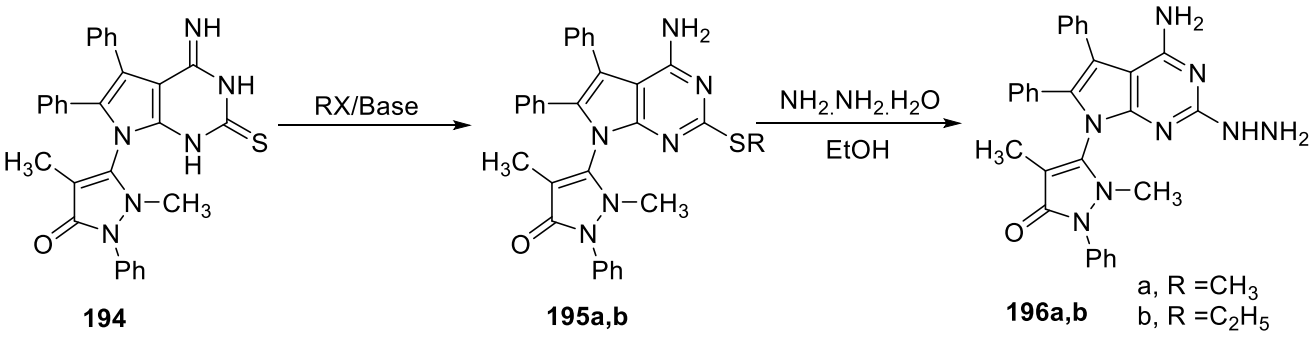
Scheme 25. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **189a,b**.

Treatment of pyrrolopyrimidinone derivatives **190a-d** with phosphorus oxychloride gave the corresponding chloropyrrolo pyrimidines **191a-d.** Reaction of choloro derivative 191a-d with with thiourea in ethanol led to the formation of the thione derivative **192b-d.** N-aryl amines **193a,d** were prepared by the reaction of **191a-d** with aromatic amine derivatives (Scheme 26).[53]



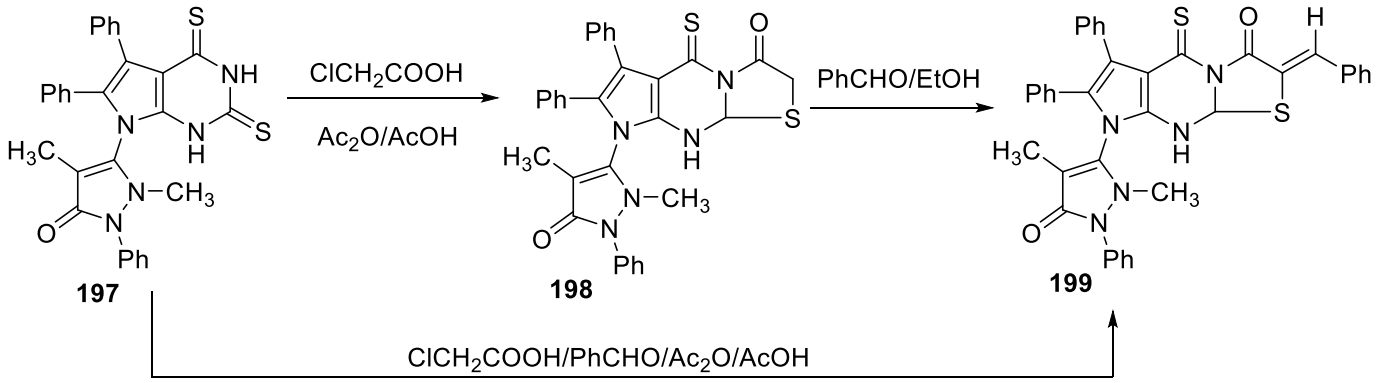
Scheme 26. Synthesis of pyrrolo[2,3-*d*]pyrimidinethiones **192b-d** and amino pyrrolo[2,3-*d*]pyrimidines **193a,d**.

Alkylation of pyrrolopyrimidin-2-thiones **194** with *α*-halo- carbonyl compounds, gave the compounds **195a,b**.[54] Hydrazinolysis of compounds **195a,b** with hydrazine hydrate, yielded the 2-amino derivative **196a,b** (Scheme 27).



Scheme 27. Synthesis of hydrazino derivatives **196a,b**.

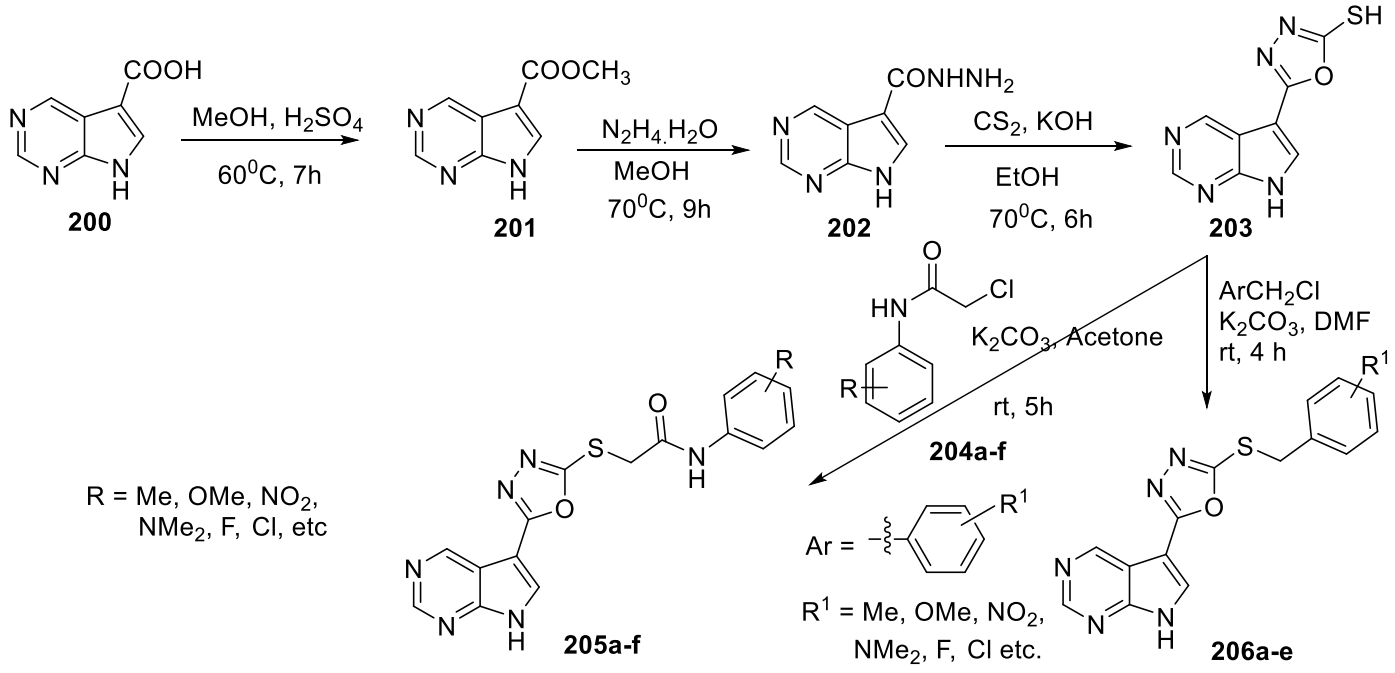
Interaction[54] of thione compounds **197** and chloroacetic acid in a mixture of Ac_2O/AcOH gave the corresponding thiazolopyrimidine derivative **198** which was reacted with aromatic aldehyde in the presence of a catalytic amount of piperidine or triethylamine to afford the corresponding compound **199**. Compound 199 could be obtained directly by the reaction of **197** with chloroacetic acid and aromatic aldehyde in acetic acid and acetic anhydride (Scheme 28).



Scheme 28. Reaction of pyrrolopyrimidine **197** with chloroactic acid to give tricyclic compound **199.**

2.5. Reactions on C-5 of pyrrolo[2,3-*d*]pyrimidine

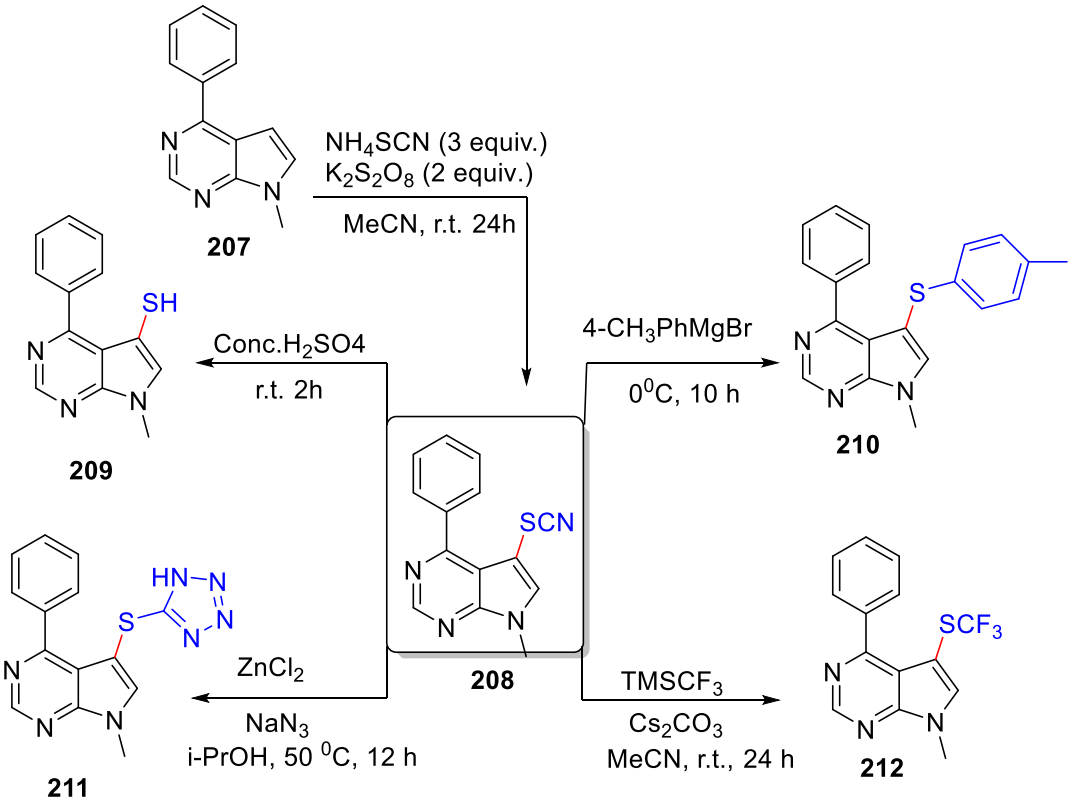
Lal Patel *et al*[27]reported that, esterification of pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid **200** was done by its reaction with methanol and sulphuric acid to give the corresponding ester **201**. Reaction of the latter compound with hydrazine hydrate afforded hydrazide **202.** Reaction of **200** with CS_2 in ethanol in the and KOH gave the corresponding 1,3,4-oxadiazole-2-thiol **203**. Alkylation of thiol **203** with some alkylating agents afforded the corresponding compounds **206a-e**. Similarly, alkylation of thiol **203** with 2-chloro-*N*-phenylacetamide **204** lead to the formation the corresponding derivatives **205a-f** (Scheme 29).



Scheme 29. Synthesis of 1,3,4-oxadiazole derivatives-based pyrrolo[2,3-*d*]pyrimidine **203**, **205a-f** and **206a-e**.

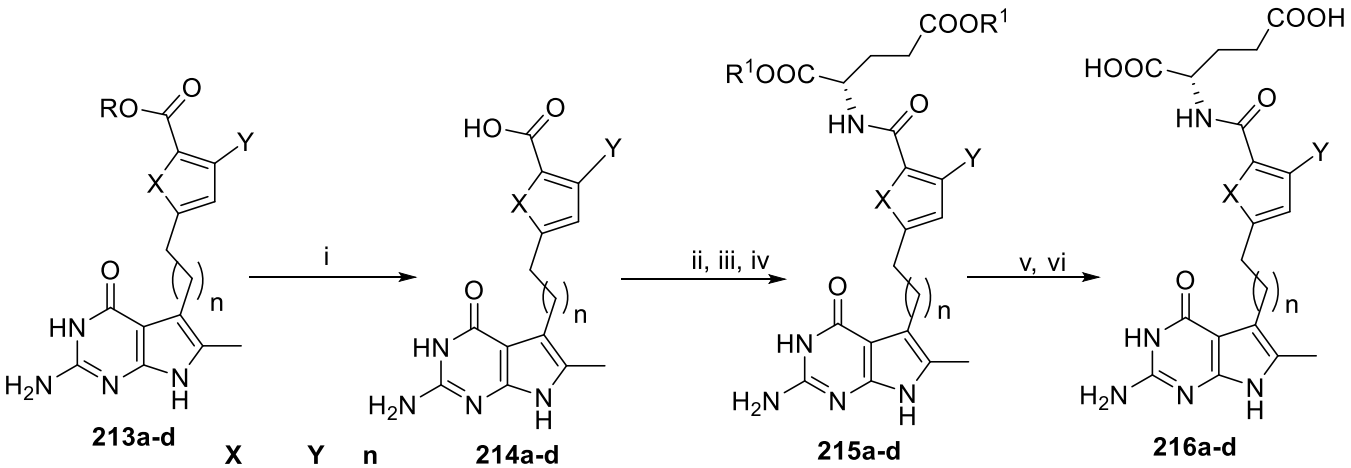
Zhang, Z. *et al*[55] described that the thiocyanation reaction of compound **207** and NH_4SCN as a thiocyanate source and two equivalent of $K_2S_2O_8$ as a catalyst, afforded the product **208**. Reaction of **208** with conc. sulfuric acid led to the formation of corresponding thiol **209**. Furthermore, treatment of **208** with 4-CH_3PhMgBr gave the thioether derivative **210**. Reaction of **208** with NaN_3 and $ZnCl_2$ as a catalyst in i-PrOH

afforded *S*-tetrazole derivative **211**. Trifluoromethylthio ether **212** could be obtained by the reaction of **208** with Prakash's reagent presence of Cs_2CO_3 as a base (Scheme 30).



Scheme 30. Synthetic application of thiocyanated product **208**.

Basic hydrolysis[56] of the aromatic esters **213a–d** gave the acids **214a–d**. The latter compounds **214a–d** were reacted with L-glutamate diesters to afford **215a–d**. Treatment of diesters **215a–d** with 1*N* NaOH, followed by neutralization and acidification yielded the corresponding compounds **216a-d** (Scheme 31).



	X	Y	n
a	CH=CH	H	1
b	CH=CH	H	2
c	S	H	1
d	CH=CH	F	1

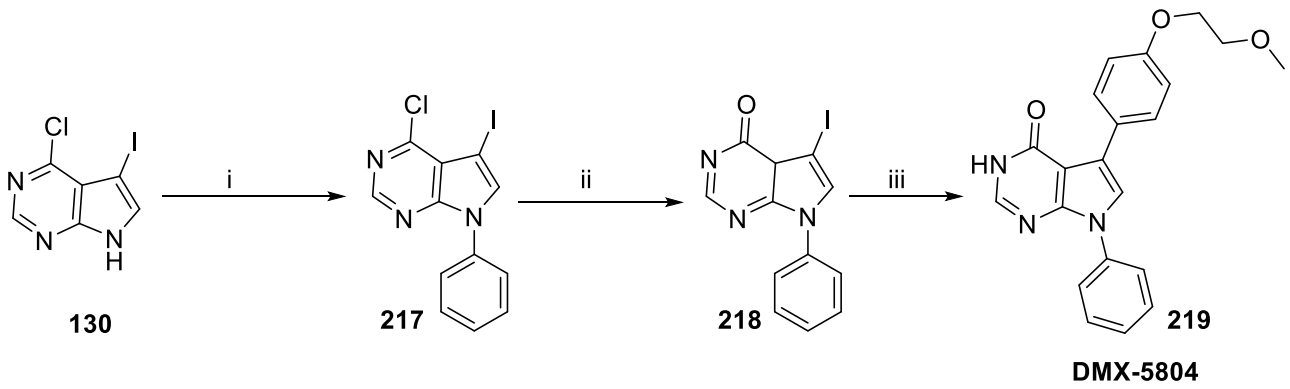
a,b,d, R = Me
c, R = Et

a,b,d, R^1= Et
c, R^1= Me

(i)1N NaOH,rt,12h,63-94% (ii) Dimethyl-ordiethyl-L-glutamate (iii) NMM,CDMT,DMF, rt or 40°C,8-12h,30-78% or (iv) isobutylchloroformate,TEA,DMF,0°C,tort,60h,61% (v)1N NaOH,rt,1-24h;(vi)0-4°C,1N HCl,19-80%.

Scheme 31. Reactions of 5-substitued pyrrolopyrimidine derivatives **213a-d**.

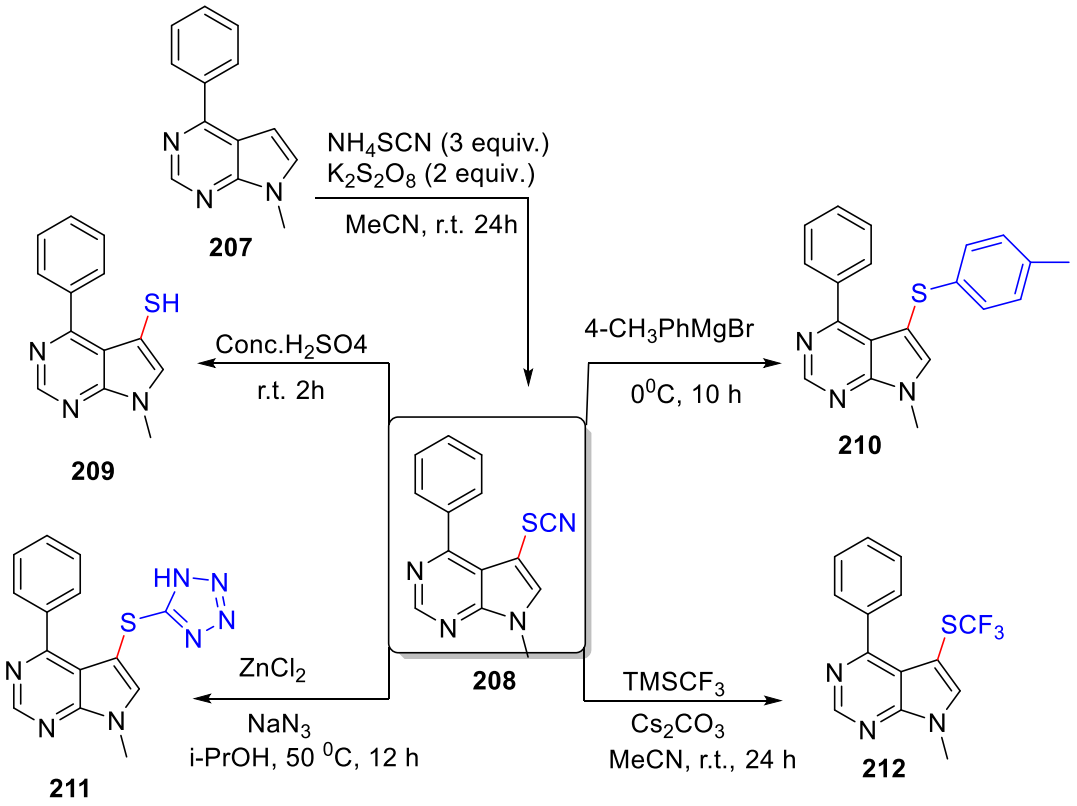
In 2021, Eeda *et al*, reported that,[31] reaction of compound **130** with 2-phenyl-1,3,2-dioxoborinone and cupric acetate in DMF afforded compound **217**. Reaction of **217** with acetic acid and sodium acetate gave the corresponding pyrrolo[2,3-*d*]pyrimidin-4-one **218**. Suzuki−Miyaura cross-coupling reaction of compound **218** with 2-(4-(2-methoxyethoxy)-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolan in the presence of Pd(dppf)Cl_2 gave derivative **219** (DMX-5804) (Scheme 32).



(i) Phenylboronic acid, Cupric acetate, dimethylformamide, 60 °C, 15-33%; (ii) Na-acetate, acetic acid, 100 °C, 15 h; (iii) 2-(4-(2-methoxyethoxy)phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolan, Pd(dppf)Cl_2, potassium carbonate, microwave reactor, 120 °C, 18% yield.

Scheme 32. New synthetic route for synthesis of substituted pyrrolo[2,3-*d*]pyrimidine **219**.

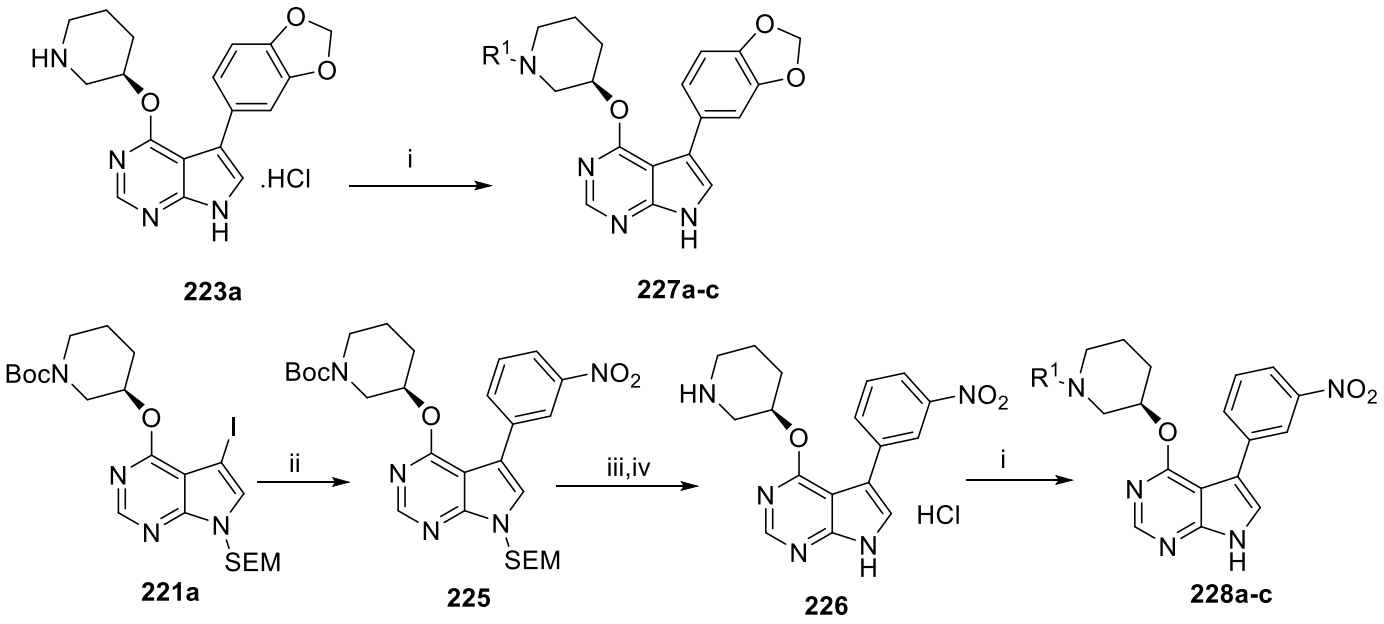
He *et al* reported that,[57] treatment of chloro derivative **1a** with *N*-iodosuccinimide provided the intermediate **130**. Reaction of compound **130** with trimethylsilylethoxymethyl (SEM) gave the corresponding compound **220**. Reaction of the latter compound **220** with various amines and alcohols in the presence of *N,N*-diisopropylethylamine (DIEA) afforded the compounds **221a-c**. Suzuki-Miyaura coupling reaction of **221a-c** with benzo[*d*][1,3]dioxol-5-ylboronic acid and Pd(PPh_3)$_4$ as a catalyst generated compounds **222a-c**. Treatment of **222a**-c with $TBAF_3 \cdot H_2O$ and HCl led to removal of the protective SEM and Boc groups and compound **223a-c** were formed. Reaction of **223a-c** with acryloyl chloride gave the derivatives **224a-c** (Scheme 33).



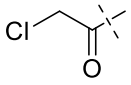
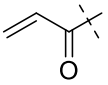
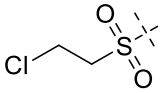
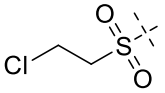
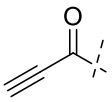
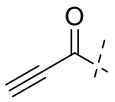
Scheme 33. Synthesis of 4-substitued pyrrolo[2,3-*d*]pyrimidines **224a-c.**

Also,[57] the 4,5-disubstituted pyrrolo[2,3-*d*]pyrimidine derivatives **227a-c** and **228a-c** were prepared following the synthetic procedure of **220a-c**, which are outlined in scheme 34 .

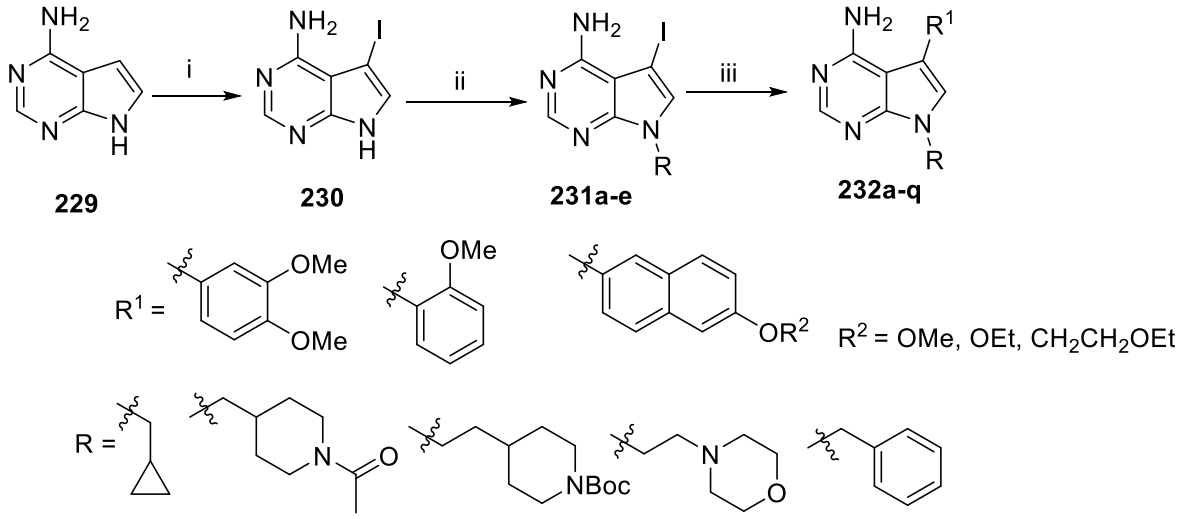
Seanego *et al* reported that,[58] reaction of compound **229** with *N*-iodosuccinimide (NIS) afforded the iodinated compound **230.** Treatment of **230** with substituted alkyl bromides or tosylates under basic conditions gave the corresponding compounds **231a**–**e**. Suzuki-Miyaura coupling reaction of **231a-e** with substituted boronic acids provided the corresponding pyrrolo[2,3-*d*]pyrimidines **232a-e** (scheme 35).



(i) **227a**: DMF, 2-chloroacetyl chloride, DIEA, r.t.; **228a**: DMF, acryloyl chloride, DIEA, r.t.; **227b** and **228b**: DCM, 2- chloroethane-1-sulfonyl chloride, DIEA, r.t.; **227c** and **228c**: DCM, propiolic acid, PyBOP, DIEA, r.t. (ii) (3-nitrophenyl)boronic acid, $Pd(PPh_3)_4$, K_2CO_3,1,4-dioxane/H_2O, reflux. (iii)$TBAF_3 \cdot H_2O$, DMF, 75^0 C. (iv) Ethyl acetate, HCl in ethyl acetate, r.t.

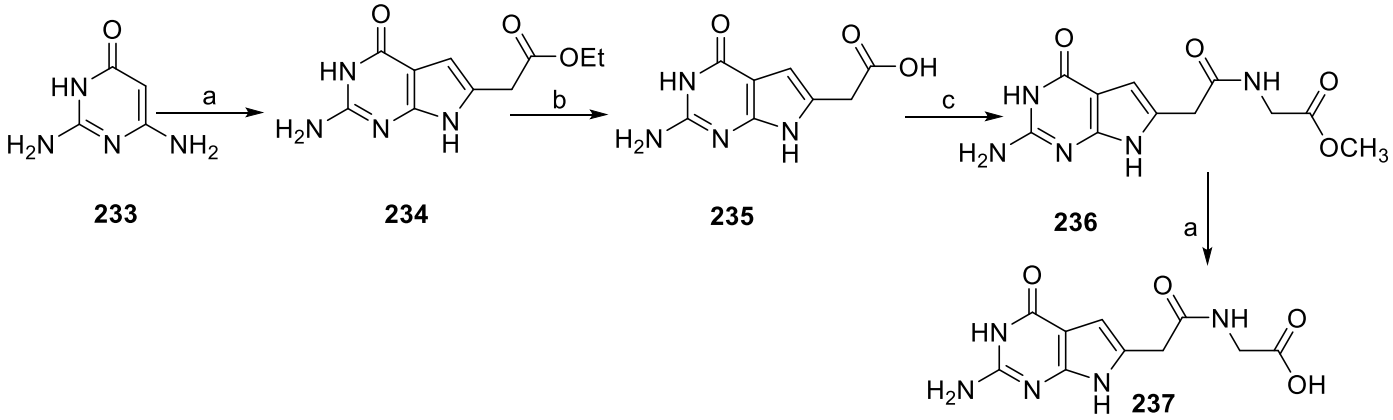
227a-c	**R^1**	**228a-c**	**R^1**
227a		**228a**	
227b		**228b**	
227c		**228c**	

Scheme 34. Synthesis of 4,5-disubstituted pyrrolo[2,3-*d*]pyrimidines **227a-c** and **228a-c.**



i) NIS, $CHCl_3$, 60 °C, 2 h, 90%; ii) R-X, Cs_2CO_3, DMF, 70°C, 18 h, 59–79%; iii) R^1-$B(OH)_2$, 10% $Pd(PPh_3)_4$, aq Na_2CO_3, DME, reflux, 18 h, 35-76% (X = Br or tosylate).

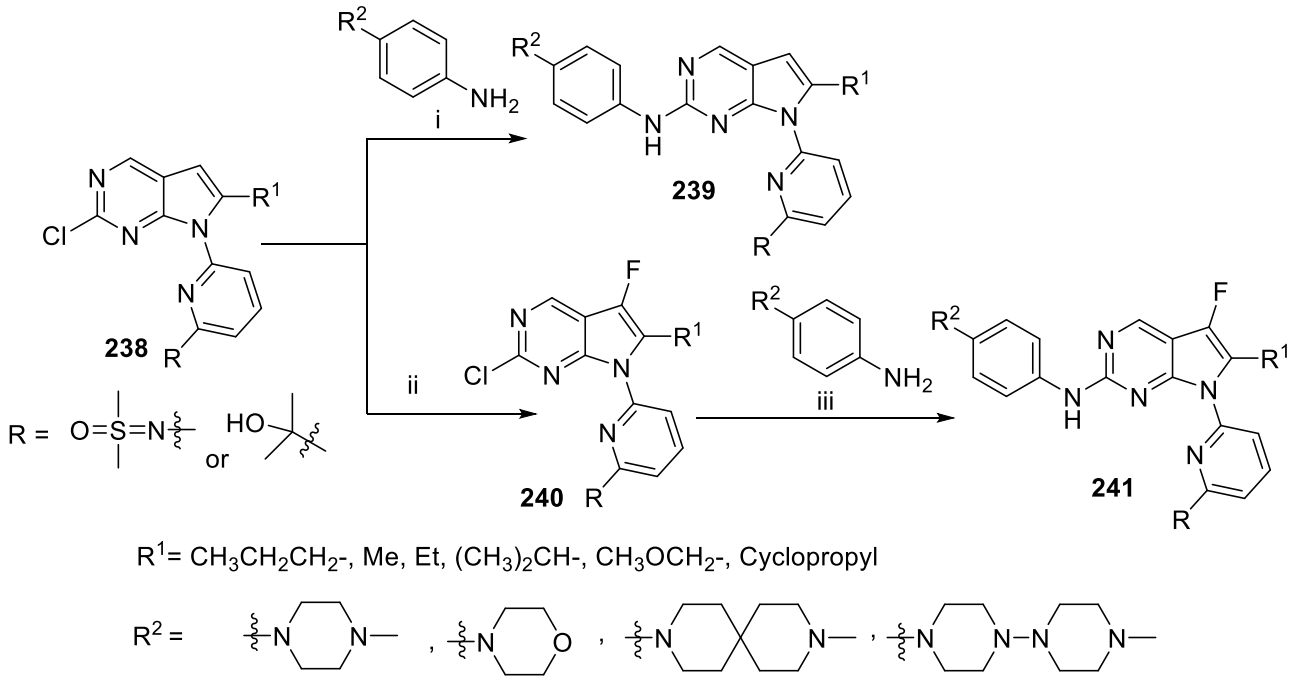
Scheme 35. Suzuki-Miyaura coupling reaction of **231a-e** with substituted boronic acids.



(a) Ethyl 4-chloroacetoacetate, NaOAc, H_2O, refux, 18 h (b) i) 1 N NaOH, RT, 1.5 h, ii) 3 N HCl;
(c) Methyl glycinate, EDCI, HOBt, Et_3N, DMF, RT, 5 h

Scheme 36. Synthesis 6-substitued pyrrolo[2,3-*d*]pyrimidines **237**.

Treatment of compound **238** with aromatic amine afforded pyrrolo[2,3-*d*]pyrimidine derivatives **239**. The fluorine atom could be introduced in C-6 of pyrrolo[2,3-*d*]pyrimidine by the reaction of with **Selectfluor** in CH_3CN to give fluorine intermediate **240.** Buchwald-Hartwig amination[60] of latter intermediate **240** and aromatic amine produced the corresponding fluorine pyrrolo[2,3-*d*]pyrimidine **241** (Scheme 37).



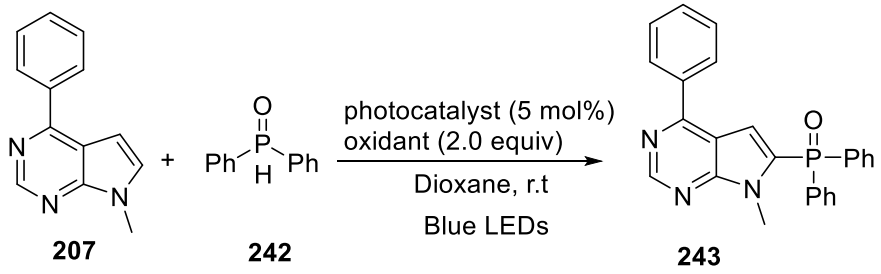
R^1= $CH_3CH_2CH_2$-, Me, Et, $(CH_3)_2CH$-, CH_3OCH_2-, Cyclopropyl

R^2 =

(i): $Pd_2(dba)_3$, X-phos, Cs_2CO_3, 1.4-dioxane, 100 ^{0}C, 18 h; (ii): Select- fluor, CH_3CN, 0 ^{0}C, 1 h, then 25 ^{0}C, 18 h; (iii) $Pd_2(dba)_3$, X-phos, Cs_2CO_3, 1.4-ioxane, 100 ^{0}C, 18 h.

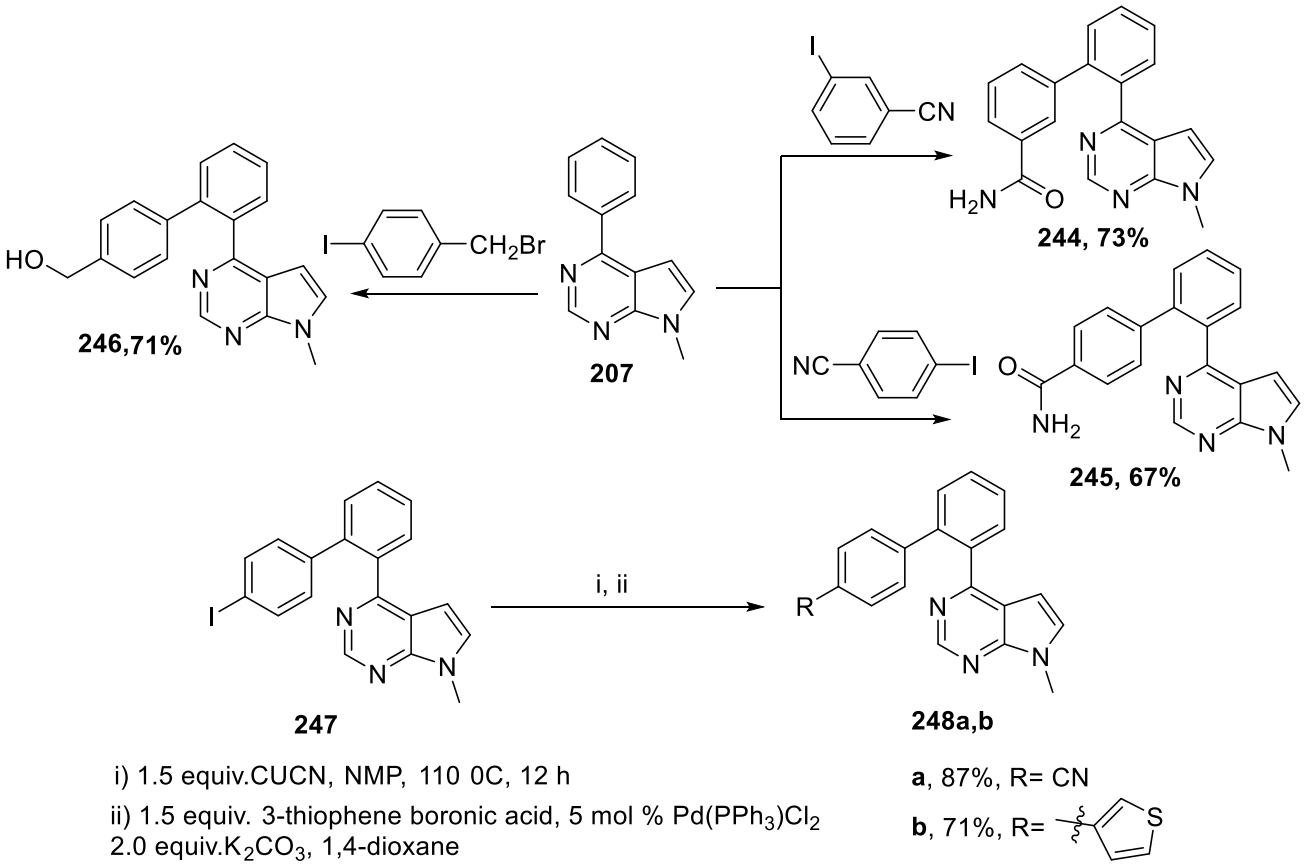
Scheme 37. Synthesis of Pyrrolo[2,3-*d*] pyrimidine heterocycle series **242**.

Zhang, Z. *et al*,[61] reported that the photochemical reaction of 4-phenyl-*N*-methylpyrrolo[2,3-*d*] pyrimidine **207** with diphenylphosphine oxide **242** in the presence of benzoyl peroxide (BPO) as an oxidant or using Na_2-eosin Y as a photocatalyst afforded the corresponding the C6-phosphorylated product **243** (Scheme 38).



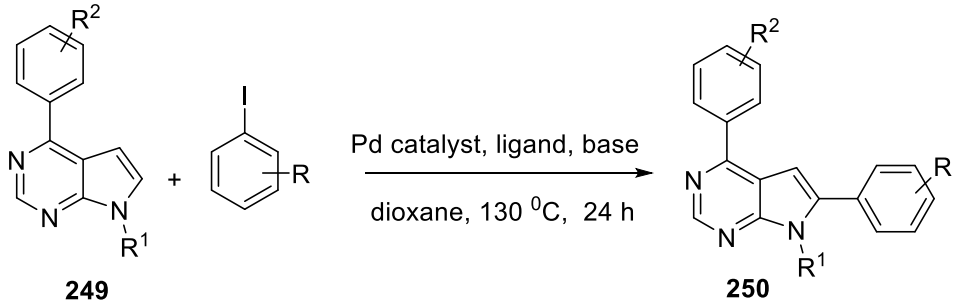
Scheme 38. Photochemical reaction of pyrrolo[2,3-*d*]pyrimidine **207** with diphenylphosphine oxide **242.**

It was found that,[62] treatment of compound **207** with 3-cyanoiodobenzene and/or 4-cyanoiodo-benzene followed by hydrolysis of cyano group afforded the corresponding amide derivatives **244** and **245** respectively**.** Arylation of compound **207** with 4-iodobenzyl bromide afforded the corresponding the product **246** with hydrolysis of bromomethyl group. Treatment of compound **247** with CuCN under the metal coordination reaction resulted in formation of the corresponding compound **248a,b** (Scheme 39).



Scheme 39. Reactions of 4-phenylpyrrolo[2,3-*d*]pyrimidine **207**.

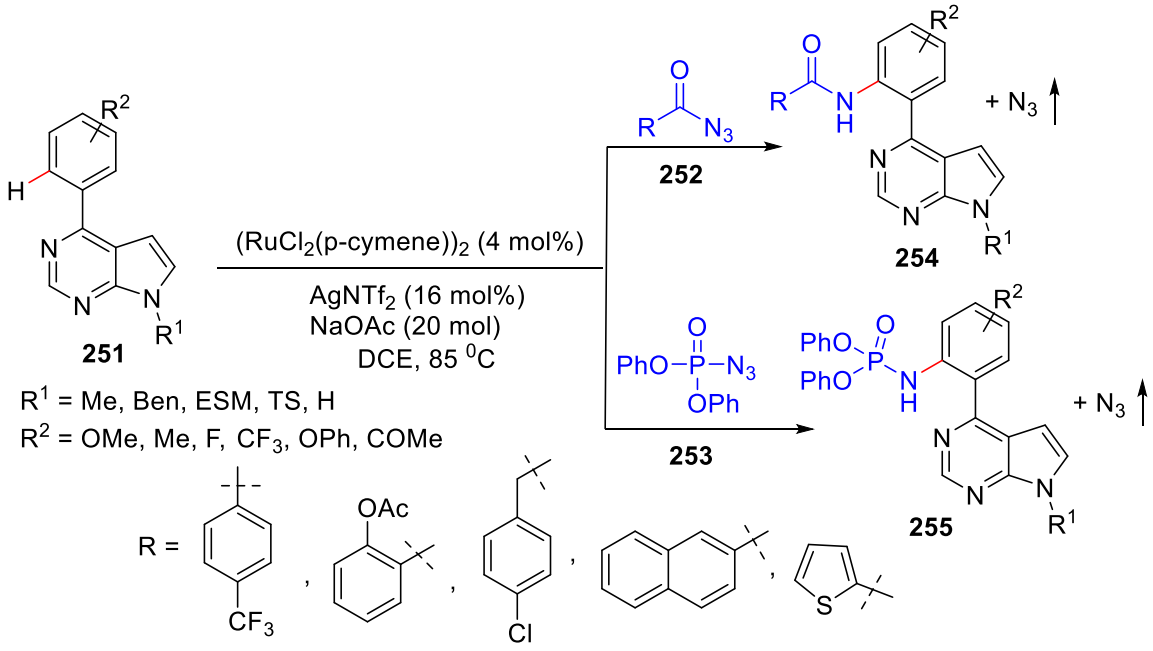
Liu, M. *et al*,[63] found that the arylation of the compound **249** with iodobenzene could be performed using palladium catalysts. Thus, the reaction could be carried out without the addition of the ligands to give the C6-arylated product. Therefore, dioxane was chosen as the preferred solvent in view of its accessibility and a variety of bases (3.0 equiv.), such as LiOH, KOAc, DBU, *N,N*-diisopropylethylamine (DIPEA), and KOH, were compared under parallel reaction conditions (10 mol % of $Pd(OAc)_2$ and 10 mol % of bpy). Only KOH could give the product **250** in a low yield, LiOH, KOAc, DBU, and DIPEA are practically inert to this arylation. Apparently, a good yield was given in the presence of (3.0 equiv., Cs_2CO_3) (Scheme 40).



R = OCH_3, ph, F, Cl, COOEt, CN; R^1= CH_3, cyclopentyl, Bn, SEM
R^2 = CH_3, OCH_3, tBu, Ph, CF_3, F, COOEt, Cl

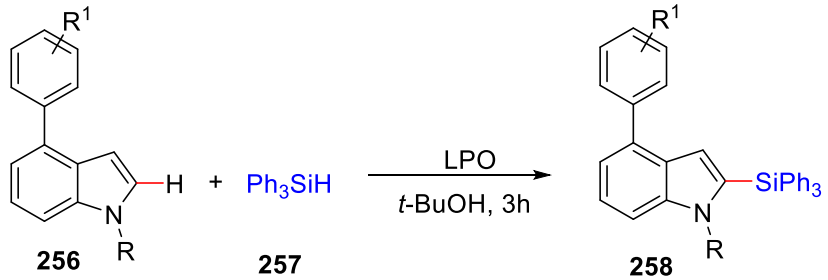
Scheme 40. Synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives **250.**

Pan, C. *et al*.[64] reported that, the reaction of compound **251** with benzoyl azide **252** in a [$RuCl_2$(*p*-cymene)]$_2$ as a catalyst, led to the formation of the desired amidated product **254**. Subsequently, phosphor-amidation reaction was achieved via Ru(II) catalysis process using **251** and diphenyl azide phosphate **253** under identical conditions employed for compound **254** to give phosphamide derivatives **255** (Scheme 41).



Scheme 41. Ru(II) catalysis process using **251** and diphenyl azide phosphate **253**.

It was reported that,[65] the reaction of compound **256** with triphenylsilane **257** in *t*-BuOH resulted in the formation of the corresponding C-6 silylated product **258**. The reaction yield was found to be sensitive to the loading amounts of LPO and triphenylsilane. The optimal amounts of LPO and triphenylsilane are 4.0 equivalents, respectively, which provided the product **258** in good yield (Scheme 42).



Scheme 42. C-H Siltation of heteroarenes **256** with hydrosilanes.

Conclusions

Pyrrolo[2,3-*d*]pyrimidine derivatives have attracted particular attention to scientists due to the high biological and therapeutic importance of these compounds in all fields, which prompted us to shed light on the modern interactions of these compounds.

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