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Synthetic strategies of benzofuro[3,2-*d*]pyrimidine derivatives and biological importance

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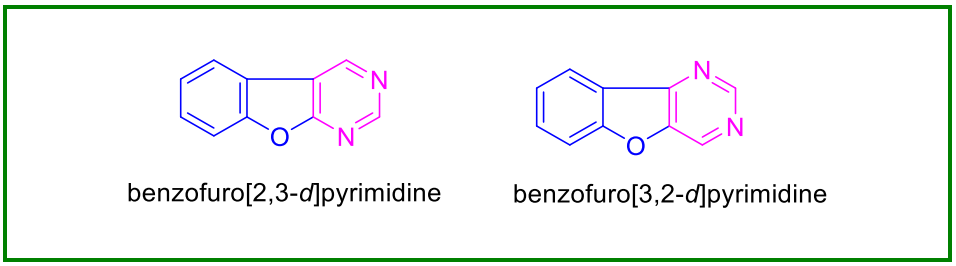
Abstract

Benzofuro[3,2-*d*]pyrimidine derivatives represent an important class of fused heterocyclic compounds, owing to their diverse biological activities and their significance as scaffolds in medicinal chemistry. combining the structural features of benzofuran and pyrimidine nuclei within a fused polycyclic scaffold. The incorporation of oxygen- and nitrogen-containing heteroatoms provides these molecules with unique electronic, hydrogen-bonding, and π–π stacking capabilities, making them attractive frameworks in medicinal chemistry and drug discovery. This review presents an overview of the synthetic methods and biological properties for benzofuro[3,2-*d*]pyrimidines reported between 1976 and 2025.



Keywords: Benzofuro[3,2-*d*]pyrimidines, synthesis, biological properties

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1. Introduction

Many naturally occurring furans exhibit diverse biological activities,[1] such as cytotoxic,[2] antitumor,[3] antispasmodic[4] antimicrobial[5] and anti-influenza virus activity.[6] In addition, benzofurans have received significant attention in recent years owing to their medical importance.[7] They have been identified as promising frameworks for the development of new antimicrobial agents.[8] The antibacterial and antifungal activity of benzofuran derivatives is predominantly modulated by substituents on the heterocyclic furan ring, with comparatively less contribution from the aromatic ring. In most cases, early structure–activity relationship (SAR) studies focused on variations in nitro substitution It was found that 3-nitrobenzofurans consistently exhibited lower antibacterial and antiprotozoal activity in vitro compared to their 2-nitro derivatives, highlighting the significance of the nitro position for bioactivity.[9, 10] Investigation of benzofurans as potential inhibitors of fungal N-myristoyltransferase (Nmt) in *Candida albicans* has facilitated the identification of a new class of antifungal agents.[11] Furthermore, several other biomolecular targets have been identified for benzofurans that possess *in vitro* antibacterial properties,[8] including bacterial enzymes engaged in the methionine cycle such as methionine aminopeptidase[12] and deformylase,[13] as well as enzymes related to peptidoglycan synthesis like UDP-*N*-acetylmuramyl-L-alanine ligase[14] and chorismate synthase, which are vital for bacterial vitality.[15] Consequently, there is an increasing interest in developing versatile and general methods for synthesizing benzofurans. Over the years, various classical and metal-mediated procedures have been established for constructing the benzofuran structure.[16] Additionally, benzofuro[3,2-*d*]pyrimidines are commonly recognized as core structures in a diverse range of compounds exhibiting significant biological activities,[17] such as anti-cancer properties.[18] Some derivatives of benzofuro[3,2-*d*]pyrimidine act as antimicrobial agents,[19] while others have been reported as protein kinase inhibitors,[20] adenosine receptor (A2A) antagonists,[21] and novel PARP-1 inhibitors.[22] Recently, *N*-aryl-7-methoxybenzo[b]furo[3,2-*d*]pyrimidin-4-amines have been described as dual inhibitors of CLK1 and DYRK1A kinases.[23, 24] Furthermore, compound **A** is a multistage tyrosine kinase inhibitor currently undergoing phase I clinical trials, while compound **B** has been identified as a histamine H4 modulator (Figure 1).[25, 26] In continuation of our previously published reviews[27-32] on the synthesis of heterocyclic compounds of biological

importance, this focused review aims to address the synthetic strategies and biological importance of benzofuro[3,2-*d*]pyrimidine derivatives.

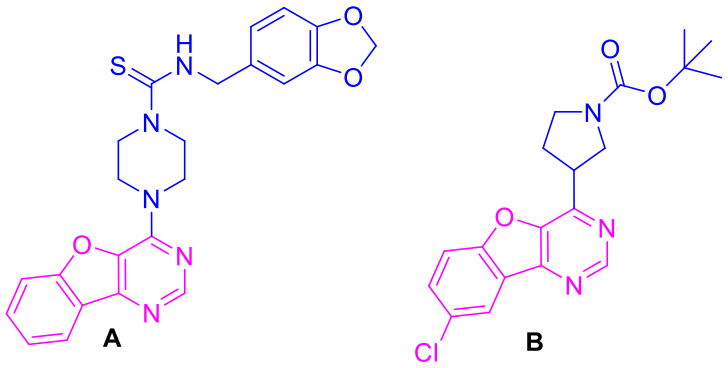
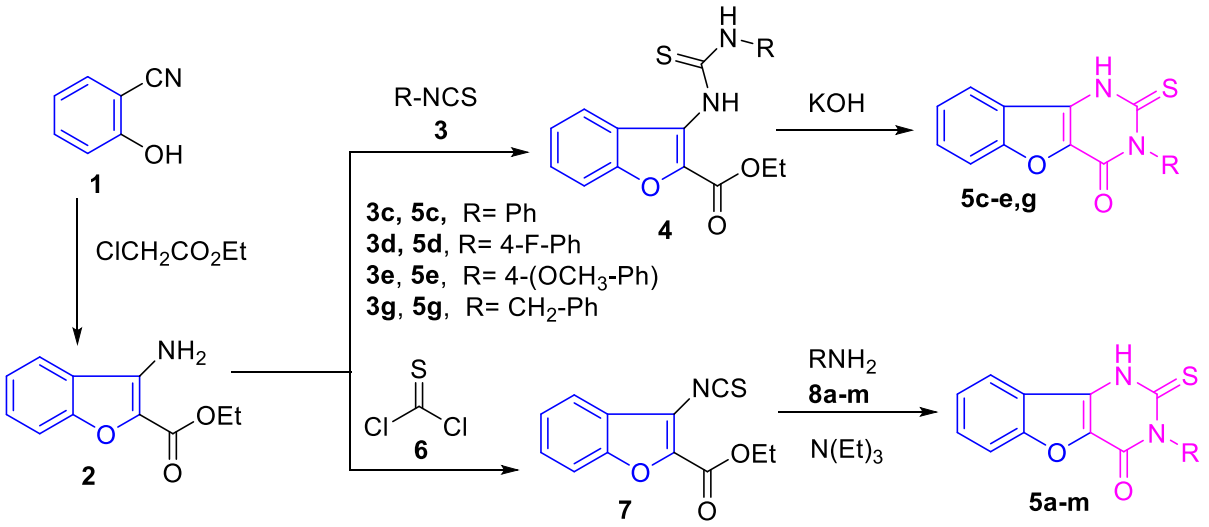


Figure 1. Selected examples of benzofuro[3,2-*d*]pyrimidine compounds displaying antimicrobial activity.

2. Synthesis of Benzofuro[3,2-*d*]pyrimidine Derivatives

2.1. From 2-hydroxybenzonitrile derivatives

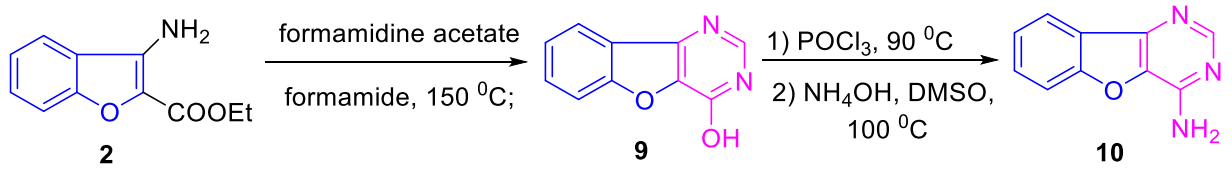
Il'chenko *et al.* reported that,[33] treatment of the 2-hydroxybenzonitrile **1** with ethyl chloroacetate afforded the corresponding ethyl 3-aminobenzofuran-2-carboxylate **2**. Compound **2** was reacted with isothiocyanates **3** in dimethylformamide to yield the associated thiourea derivatives **4**. Heating thiourea derivative **4** in alkaline medium induced cyclization, affording the 3-substituted 2-thioxo-2,3-dihydro-1*H*-benzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones (**5c-e,g**). Treatment of **2** with thiophosgene **6** afforded the corresponding ethyl 3-isothiocyanatobenzofuran-2-carboxylate **7**. Reaction of isothiocyanato derivative **7** with amine derivatives **8a-m** in the presence of triethylamine gave the benzofuro[3,2-*d*]pyrimidine derivatives **5a-m** (Scheme 1).



(8a): R = H, (**8b**): R = CH_3, **(8c)**: R = Ph, (**8d**): R = 4-F-Ph, **(8e)**: R = 4-(OCH_3-Ph), **(8f)**: R = C_4H_9 (8g): R = CH_2-Ph, **(8h)**: R = $(CH_2)_2$-OCH_3, **(8i)**: R = CH_2-(4-F-Ph), **(8j)**: R = CH_2-(4-OCH_3-Ph), **(8k)**: R = CH_2-(4-CH_3-Ph), **(8l)**: R = CH_2COOH, **(8m)**: R = $(CH_2)_2COOH$.

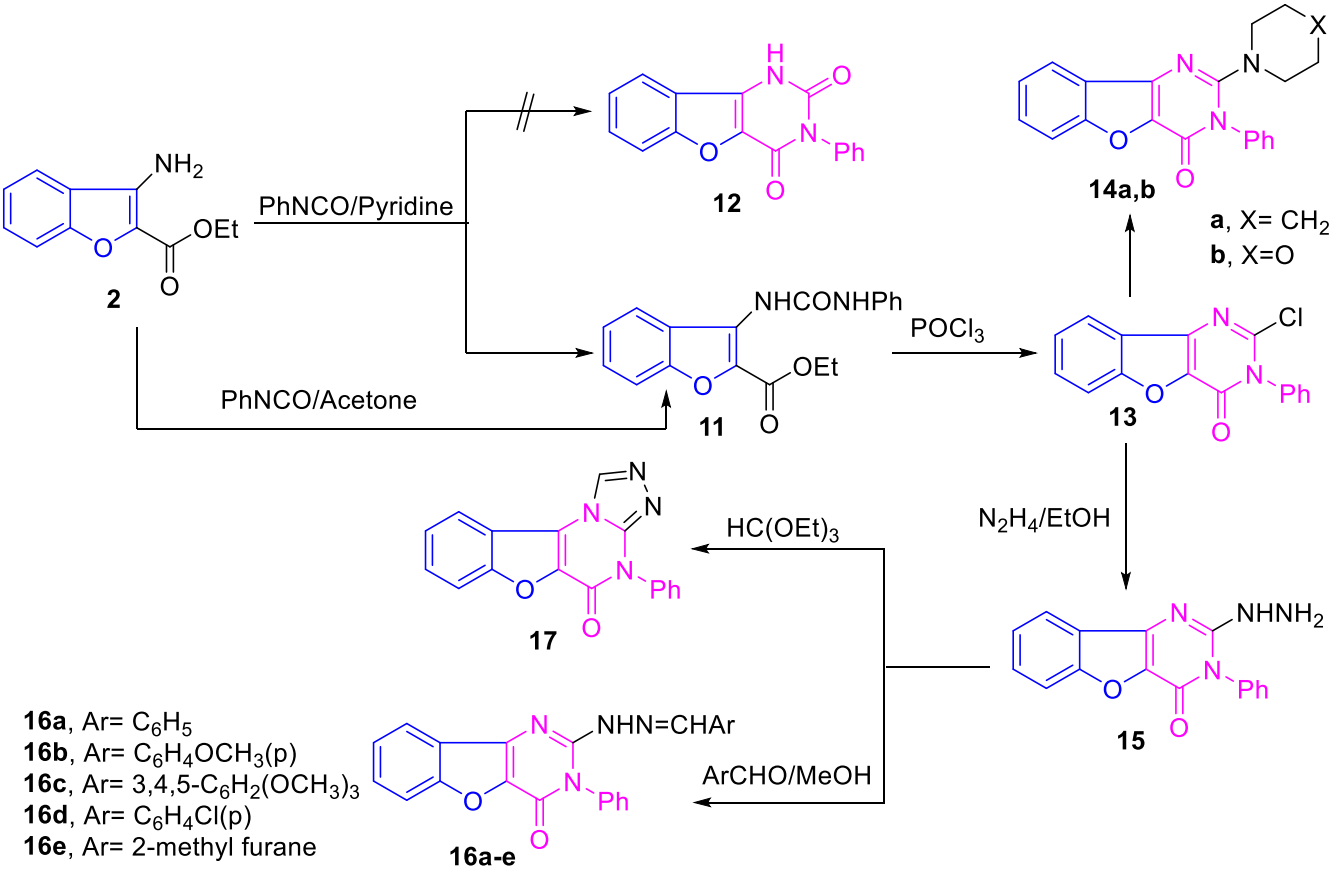
Scheme 1. Synthesis of 3-*N*-substituted-2-thioxo-2,3-dihydrobenzofuro[3,2-*d*]pyrimidin-4(1*H*)-ones **5a-m**.

Furthermore, cyclization[34] of ethyl 3-amino-2-carboxylate **2** with formamidine acetate in formamide at 150 ^{0}C gave the 4-hydroxypyrimidine **9**. Chlorination of **9** with phosphorus oxychloride subsequently reaction of the resulting product with ammonium hydroxide in DMSO afforded 4-aminopyrimidine **10** (Scheme 2).



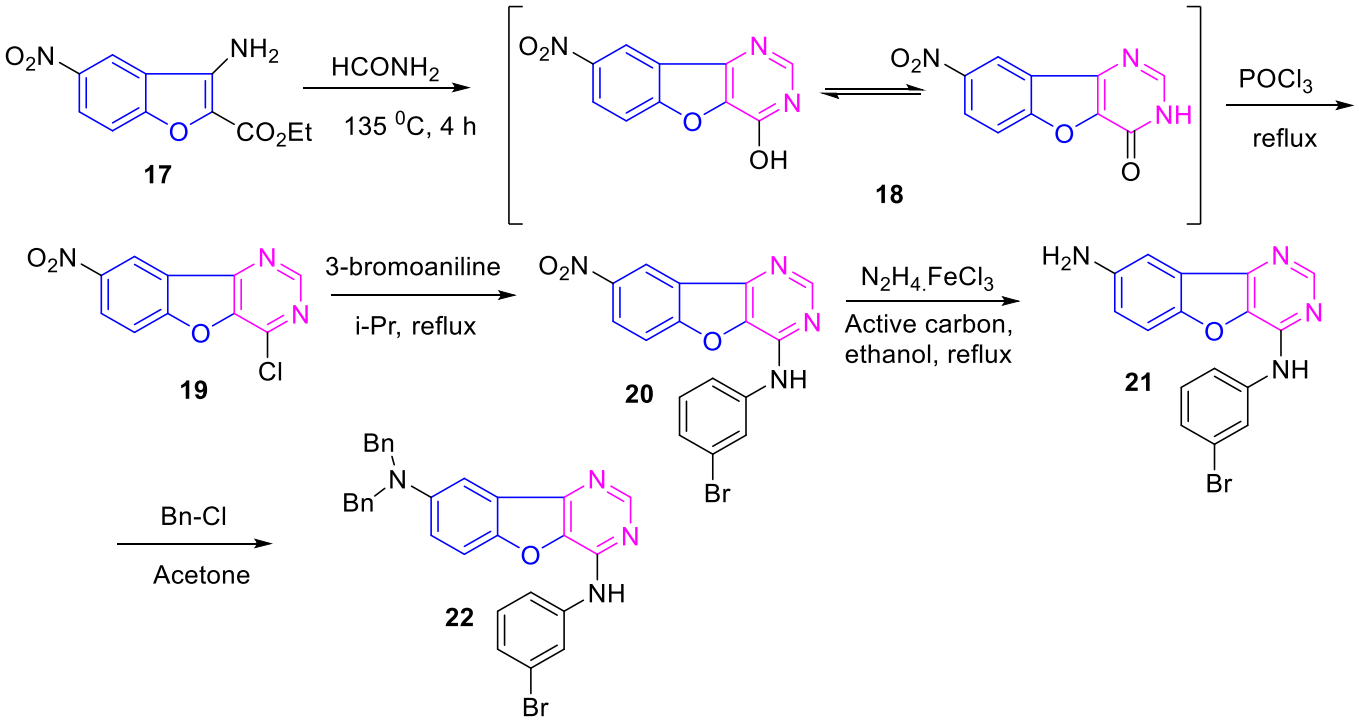
Scheme 2. Synthesis of benzofuro[3,2-*d*]pyrimidine derivatives **9** and **10**.

It was found that,[35] the reaction of benzofuran derivative **2** with phenyl isocyanate in anhydrous pyridine under reflux gave ethyl 3-phenylureido-2-benzofuran carboxylate **11** and not the expected tricycle **12**. Similarly, treatment of **2** with phenyl isocyanate in acetone under mild conditions gave compound **11**. Reaction of **11** with phosphoryl chloride at reflux temperature gave 2-chloro-3-phenyl-3,4-dihydro-4-oxobenzofuro[3,2-*d*] pyrimidine (**13**), probably the result of both cyclization and halogenation. Reaction of **13** with piperidine and morpholine in ethanol afforded the corresponding compounds **14a** and **14b**. The reaction of **13** using hydrazine hydrate in ethanol at reflux furnished **15**. The condensation of **15** with different aromatic aldehydes in methanol at room temperature led to formation of the corresponding benzofuro[3,2-*d*]pyrimidines (**16a-e**). Treatment of **15** with ethyl orthoformate gave a tetracyclic heterocycle **17** (Scheme 3).



Scheme 3. Synthesis of 2-arylideneamino-3-phenyl-3,4-dihydro-4-oxobenzofuro[3,2-*d*]pyrimidines **16a-e**.

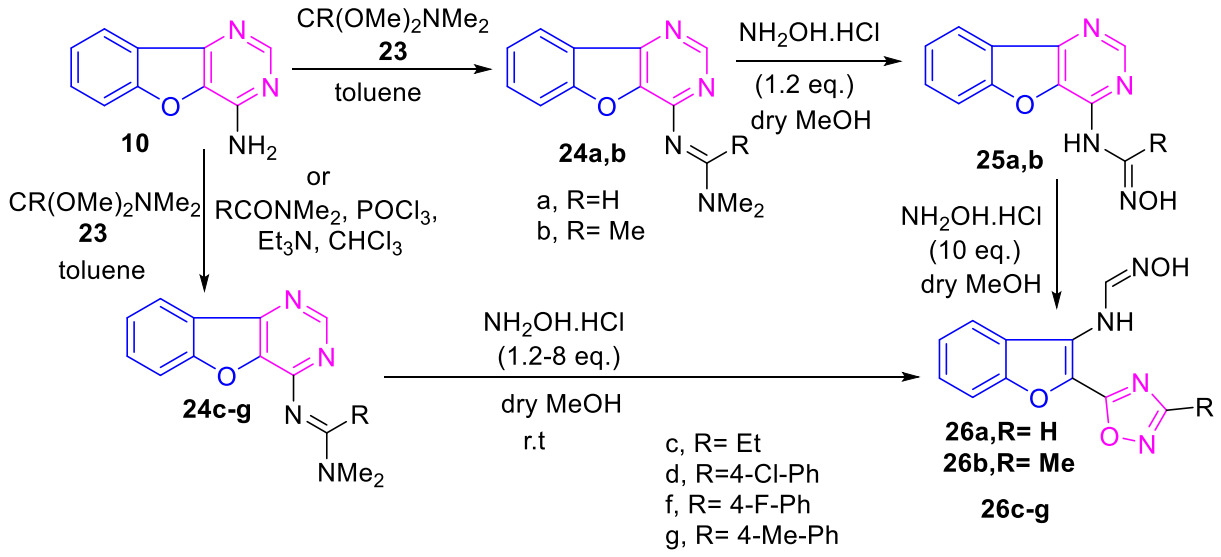
Wu W-N. *et al.* mentioned that,[36] treatment of amino ester **17** with formamide gave the corresponding 8-nitrobenzofuro[3,2-*d*]pyrimidin-4-ol (**18**). Chlorination of the latter compound with phosphorous oxychloride gave the 4-chloro derivative **19**. Reaction of the latter compound with 3-bromoaniline gave corresponding compound **20**. Reduction of nitro derivative **20** lead to the formation of amine **21**. Reaction of **21** with benzyl chloride gave dibenzylamino derivative **22** (Scheme 4).



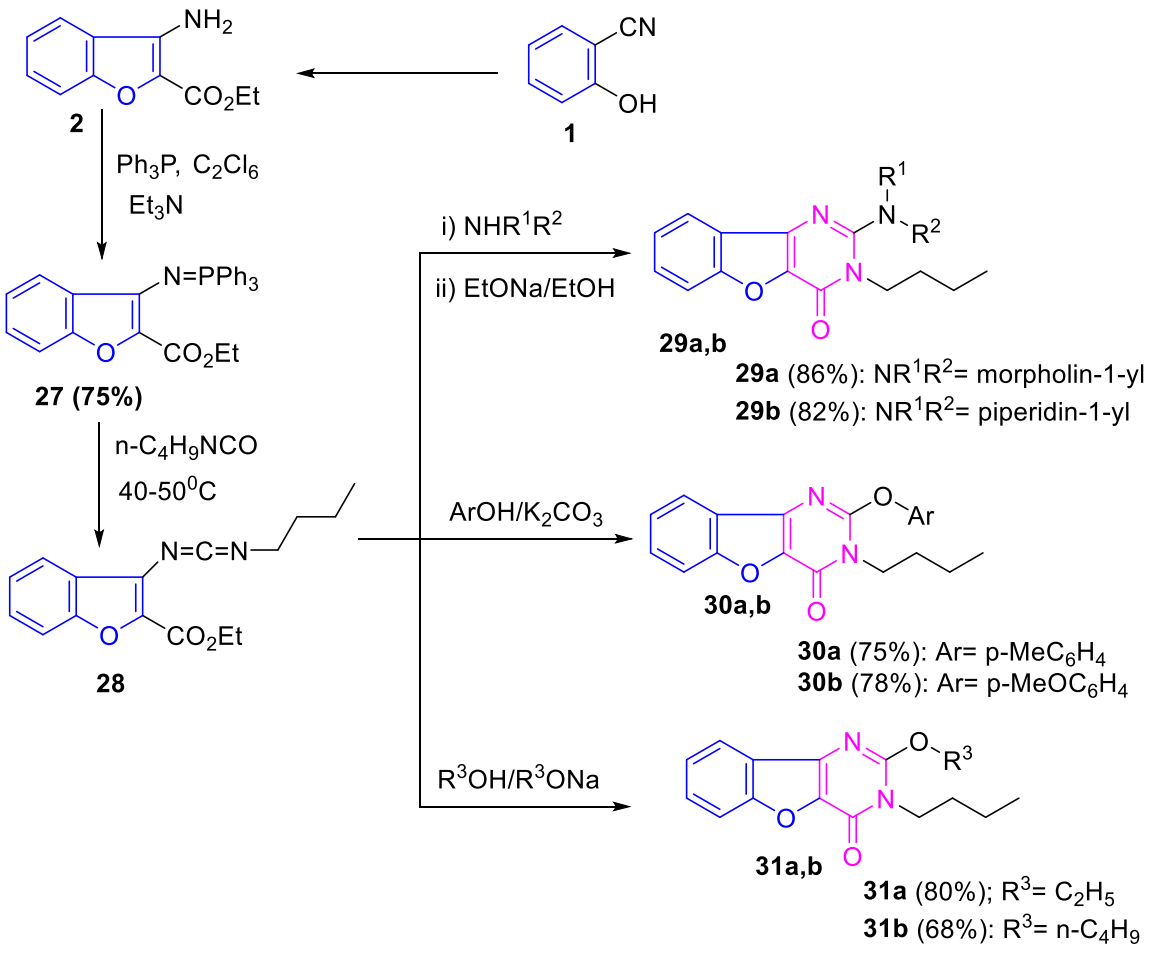
Scheme 4. Synthesis of benzofuro[3,2-*d*]pyrimidines **18-22**.

In 2012, Okuda *et al.*[37] found that treatment of amino derivative **10**[38] with *N,N*-dimethylformamide or *N,N*-dimethylacetamide dimethyl acetal (DMAC) **23** in toluene, under reflux, gave compounds **24a,b**. On the other hand, reaction of **10** with Vilsmeier reagent afforded *N'*-(benzofuro[3,2-*d*]pyrimidin-4-yl)-*N,N*-dimethylformimidamides **24c-g** which were previously synthesised.[39] The amide oxime **25a** was obtained by the reaction of **24a** with hydroxylamine hydrochloride (1.2 equiv.) in methanol at ambient temperature, whereas, when the same reaction was performed using hydroxylamine hydrochloride (10 equiv.) in boiling methanol and dioxane mixture, the 1,2,4-oxadiazole compound **26a** was formed. Similarly, the 1,2,4-oxadiazole derivative **26b** was obtained when the compound **24b** was allowed to react with 6.0 equiv. of hydroxylamine hydrochloride at reflux in methanol. In addition, reaction of other amidines **24c-g** with of hydroxylamine hydrochloride (1.2-8 equiv.) in methanol at ambient temperature gave the oxadiazole derivatives **26c-g** (Scheme 5).

Wang *et al.* mentioned that,[40] the synthetic approach of the crucial intermediate **27** has been reported previously.[18,41] Thus, reaction of **2** with Ph_3P and Et_3N in C_2Cl_6 gave the iminophosphorane **27**. Treatment of the latter compound **27** with with n-butyl isocyanate at 40–50 °C afforded the carbodiimide **28**. Reaction of **28** with morpholine and piperidine followed by treatment with sodium ethoxide yielded the corresponding benzofuro[3,2-*d*]pyrimidine derivatives **29a** and **29b** respectively. Interaction of **28** with phenols using anhydrous K_2CO_3 at 50–60 °C afforded **30a**,**b**. The benzofuro[3,2-*d*]pyrimidines **31a**,**b** were obtained by treatment of compound **28** with aliphatic alcohols (R^3OH) using R^3ONa (Scheme 6).

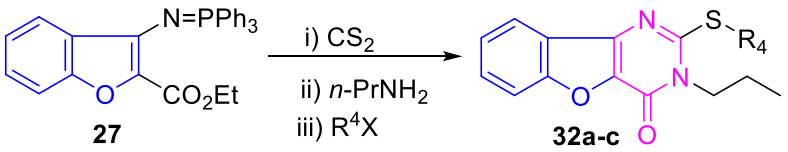


Scheme 5. Reactions of formamidine derivatives **24a-g** with hydroxylamine hydrochloride.



Scheme 6. Preparation of benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one derivatives **31a,b.**

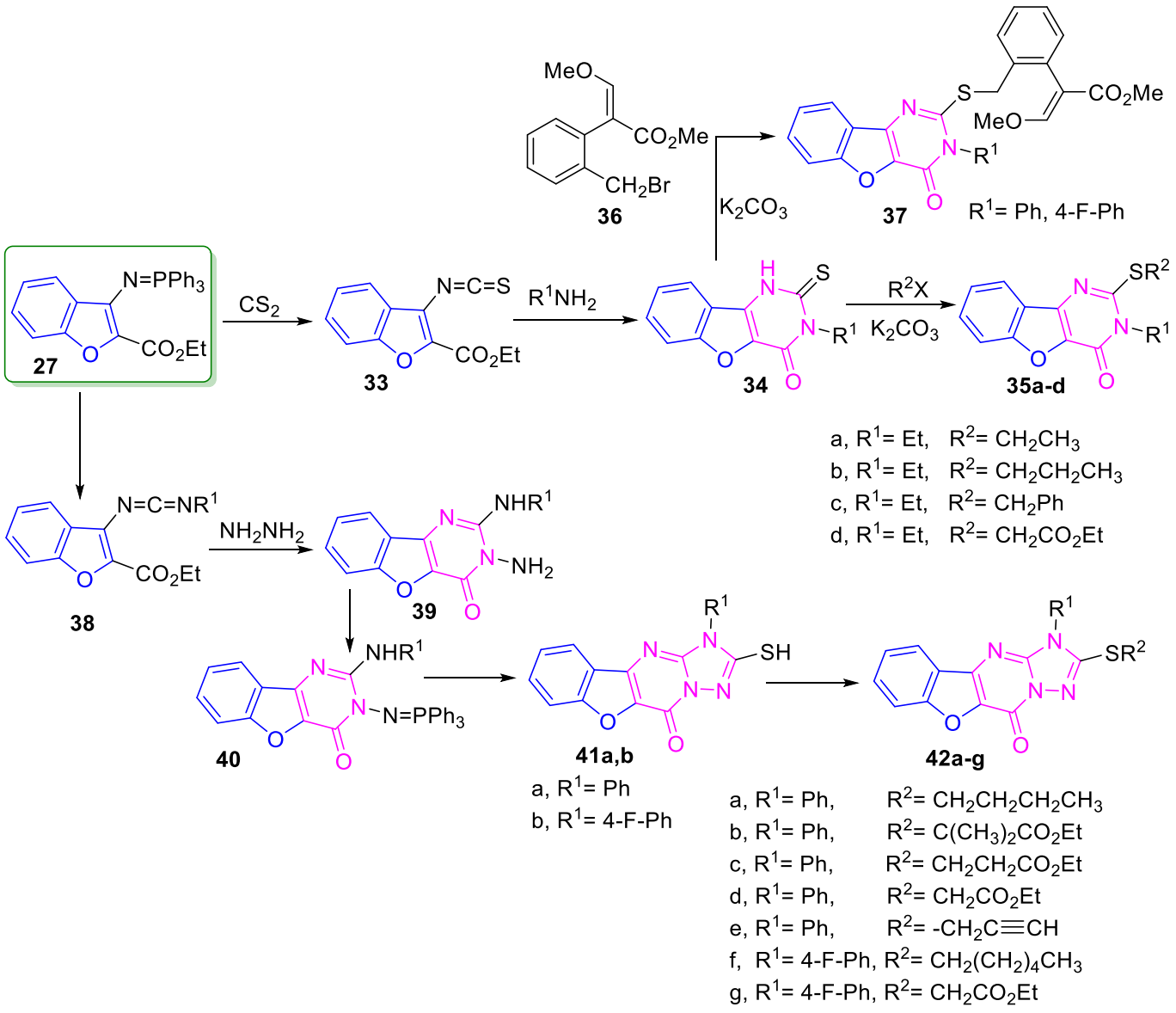
Moreover, the same authors[40] described the reaction of iminophosphorane **27** with an excess of carbon disulfide and prolonged heating at 40–50 °C, followed by subsequent treatment with *n*-propylamine. Further treatment with alkyl halides or halogenated aliphatic esters under anhydrous K_2CO_3 yielded 2-substitutedthio-3-*n*-propylbenzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones **32a**-**d** (Scheme 7).



32a (86%): R^4= $CH_2CO_2C_2H_5$
32b (86%): R^4= $CH_2CH_2CH_3$
32c (82%): R^4= $CH_2CH_2CH_2CH_3$
32d (85%): R_4= CH_2Ph

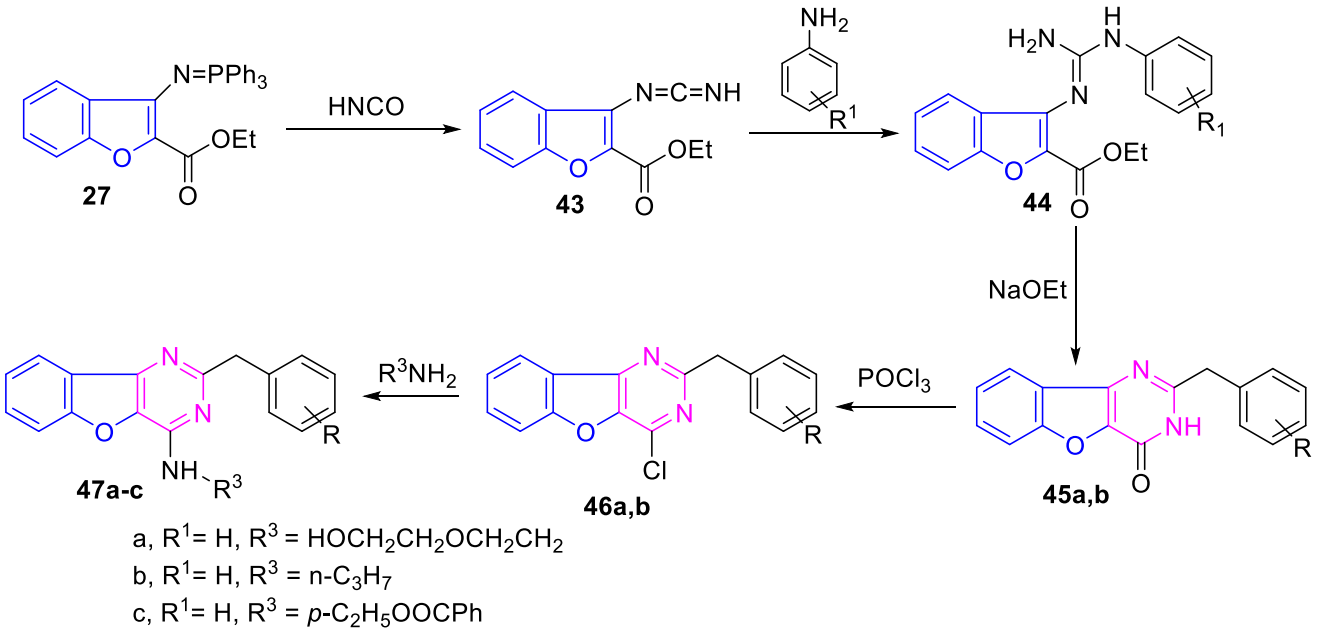
Scheme 7. Construction of 2-substitutdthio-3-*n*-propyl-benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones **32a**-**d.**

In 2016, it was reported that,[42] reaction of compound **27**[43] with of carbon disulfide used in excess gave the isothiocyanate **33**. Reaction of latter derivative with aliphatic primary amines gave the corresponding 2-thione derivatives **34**. The 2-substituedthio benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones **35a-d** and **37** were obtained by the reaction of **34** with alkyl halides or methyl 3-(2-(bromomethyl)phenyl)-3-methoxyacrylate **36** in the presence of K_2CO_3. The synthesis of derivatives **38**-**40** has been described earlier.[44,45] The 1-aryl-2-thioxobenzofuro[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones (**41a,b**) were prepared by treatment of iminophosphoranes **40** with excess carbon disulfide. The 1-aryl-2-alkylthiobenzofuro[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones (**42a-g**) were obtained when compound **41** was treated with alkyl halides in the presence of K_2CO_3 (Scheme 8).



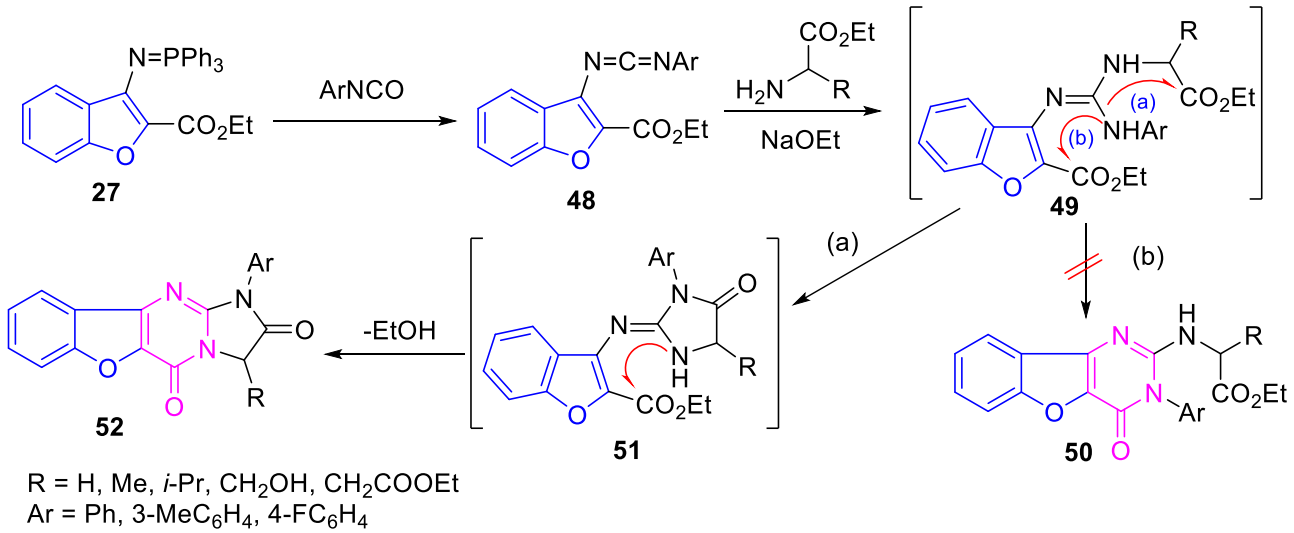
Scheme 8. Synthesis of 1-aryl-2-substitutedthio benzofuro[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(1*H*)-ones **42a-g**.

Tang *et al.*[18] found that the reaction of iminophosphorane **27**[46, 47] with isocyanates at 0-5 °C afforded the corresponding compound **43**. Treatment of latter compound **43** with substituted anilines provide guanidine intermediates **44**. The intermediates **44** were converted easily under mild conditions using sodium ethoxide to benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one derivatives **45a,b**. Chlorination of the pyrimidinone derivatives **45a,b** with $POCl_3$ afforded the chloro derivatives **46a,b**. Nucleophilic substitution reaction of the chloro derivative **46a,b** with amines gave the corresponding compounds **47a-c** (Scheme 9).



Scheme 9. Synthesis of benzofuro[2,3-*d*]pyrimidine derivatives **47a-c**.

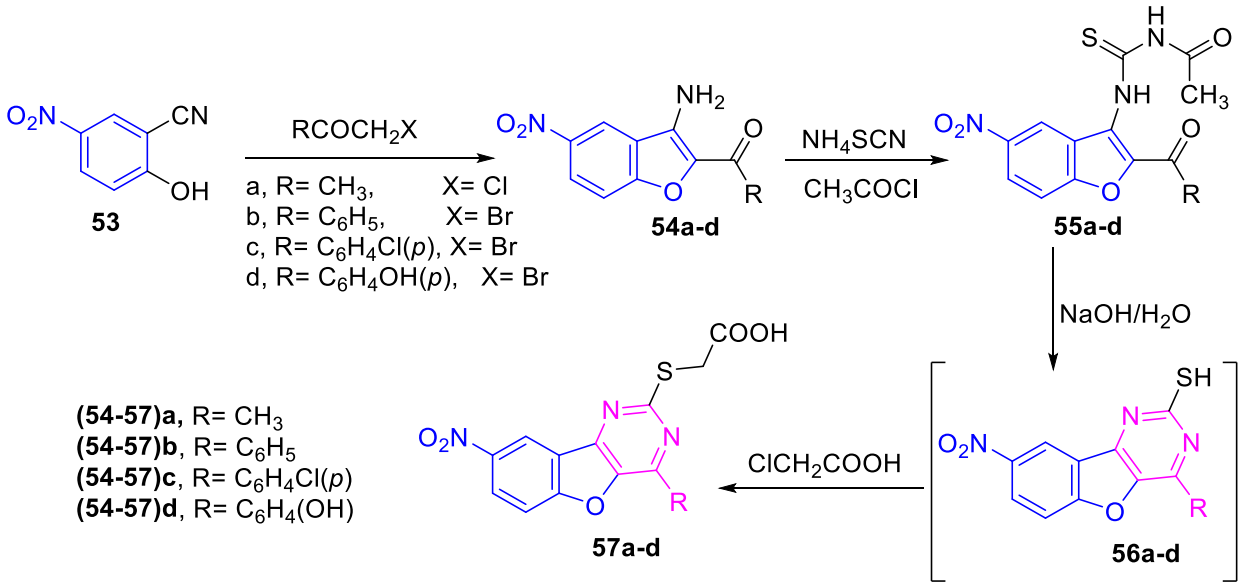
It was also reported that[44] the carbodiimides **48** were prepared by the reaction of iminophosphorane **27** with isocyanates. Treatment of **48** with α-amino esters in presence of sodium ethoxide afforded the guanidine intermediates **49**, which did not cyclize to benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones **50** but the reaction preferentially formed imidazolones **51** which underwent base-catalyzed intramolecular cyclization to the corresponding benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-diones **52** (Scheme 10).



Scheme 10. Synthesis of benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-diones (**52**).

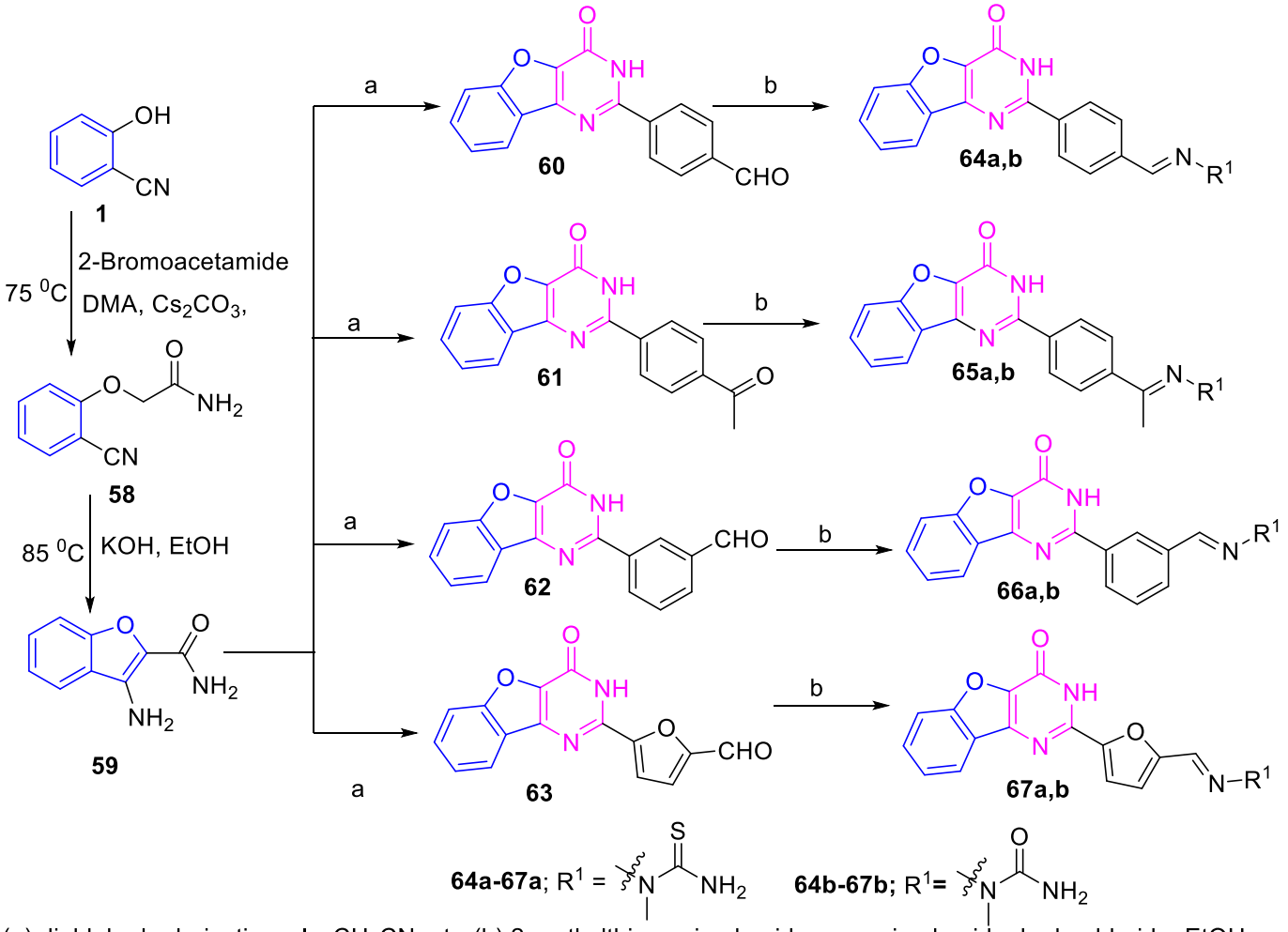
In 2024, Bharathi Sh. V. *et al.*[19] mentioned that the cyclization of hydroxybenzonitrile **53** with different ketones in alcoholic media furnished the benzofuran derivatives (**54a-d**). Subsequent reaction of **54a-d** with ammonium thiocyanate and acetyl chloride under mild conditions afforded the carbamothioylacetamide derivatives **55a-d**. Cyclization of the latter with aqueous NaOH probably formed thiol intermediates **56a-d**,

which were treated with chloroacetic acid that produced the corresponding [(4-methyl-8-nitrobenzofuro[3,2-*d*] pyrimidin-2-yl)sulfanyl]acetic acids (**57a-d**) (Scheme 11).



Scheme 11. Synthesis of benzofuro[3,2-*d*]pyrimidine derivatives **(57a-d)**.

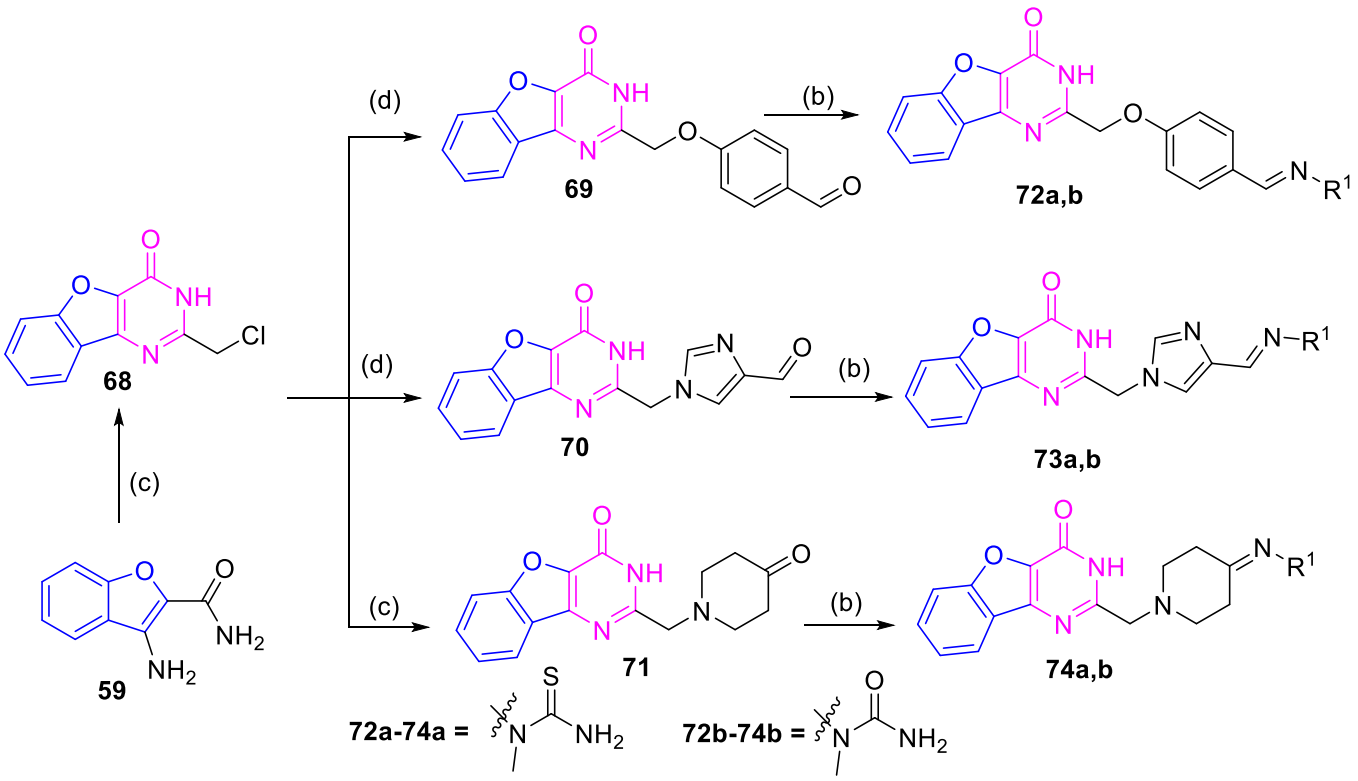
Wang Y. *et al.* found that[22] when 2-hydroxybenzonitrile **1** was reacted with 2-bromoacetamide in DMA in the presence of Cs_2CO_3, the corresponding cyano derivative **58** was isolated. Treatment of **58** with ethanolic KOH afforded the cyclized product **59**. Reaction of **59** with dialdehydes in acetonitrile using iodine under mild conditions yielded benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one derivatives **60-63**. The Schiff base condensation of intermediates **60-63** with 2-methyl-3-thiosemicarbazide and semicarbazide yielded the target products **64a,b-67a,b** (Scheme 12).



(a) dialdehyde derivatives, I_2, CH_3CN, r.t.; (b) 2-methylthiosemicarbazide or semicarbazide hydrochloride, EtOH, HAc, reflux.

Scheme 12. Construction of benzofuran[3,2-*d*]pyrimidine derivatives and related heterocycles **60-67.**

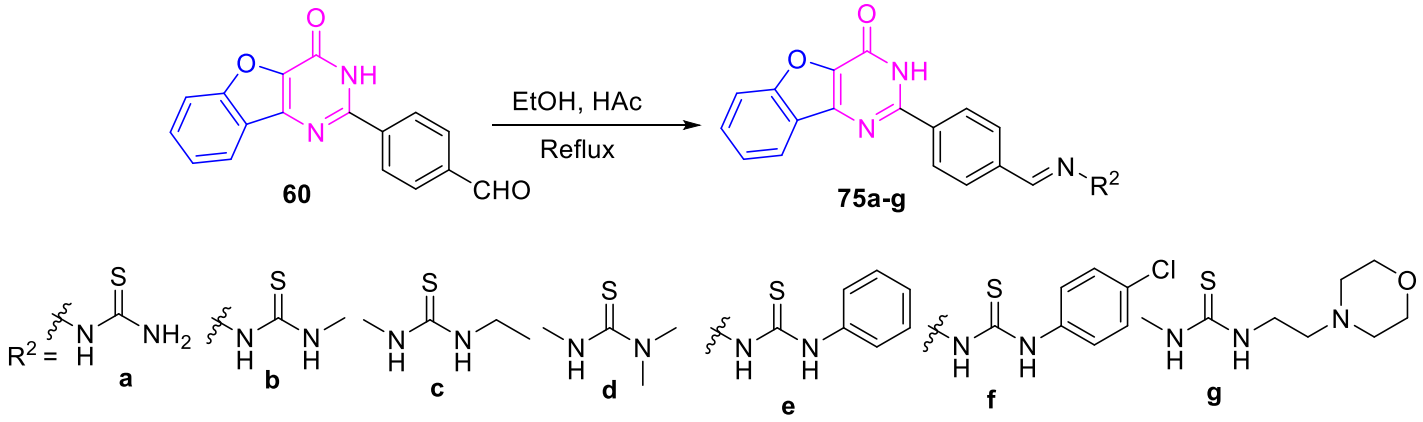
Furthrmore,[22] compound **68** was obtained when compound **59** was reacted with 2-chloro-1,1,1-trimethoxyethane and catalytic amount of *p*-toluene sulfonic acid. Treatment of **68** with *p*-hydroxybenzaldehyde, 1*H*-imidazole-4-carbaldehyde, and 4-piperidinone, formed the corresponding derivatives **69-71**. Condensation of **69-71** with 2-methyl-3-thiosemicarbazide and semicarbazide furnished the corresponding Schiff bases **72a,b-74a,b** (Scheme 13).



(c) 2-chloro-1,1,1-trimethoxyethane, p-toluenesulfonic acid, toluene, 110 ^{0}C; (d) aldehyde or ketone erivatives, K_2CO_3, KI, DMF, 80 ^{0}C; (e) 4-piperidone hydrate hydrochloride, Et_3N, KI, DMA, 80 ^{0}C.

Scheme 13. Synthesis of 2-substitued benzofuran[3,2-*d*]pyrimidine derivatives **69-74.**

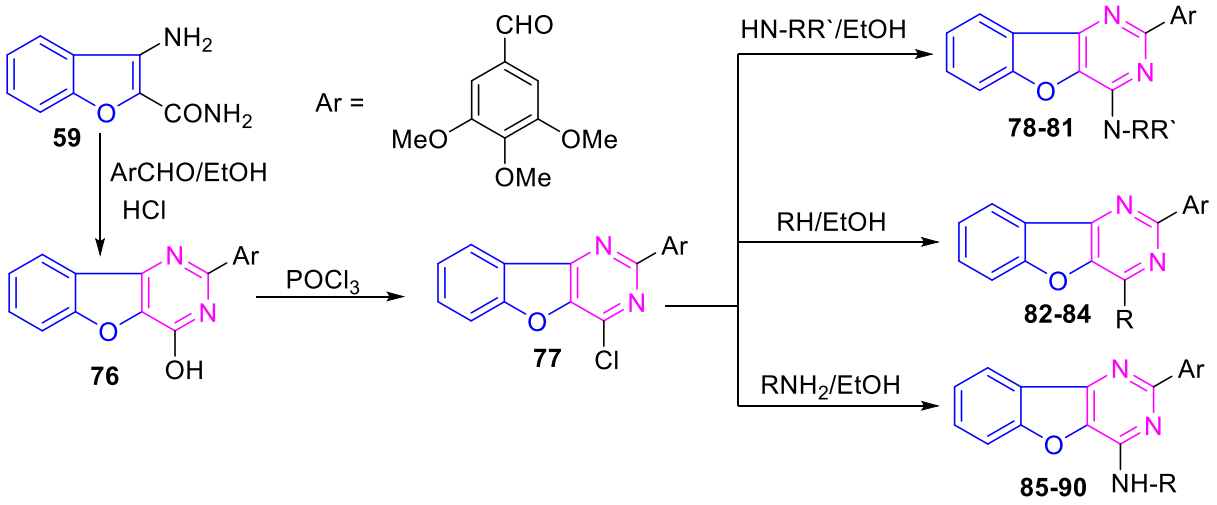
Reaction of pyrimidinone **60** with different amines in ethanol using acetic acid under reflux afforded of the corresponding benzofuran[3,2-*d*]pyrimidine-4(3*H*)-one derivatives **75a-g**[22] (Scheme 14).



Scheme 14. Synthesis of some hydrazone derivatives of benzofuran[3,2-*d*]pyrimidines **75a-g.**

Raga Basawaraj *et al.* mentioned that[48] the reaction of versatile intermediate **59** with aromatic aldehydes in absolute ethanol and conc. HCl gave the benzofuro[3,2-*d*]pyrimidine derivatives **76**.[49] Treatment of compounds **76** with $POCl_3$ underwent nucleophilic substitution reaction to give the corresponding 2-(3,4,5-triethoxy-phenyl)-3,4-dihydro-4-chlorobenzofuro[3,2-*d*]pyrimidines **77.** Reaction of chloro derivatives **77** with

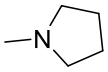
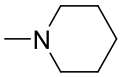
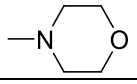
primary and secondary aliphatic amines, heterocyclic amines such as pyrrolidine, piperidine morpholine and/or aromatic amines in absolute ethanol under reflux, yielded the corresponding 4-substitutedamino-2-(3,4,5-triethoxyphenyl)benzofuro[3,2-*d*]pyrimidine derivatives **78-90** respectively (Scheme 15).



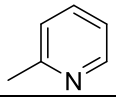
Compounds 78-81

No	R`	R
78	H	CH_3
79	H	C_2H_5
80	CH_3	CH_3
81	C_2H_5	C_2H_5

Compounds 82-84

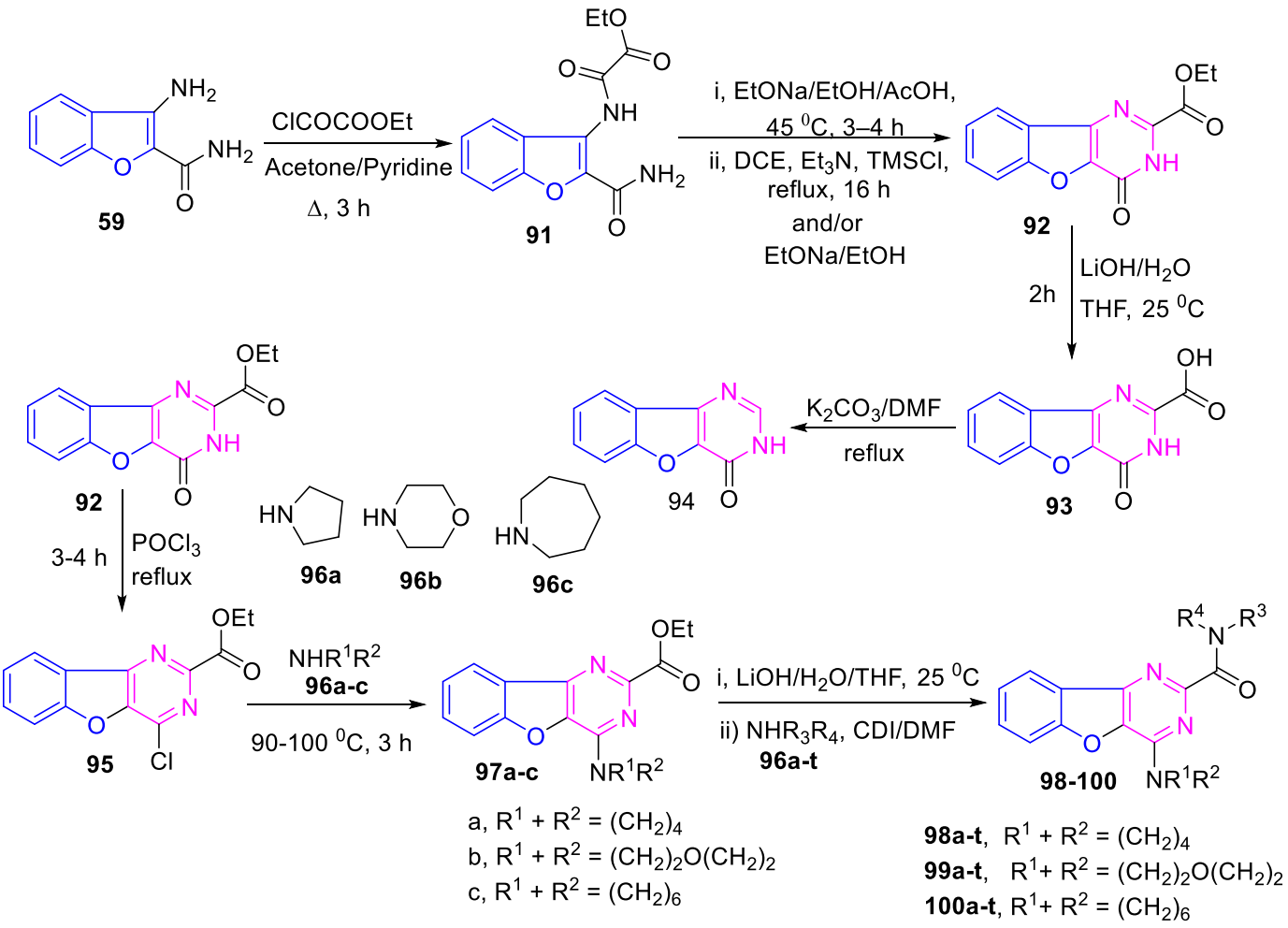
No	R
82	
83	
84	

Compounds 85-90

No	R
85	C_6H_5
86	$C_6H_4CH_3(p)$
87	$C_6H_4OCH_3(p)$
88	$C_6H_4Cl(p)$
89	$C_6H_4Br(p)$
90	

Scheme 15. Nucleophilic substitution reactions of choro derivatives **77** with different amines (**78-90**).

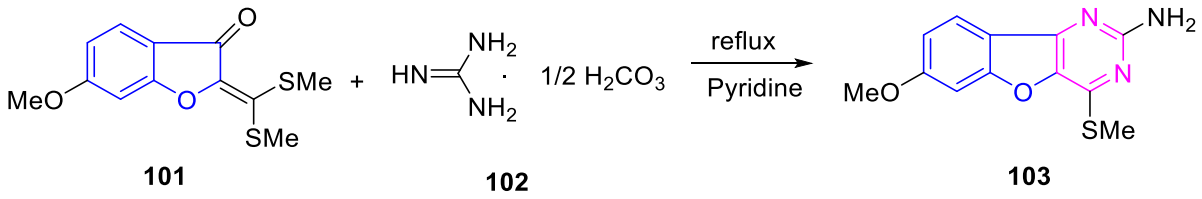
It was also found that[50] reaction of amino amide derivative **59** with ethyl chloro(oxo)acetate in acetone/pyridine mixture gave compound **91**. Compound **91** was considered as a valuable precursor for the synthesis of heterocyclic-fused benzofurans. Thus, treatment of **91** with EtONa in dry ethanol afforded the ester derivative **92**. An alternative synthesis of ester **92** was achieved via reaction of **91** in DCE using Et_3N and TMSCl, following a previously described[51] protocol, providing the ester in 60% yield. Saponification of the ester **92** furnished acid **93** (88% yield) which underwent decarboxylation to give benzofuro[3,2-*d*]pyrimidine **94**. Treatment of Ester **92** with $POCl_3$ according to Sangapure *et al.*[52] produced 4-chlorobenzofuro[3,2-*d*]pyrimidine **95**. The chloro derivative **95** was subsequently converted into amines **97a-c** through reactions with secondary amines **96a-c**. Hydrolysis of esters **97a-c** with LiOH in THF–water yielded the corresponding acids, which were reacted with primary and secondary amines **96a-t** to produce the carboxamide derivatives (**98-100)a-t** (Scheme 16).



Scheme 16. Synthesis of carboxamide derivatives-based benzofuro[3,2-*d*]pyrimidine **98-100**.

2.2. From benzofuran derivatives

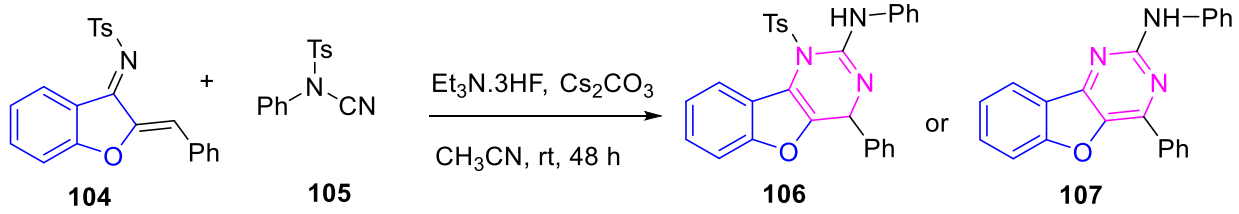
Yokota *et al.* suggested that,[53] the reaction of the ketene dithioacetal **101** with guanidine carbonate **102** in pyridine under reflux afforded the 7-methoxy-4-(methylthio)benzofuro[3,2-*d*]pyrimidin-2-amine **103** in good yield (Scheme 17).



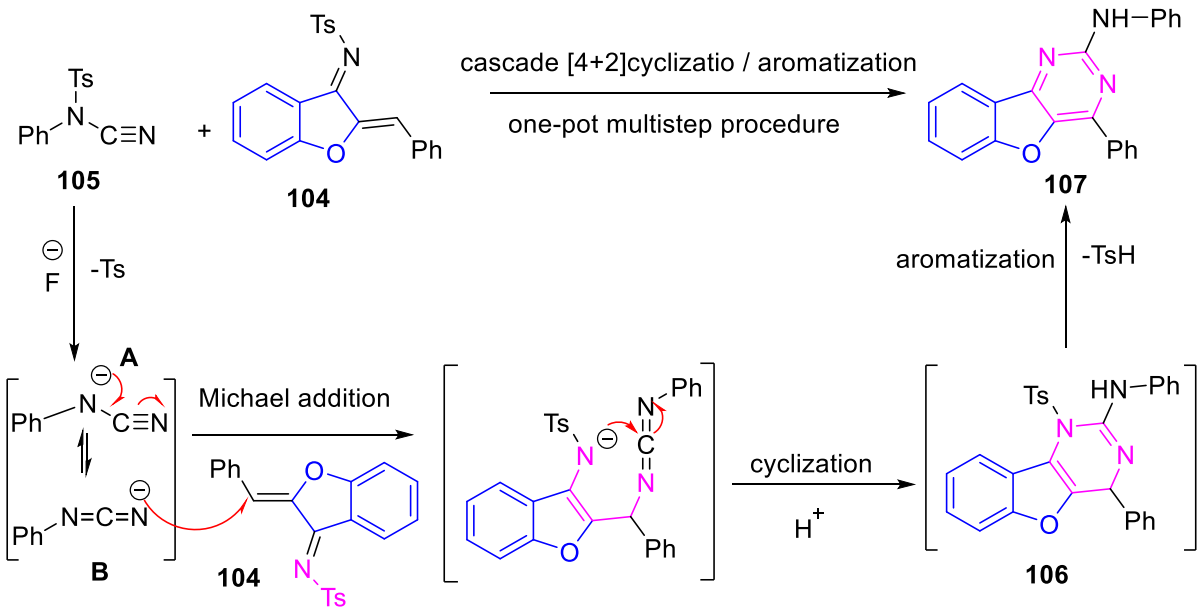
Scheme 17. Synthesis of 7-methoxy-4-(methylthio)benzofuro[3,2-*d*]pyrimidin-2-amine **103**.

In 2024, Wang *et al.* reported that[21] reaction of benzofuran-derived azadiene **104** with N-Ts cyanamide **105** under the action of Cs_2CO_3 and $Et_3N{\cdot}HF$ in CH_3CN under mild conditions, afforded the 2-anilino derivative **107** in 68%. Moreover, the corresponding nonaromatic cyclization derivative **106**, which served as the precursor to the final product **107**, was observed early in the reaction mixture by TLC and disappeared after the completion

of the reaction (Scheme 18). The exclusive chemo selectivity for this tandem[4+2]cyclization/aromatization strategy was identified in this reaction. A proposed mechanism was suggested, as illustrated in the scheme 19.



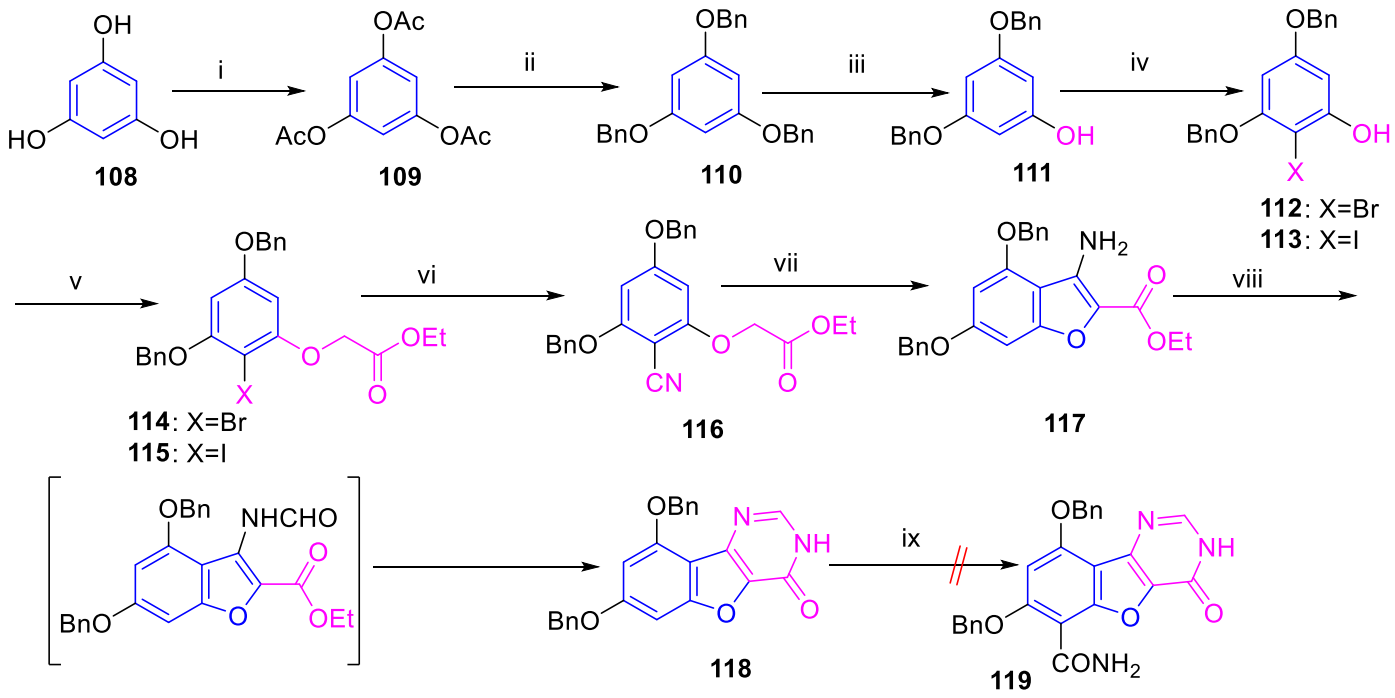
Scheme 18. Synthesis of *N*,4-diphenylbenzofuro[3,2-*d*]pyrimidin-2-amine **107**.



Scheme 19. A suggested mechanistic pathway for the formation of compound **107**.

2.3. From benzene-1,3,5-triol

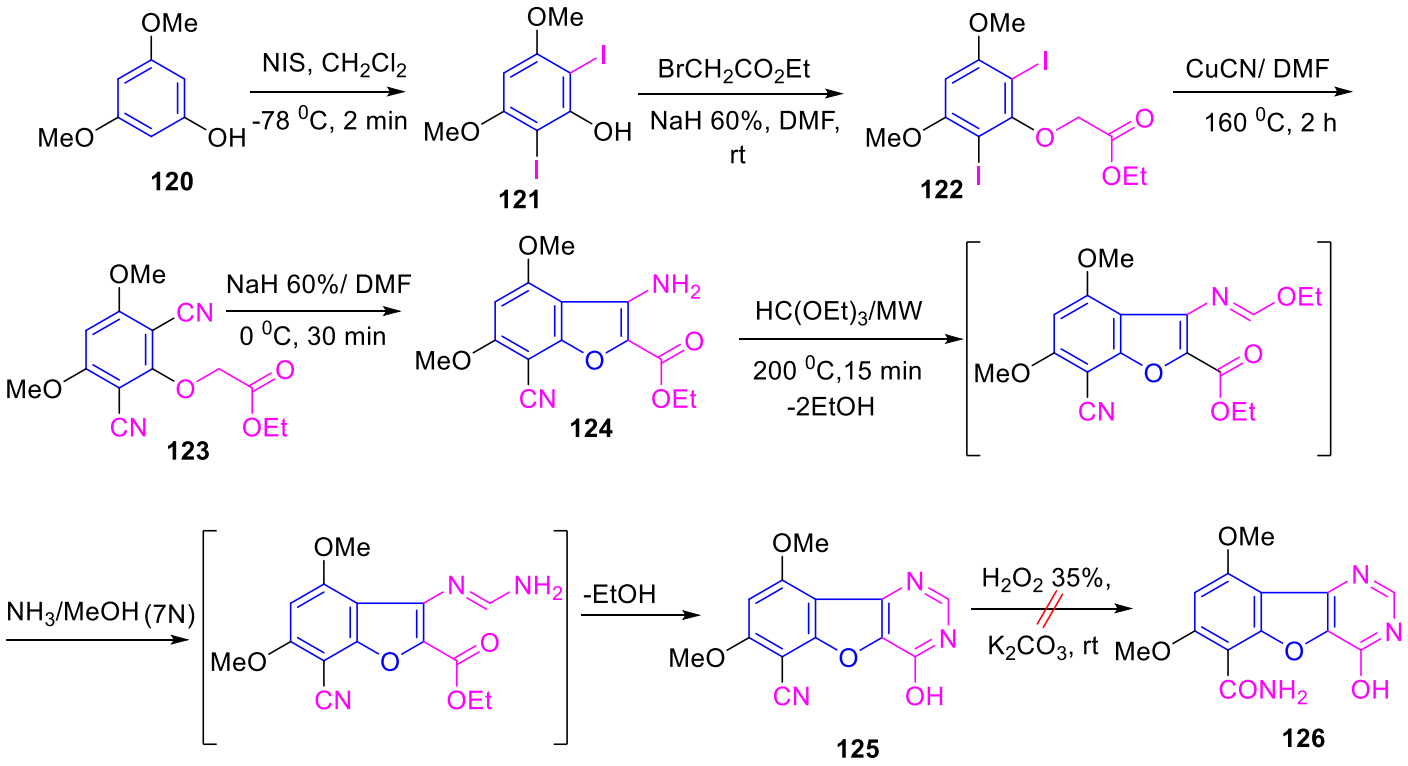
In 2018, it was reported that [54] the initial tribenzylation of benzene-1,3,5-triyl triacetate **109** was used to prevent additive C-benzylation via direct O-benzylation of benzene-1,3,5-triol **108**. This gave rise to the formation of 1,3,5-tris(benzyloxy)benzene **110**. Mono-deprotection was then carried out under transfer hydrogenation conditions using Pd/C and cyclohexene, in ethyl acetate/ethanol mixture under reflux, which gave 3,5-dibenzyloxyphenol **111** in moderate yield. The 2-halo-3,5-dibenzyloxyphenols **112** and **113** were prepared by mono-bromination and mono-iodination, respectively. Following this, O-alkylation was achieved employing sodium hydride (NaH) as a base and ethyl bromoacetate under mild conditions, that produced esters **114** and **115** in high yields. Cyanation of esters **114** and **115** with copper cyanide in DMF resulted in the formation of ester **116** in good yield. Cyclization of ethoxycarbonylmethylether **116** was carried out with NaH to yield benzofuran derivative **117**, which incorporated an amino group at position 3 and an ester group at position 2. A ring closure reaction of the benzofuran precursor **117** was attempted via treatment of a formamide intermediate with ammonia, yielding the corresponding benzofuro[3,2-*d*]pyrimidin-4-one **118**. Attempts to further convert **118** to **119** were unsuccessful (Scheme 20).



(i) Ac_2O, pyridine, 120 °C, 5 h, 87%; (ii) BnCl, NaH, DMF, H_2O, 0 °C to rt, 10 h, 96%; (iii) C_6H_{10}, Pd-C 10%, AcOEt/EtOH (3/1), 110 °C, 2 h, 45%; (iv) NBS(1.0 eq.), CH_2Cl_2, -78 °C, 2 min, 95% for **112** or NIS (1.0 eq.),CH_2Cl_2, -8 °C, 2 min, 76% for **113**; (v) NaH, $BrCH_2CO_2Et$, DMF, rt, 12 h, 83% for **114** and 96% for **115**; (vi) CuCN, DMF, 160 °C, 1 h, 19% from **114** and 92% from **115**; (vii) NaH, DMF, 0 °C, 30 min, 66%; (viii) $HC(OEt)_3$, MW, 200 °C, 15 min then NH_3/MeOH 7 N, MW, 140 °C,15 min, 31%; (ix) CSI, CH_3CN, rt, 24 h then HCl 1 N, rt, 24 h, failure.

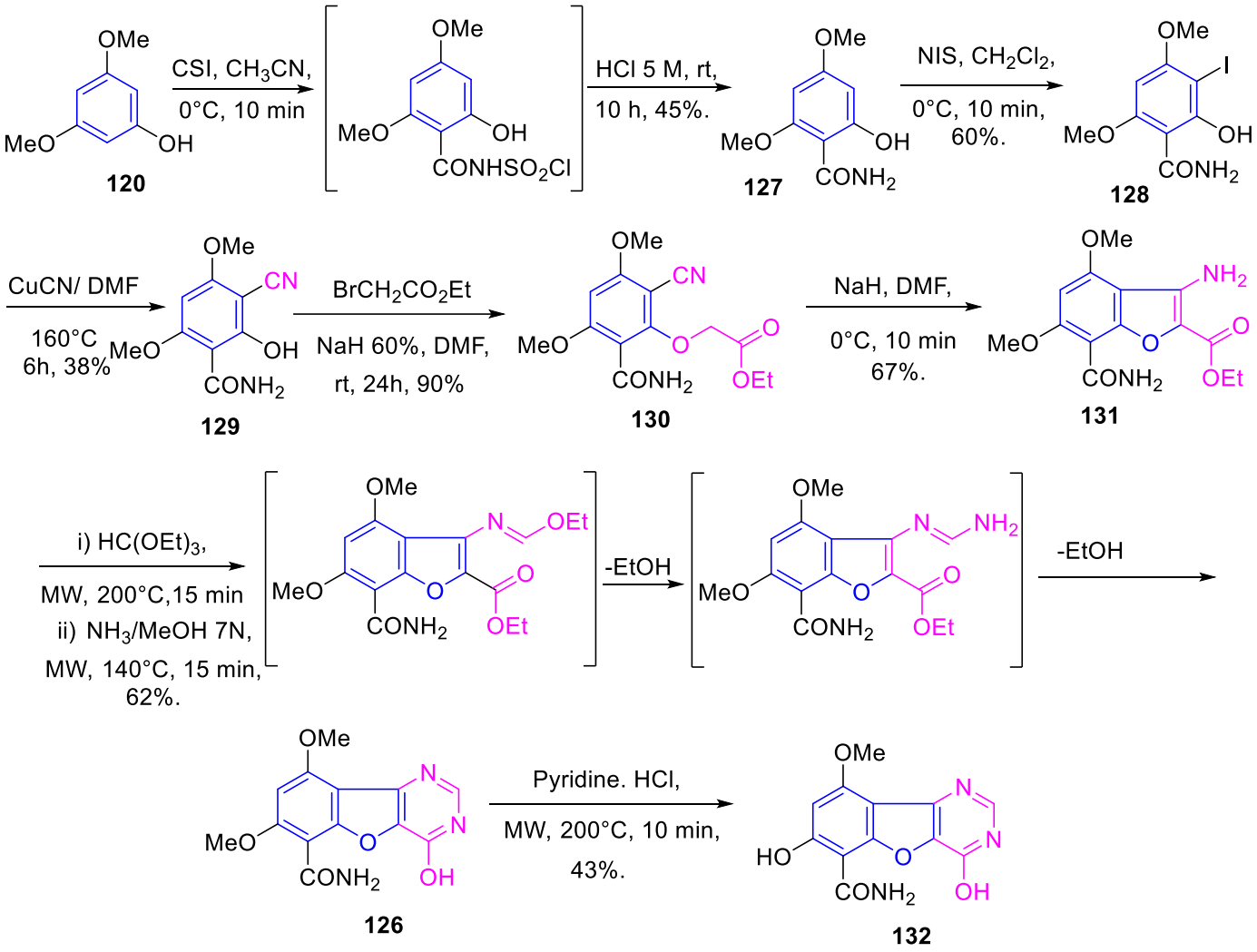
Scheme 20. Construction of benzofuro[3,2-*d*]pyrimidin-4(3H)-one derivatives **118.**

In 2021, it was reported that[60] the diiodination of compound **120** under mild conditions using *N*-iodosuccinimide (NIS), followed by *O*-alkylation with ethyl bromoacetate[58, 61] using NaH as base, resulted in the formation of compound **122** with a yield of 72%.[62] Cyanation of **122** with cuprous cyanide in DMF resulted in dicyano derivative **123** in 75% yield. Cyclization of compound **123** was performed using sodium hydride to produce the ester **124**.[59] Treatment of **124** with the triethyl orthoformate using microwave irradiation gave the pyrimidine derivative **125**.[63] However, several trials to transform nitrile **125** to carboxamide **126**, for example, oxidation with aqueous H_2O_2, were fruitless (Scheme 21).[61, 64-66]



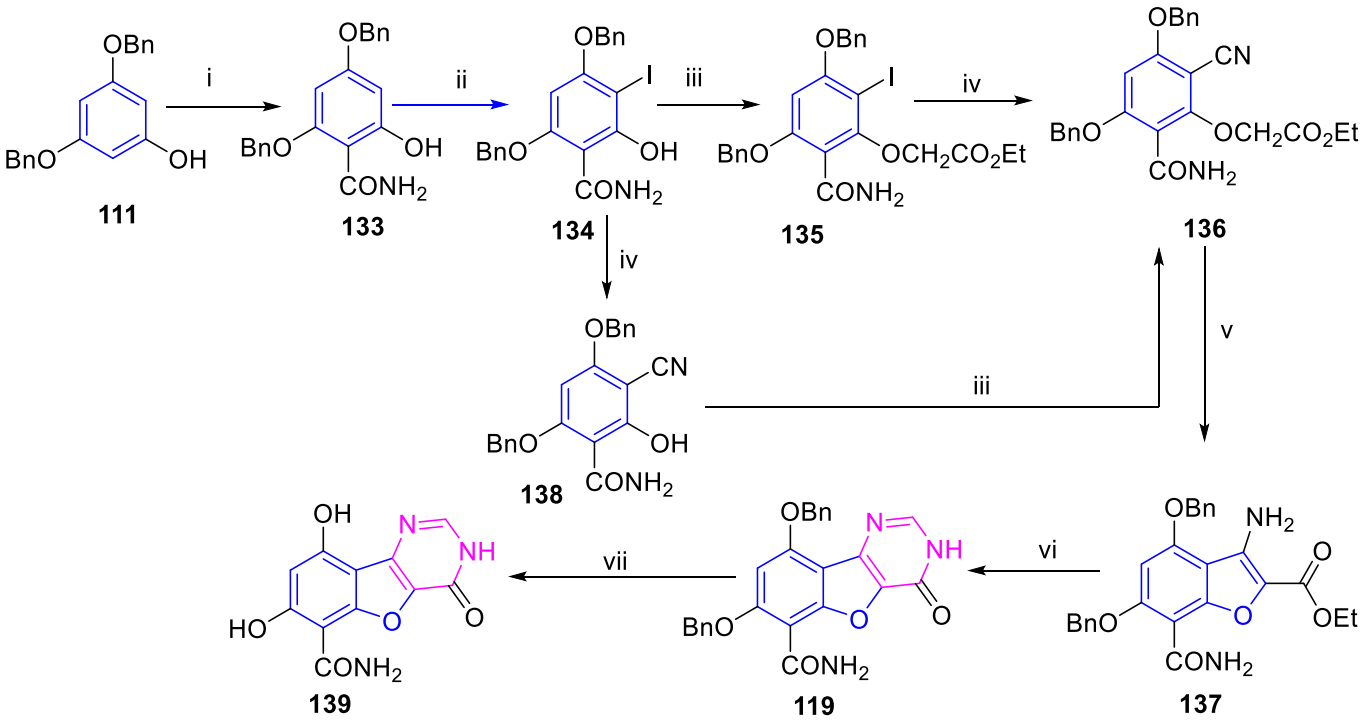
Scheme 21. Synthesis of 4-hydroxy-7,9-dimethoxybenzofuro[3,2-*d*]pyrimidine-6-carbonitrile derivative (**125**).

In 2021, another published approach[60] was to incorporate the carboxamide group before the cyclization step. The direct aminocarbonylation of compound **120** using chlorosulfonylisocyanate (CSI) as the electrophilic reagent, most probably led to the formation of an *N*-chlorosulfonyl carboxamide intermediate, which subsequently underwent acidic hydrolysis to yield benzamide derivative **127**. Compound **127** was iodinated at 0 ^{o}C using NIS, that produced the iodo derivative **128**. The subsequent cyanation of compound **128** with cuprous cyanide in DMF afforded the cyano derivative **129**. *O*-alkylation of compound **129** and ethyl bromoacetate using a base resulted in ester **130**, in 90% yield. Compound **130** was cyclized by treatment with NaH to produce benzofuran derivative **131**. The same reaction sequence outlined in Scheme 21 was utilized to synthesize the carboxamide derivative **126**. The 7-methoxy group of compound **126** was demethylated by heating in pyridine hydrochloride at 200 ^{o}C under microwave-assisted conditions, yielding carboxamide **132** (Scheme 22).[67]



Scheme 22: Synthesis of benzofuro[3,2-*d*]pyrimidine-6-carboxamide derivatives **132**.

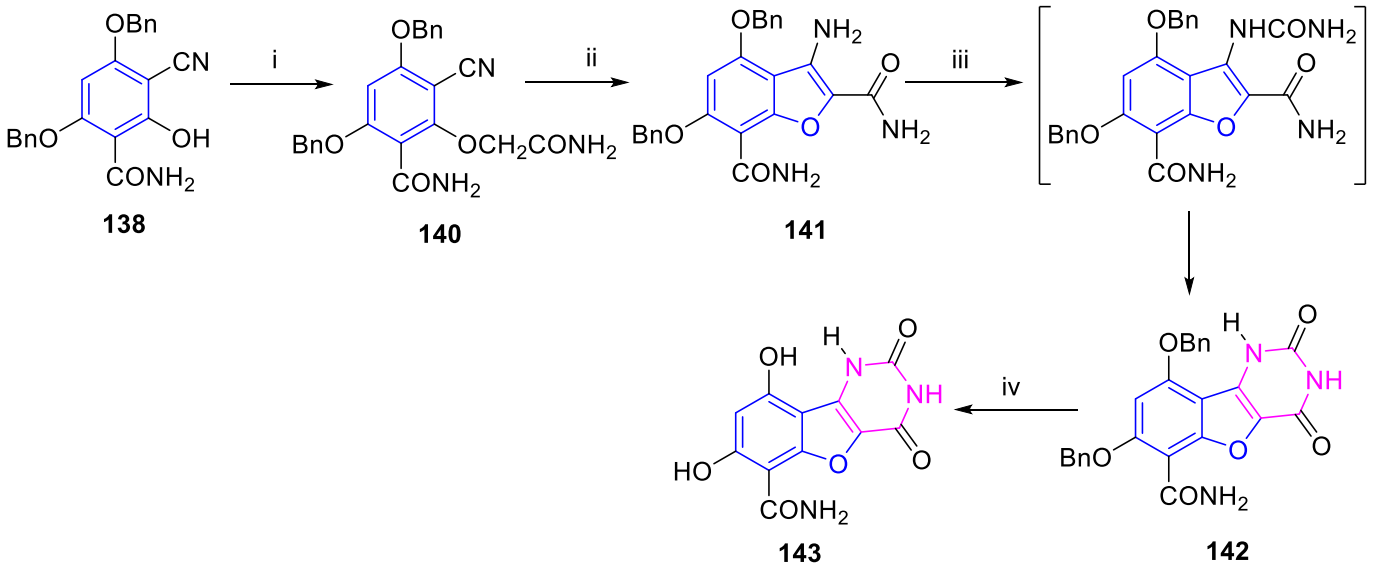
Moreover,[54] interaction of compound **111** with chlorosulfonyl isocyanate (CSI) followed by an acidic hydrolysis[55] gave carboxamide **133**. Iodination of the latter with NIS gave iodo derivative **134** which was treated with ethyl bromoacetate in DMF to yield compound **135**. Cyanation of **135** with CuCN in DMF afforded the corresponding cyano derivative **136**. Compound **136** was cyclized in DMF containing NaH, giving ethyl 3-amino-4,6-bis(benzyloxy)-7-carbamoyl-benzofuran-2-carboxylate **137**. Treatment of compound **137** with triethylorthoformate under microwave at 200 °C afforded the pyrimidinone derivative **119**. Treatment of **134** with CuCN afforded the cyano derivative **138** that was *O*-alkylated to compound **136**. Reaction of carboxamide **119** with concentrated sulfuric acid provided the 7-hydroxy derivative **139** (Scheme 23).



(i) CSI, CH_3CN, 0 °C, 10 min then HCl 1 N, rt, 10 h, 53%; (ii) NIS, CH_2Cl_2, 0 °C, 10 min, 80%; (iii) NaH, $BrCH_2CO_2Et$, DMF, rt, 24 h, 86% for **135** and 90% for **136** (iv) CuCN, DMF, 160 °C, 6 h, 20% for **136** and 73% for **138**; (v) NaH, DMF, 0 °C, 10 min, 67%; (vi) $HC(OEt)_3$, MW, 200 °C, 15 min then NH_3/MeOH 7 N, MW, 140 °C, 15 min, 62%; (vii) H_2SO_4, rt, 15 min, 53%.

Scheme 23. Synthesis of 7,9-dihydroxy-4-oxo-3,4-dihydrobenzofuro[3,2-*d*]pyrimidine-6-carboxamide **139.**

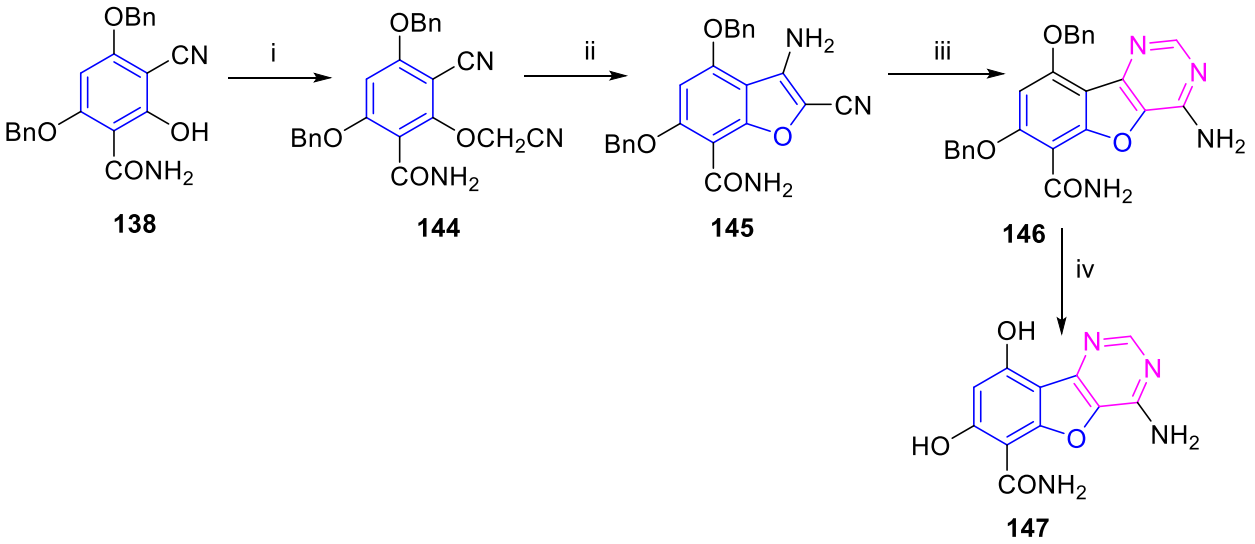
Building on previously reported work,[54] o-alkylation of benzamide derivative **138** was achieved via in situ generation of its sodium salt employing NaH as a base, followed by reaction with 2-iodoacetamide. This process afforded 2-(2-amino-2-oxoethoxy)-4,6-bis(benzyloxy)-3-cyanobenzamide **140**, analogous to the procedure described for the corresponding ester **136**, upon heating the reaction mixture to 60 °C.[34] Compound **140** was cyclized subsequently using KOH/EtOH at 60 °C to produce the benzofuran-2,7-dicarboxamide **141** in acceptable yield. Compound **141** was then converted into 7,9-bis(benzyloxy)-2,4-dioxo-1,2,3,4-tetrahydro-benzofuro[3,2-*d*]pyrimidine-6-carboxamide **142** through a postulated urea intermediate. Debenzylation of derivative **142**, achieved by treatment with concentrated sulfuric acid, yielded the corresponding 2,4-dioxo-1,2,3,4-tetrahydro[1]benzofuro[3,2-*d*]pyrimidine-6-carboxamide analogue **143** (Scheme 24).



(i) NaH, ICH_2CONH_2, DMF, 60 °C, 12 h, 69 %; (ii) KOH, EtOH, 60 °C, 30 min, 60 %; (iii) 1) KOCN, CH_3COOH, 100 °C, 1 h – 2) KOH, EtOH, 90 °C, 1 h, 56 %; (iv) H_2SO_4, rt, 5 min, 48%.

Scheme 24. Synthesis of benzofuro[3,2-*d*]pyrimidine-6-carboxamide **143.**

It was found that[54] the *O*-alkylation of 3-cyano-2-hydroxybenzamide **138** with bromoacetonitrile using K_2CO_3 in DMF at 80 °C afforded 4,6-bis(benzyloxy)-3-cyano-2-(cyanomethoxy)benzamide **144**. Treatment of **144** with NaH led to smooth cyclization, that afforded 3-amino-2-cyanobenzofuran-7-carboxamide **145**. Compound **145** was subsequently converted with ethyl orthoformate into 4-aminobenzofuro[3,2-*d*]pyrimidine-6-carboxamide **146**. Employing the previously reported debenzylation protocol to **146** furnished the corresponding unprotected analogue, 4-amino-7,9-dihydroxybenzofuro[3,2-*d*]pyrimidine-6-carboxamide **147** (Scheme 25).

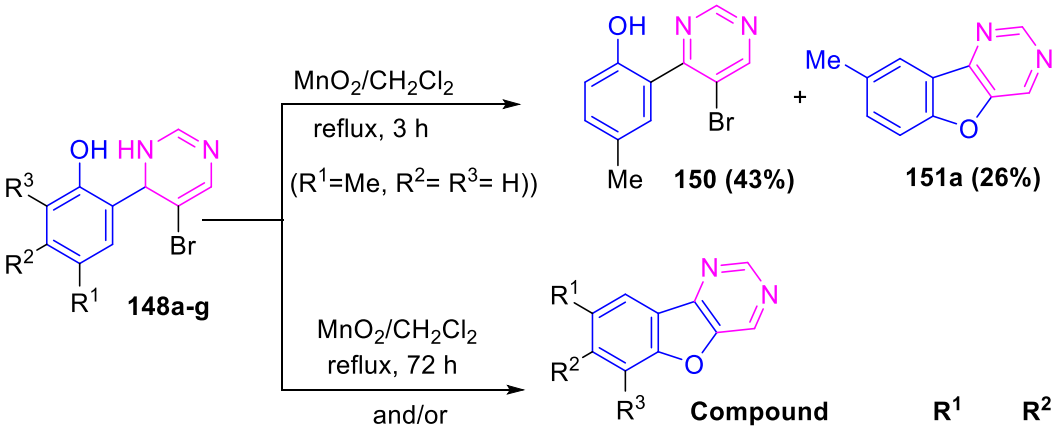


(i) $BrCH_2CN$, K_2CO_3, DMF, 80 °C, 24 h, 72%; (ii) NaH, DMF, 0 °C, 5 min, 64%; (iii) $HC(OEt)_3$, MW, 200 °C, 15 min then NH_3/MeOH 7 N, MW, 140 °C,15 min, 45%; (iv) H_2SO_4cc, rt, 5 min, 66%.

Scheme 25. Synthesis of 4-amino-7,9-dihydroxybenzofuro[3,2-*d*]pyrimidine-6-carboxamide **147**.

2.4. From 2-(5-bromo-3,4-dihydropyrimidin-4-yl)-4-methylphenol

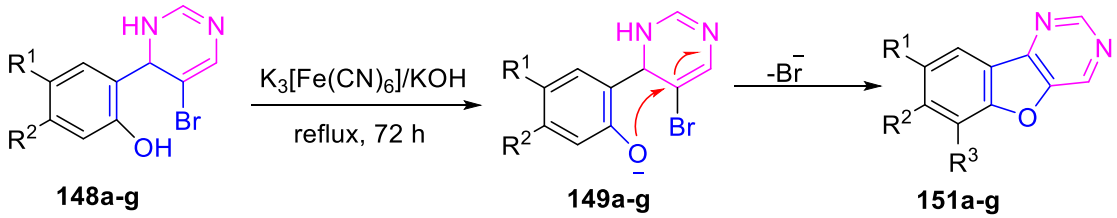
In 2023, Shcherbakov *et al.* reported[68] utilizing manganese(IV) oxide for the oxidation of the dihydropyridine ring. Refluxing 2-(5-bromo-3,4-dihydropyrimidin-4-yl)-4-methylphenol **148b** in dichloromethane for 3 h afforded a mixture of two products, which were isolated and identified as the oxidative aromatization product **150** and the intramolecular furan ring closure product, 8-methylbenzofuro[3,2-*d*]pyrimidine **151a**. Extending the reaction time to 12 h, led to the formation of benzofuro[3,2-*d*]pyrimidines **151a-c** in 63–69% yields. A similar outcome was noted when the reaction time was prolonged using aqueous potassium ferrocyanide. Conducting the reaction for 72 h afforded compounds **151a-g** (Scheme 26).



Compound	R^1	R^2	R^3	Yield (%)
148a, 151a	Me	H	H	82
148b, 151b	Et	H	H	74
148c, 151c	Pr^i	H	H	79
148d, 151d	Me	Me	H	84
148e, 151e	F	H	H	76
148f, 151f	Cl	Me	H	65
148g, 151g	Me	H	Br	68

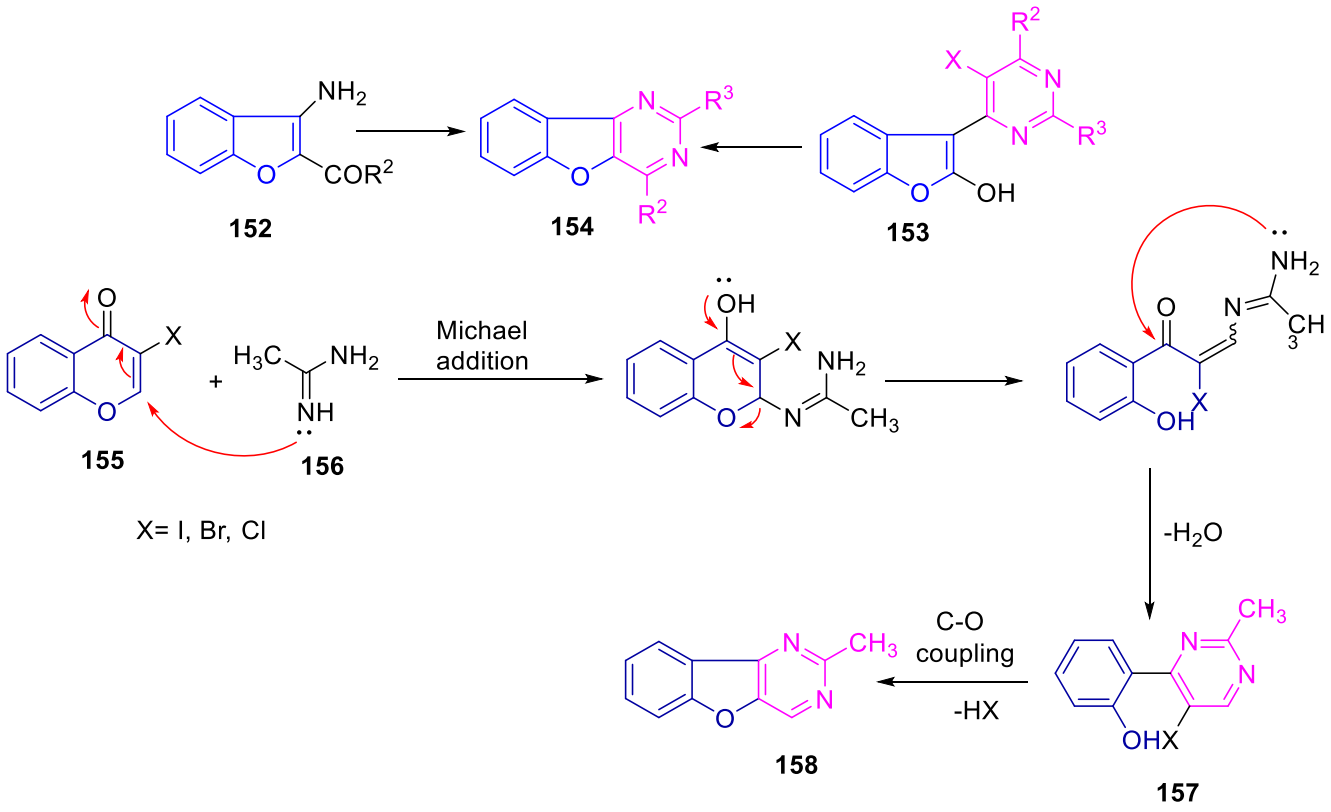
Scheme 26. Synthesis of benzofuro[3,2-*d*]pyrimidines **151a-g.**

The reaction mechanism leading to the formation of benzofuro[3,2-*d*]pyrimidines **151a-g** was proposed to proceed through initial proton abstraction from 2-(5-bromo-3,4-dihydropyrimidin-4-yl)phenols **148a-g**, yielding the corresponding 2-(5-bromopyrimidin-4-yl)phenolates **149a-g**, followed by intramolecular nucleophilic substitution of the bromine atom and then oxidation, ultimately yielding the target benzofuro[3,2-*d*]pyrimidines **151a-g** (Scheme 27).



Scheme 27. Proposed mechanism of formation of benzofuro[3,2-*d*]pyrimidines **151a-g.**

It was reported that[69] the traditional synthetic approach to benzofuro[3,2-*d*]pyrimidines (Scheme 28) involves the use of 2-carbonyl-3-aminobenzofurans **152** and related analogues, which are converted into benzofurans **153** that subsequently serve as key intermediates for the synthesis of pyrimidines **154**.[70,71] More recently, an alternative synthetic strategy has been developed in which Suzuki coupling of 2-chloropyrimidine with 2-methoxyphenylboronic acid is subsequently subjected to demethylation and intramolecular C–O bond formation.[70,72] Accordingly, interaction of 3-halogenated chromones **155** with amidines **156** through a Michael addition–elimination sequence and subsequent double intramolecular cyclization afforded phenols **157**, which further undergo C–O bond-forming cyclization to yield benzofuro[3,2-*d*]pyrimidine derivatives **158** (Scheme 28).



Scheme 28. Construction of benzofuro[3,2-*d*]pyrimidine derivatives **158**.

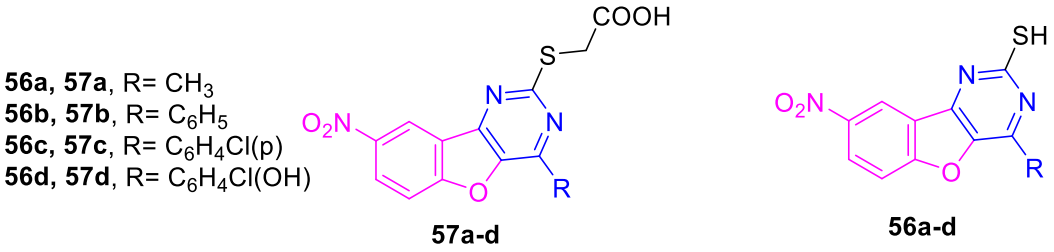
3. Biological Importance

Benzofuro[3,2-*d*]pyrimidines represent an important heterocyclic scaffold with broad biological significance**.** Their fused benzofuranpyrimidine framework provides a rigid, planar structure that interacts effectively with diverse biological targets, making them valuable in medicinal chemistry. Compounds of this class have demonstrated notable pharmacological activities, including:

3.1. Antimicrobial agents

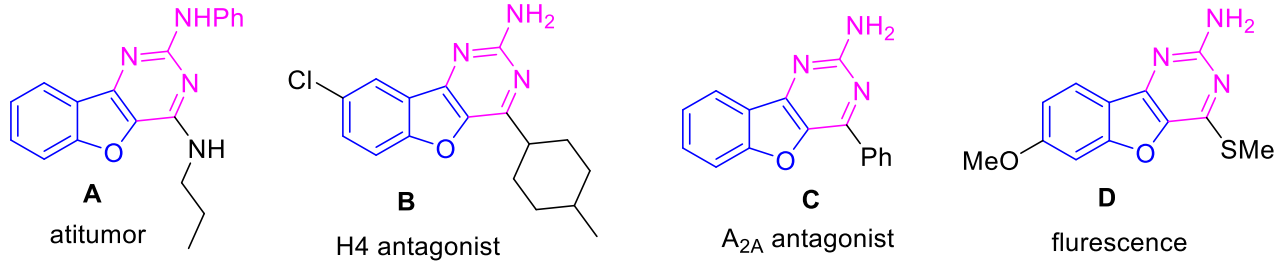
Most substituted benzofuranyl pyrimidine derivatives[19] exhibit moderate to high antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas* spp., and *Escherichia coli*, in addition to notable antifungal activity against *Candida* and *Aspergillus* species. The biological activities of compounds **56a-**

d and **57a-d** are further supported by molecular docking studies targeting staphylococcal enterotoxin C2 from *Staphylococcus aureus***.**



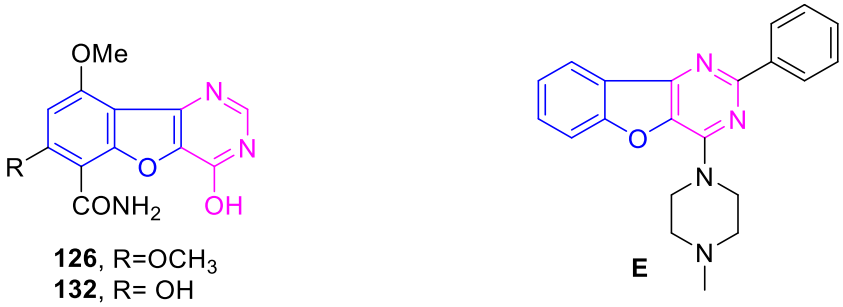
3.2. Antitumor agents and adenosine receptors antagonists

Benzofuro[3,2-*d*]pyrimidin-2-amine scaffolds[21] are widely present in diverse classes of compounds exhibiting significant biological and physicochemical properties, including compound **A** with antitumor activity,[18] compound **B** as a histamine H_4 receptor antagonist,[73] compound **C** as an adenosine (A_2A) receptor antagonist,[74] and compound **D**, which displays solid-state fluorescence properties.[53]

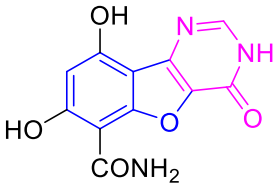


3.3. Protein Kinase inhibitors

The 4,7,9-trihydroxybenzofuro[3,2-*d*]pyrimidine-6-carboxamides **126** and **132** were reported[60] to exhibit inhibitory potency against protein kinase **C** (CaPkc1). In addition, 4-(4-methyl-1-piperazinyl)-2-phenylbenzofuro[3,2-*d*]pyrimidine (**E**)[75] demonstrated a binding energy of −8.6 kcal/mol when docked with the human thymidylate synthase (TS) protein.



It was reported[54] that cercosporamide represents a valuable structural template for the development of promising tricyclic compounds capable of restoring susceptibility in fluconazole-resistant strains through protein kinase C (PKC) inhibition. Moreover, other kinases have emerged as potential molecular targets for certain benzofuro[3,2-*d*]pyrimidine derivatives, including compounds **139**, **143**, and **147**.



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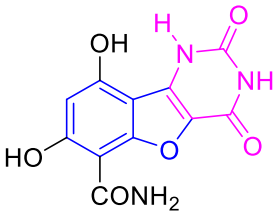

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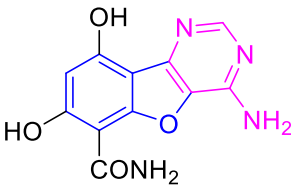
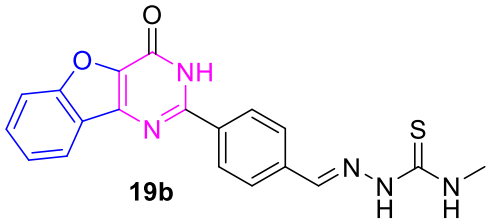


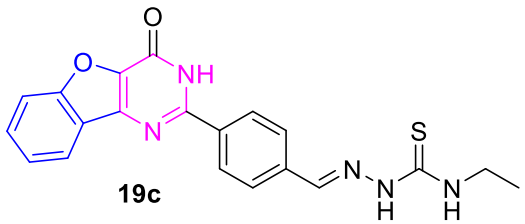
147

3.4. PARP-1 inhibitors

It has been reported that[22] the design, synthesis, and biological evaluation of a series of benzofuran[3,2-d] pyrimidine-4(3*H*)-one derivatives incorporating thiosemicarbazone moieties led to the identification of novel PARP-1 inhibitors. The benzofuran[3,2-*d*]pyrimidine-4(3*H*)-one core was employed as a privileged scaffold, into which thiosemicarbazone or related functionalities were introduced to generate a series of target compounds. Among these, compounds **19b** and **19c** exhibited superior inhibitory activity and selectivity toward PARP-1 compared with olaparib. Notably, compound **19c** showed an IC_{50} value of 0.026 μM against PARP-1 and demonstrated a PARP-2/PARP-1 selectivity of 85.19-fold relative to olaparib. Furthermore, compound **19c** displayed pronounced cytotoxicity against the evaluated cancer cell lines, with the greatest sensitivity observed in SK-OV-3 cells (IC_{50} = 4.98 μM), surpassing that of olaparib. Mechanistic studies indicated that **19c** inhibits DNA single-strand break repair, enhances DNA double-strand damage through PARP-1 inhibition, and induces cancer cell apoptosis via the mitochondrial apoptotic pathway.



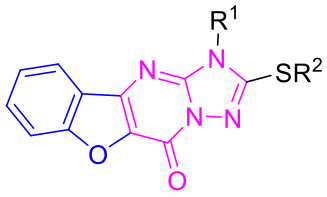
19b



19c

3.5. Dual analgesics

Compounds **42a-g** were found to exhibit promising dual analgesic[42] and antitumor activities within a single molecular framework, highlighting their potential for further development as effective chemotherapeutic agents for the management of cancer-associated pain.



42a-g

a, R^1= Ph, R^2= $CH_2CH_2CH_2CH_3$
b, R^1= Ph, R^2= $C(CH_3)_2CO_2Et$
c, R^1= Ph, R^2= $CH_2CH_2CO_2Et$
d, R^1= Ph, R^2= CH_2CO_2Et
e, R^1= Ph, R^2= $-CH_2C{\equiv}CH$
f, R^1= 4-F-Ph, R^2= $CH_2(CH_2)_4CH_3$
g, R^1= 4-F-Ph, R^2= CH_2CO_2Et

Conclusions

In conclusion, benzofuro[3,2-*d*]pyrimidine derivatives constitute an important heterocyclic scaffold that bridges synthetic and medicinal chemistry, owing to their structural versatility and broad biological relevance. Significant progress has been made in the development of efficient synthetic strategies, ranging from classical multistep approaches to modern methodologies such as intramolecular cyclization, oxidative aromatization, Michael addition–elimination cascades, and transition-metal-catalyzed reactions, enabling access to diverse substitution patterns. Biologically, these compounds have demonstrated a wide spectrum of activities, including anticancer, antimicrobial, antifungal, analgesic, and kinase-inhibitory effects, with several derivatives showing promising interactions with clinically relevant molecular targets. Despite these advances, further studies focusing on sustainable synthesis, detailed mechanistic insights, and comprehensive in vivo and pharmacokinetic evaluations are essential. Overall, benzofuro[3,2-*d*]pyrimidines remain a promising platform for the development of novel therapeutic agents and warrant continued investigation.

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