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Synthesis of Purine Derivatives as Scaffolds for a Diversity of Biological Activities

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Abstract: The purine ring is undoubtedly among the most ubiquitous of all the heterocyclic compounds. This arises not only from the universal occurrence of adenine and guanine in DNA and RNA and of additional modified derivatives in the various tRNAs but also from the subsidiary uses of the ring system in a great number of biochemical systems. The development of new methods for metal-mediated coupling with aryl or heteroaryl halide substrates has expanded the range of synthetically accessible arylpurine derivatives. Aryl boronic acids have proved to be extremely available reagents for metal-mediated C-C and C-N coupling reactions. Coupling reactions resulting in C-C bond formation are catalyzed by palladium and nickel catalysts at positions C2, C6 and C8. The reactivity at C6 position has been demonstrated using fluoro-, chloro-, bromo-, iodo-, sulfanyl, sulfonyl, sulfonyloxy- and azole-substrates. The ease of obtaining the activated purine substrates is an important factor when selecting appropriate coupling conditions. Copper-mediated *N*-arylations occur at positions *N*7 and *N*9. These methods are also applicable using solid-supported purine substrates and provide convenient access to structurally unique derivatives with applications in drug discovery. Continuing advances in this field can be expected to result through improved mechanistic understanding and the development of new catalysts and ligands.

Keywords: Alkyl-purine derivatives, aryl-purine derivatives, cross-coupling, ferrocene-modified purines, fluorinated compounds, microwave, nucleosides, solid-phase synthesis.

1. INTRODUCTION

The purine ring system is undoubtedly among the most ubiquitous of all heterocyclic compounds. A great number of enzymes use purine bases. Furthermore, purines are also constituents of several cofactors (e.g., NADH, FAD, AcCoA, SAM, ATP, etc.) used by many important classes of enzymes (oxidoreductases, transferases, ligases, etc.). Therefore, most enzymes using nucleotide cofactors contain a purine (usually adenine) binding site. In recent years, modified structures both of natural and synthetic origin have been a rich source of biologically active materials. Purine bases, nucleosides and nucleotides have been the subject of extensive research and their structural modifications led to the discovery of thousands of biologically active compounds including many clinically used drugs. For instance, purine bases and their nucleosides constitute an important group of antineoplastic [1,2], antibiotic [3], and antitubercular agents [4]. Moreover, these compounds have found a wide application as adenosine receptor ligands [5,6], antiparasitic agents [7], cyclin-dependent kinase inhibitors [8], antitumour [9], and antiviral compounds [10]. There are excellent reviews on purine derivatives, such as those of Rosemeyer [11], Hocek [12], and Legraverend [13]. Very recently, we have reviewed the mechanistic aspects of the thermal *N*9 → *N*7 isomerization of (6-substituted)-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purines in solution [14]. The number of publications on purines is endless. It is difficult to write a comprehensive review on a subject as broad as this. Publications that appeared after 1999 are included in this review. We will try to concentrate on aspects that have not been dealt with in previous reviews. We apologize to all colleagues who have made significant contributions to the matter of this article and whose work is not cited here.

Three main synthetic approaches leading to purine derivatives are described in the literature (Fig. (**1**)): a) syntheses that start from

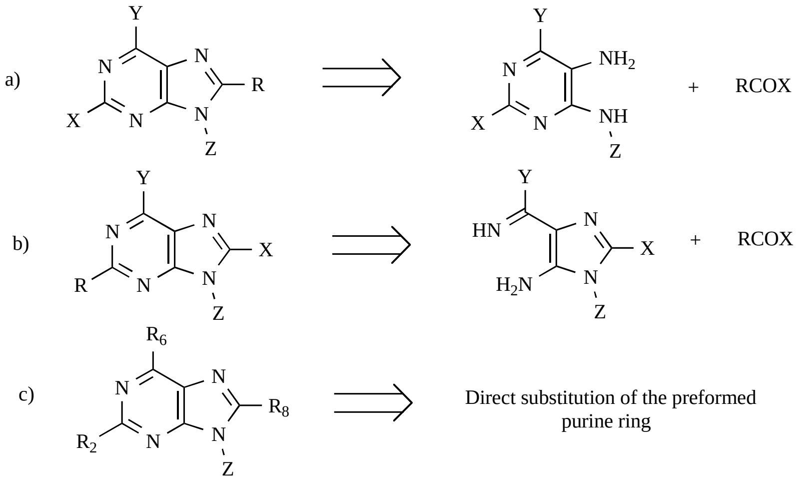

Fig. (1). Synthetic approaches to purine derivatives.

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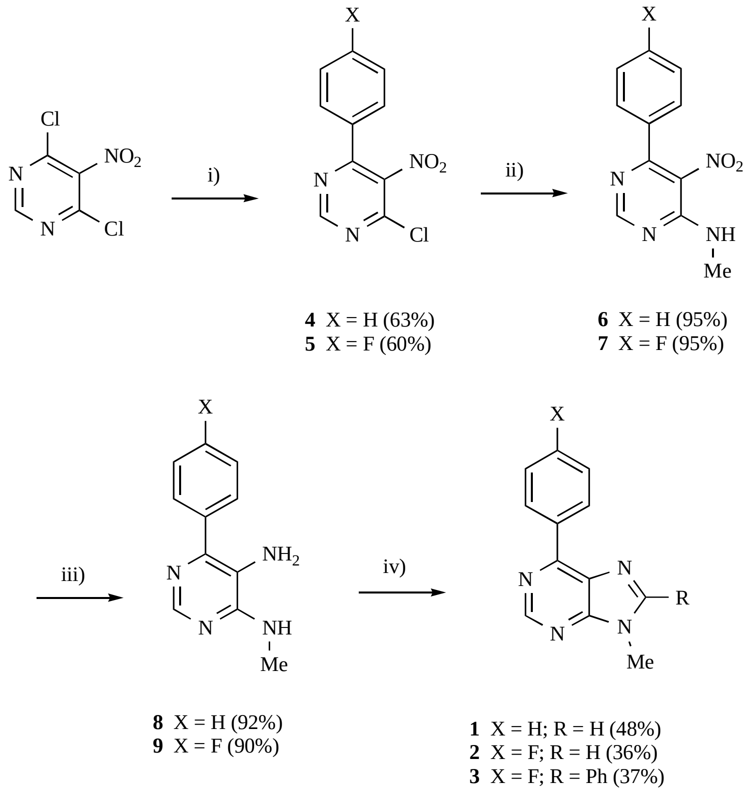
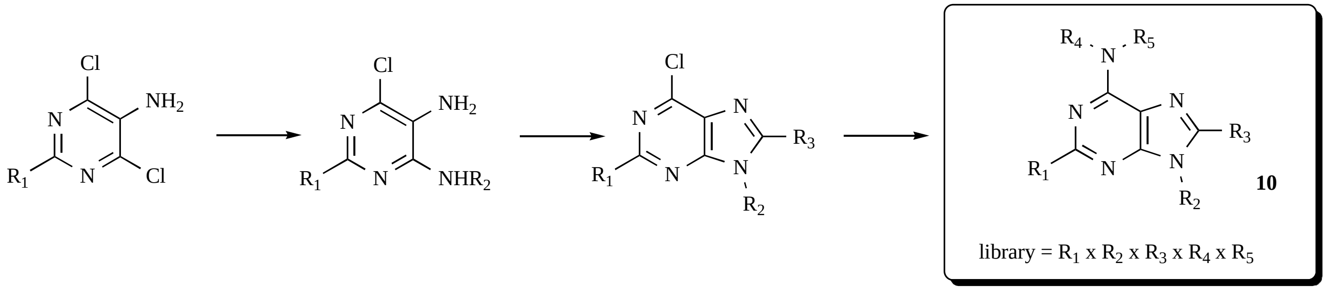


Scheme 1. *Reagents and conditions*: i) (*p*)-X-C_6H_4-$B(OH)_2$, Na_2CO_3, toluene, $Pd(PPh_3)_4$, 90 ºC; ii) $MeNH_2$ 40% in H_2O, reflux; iii) Pd/C, H_2, 4 bars, rt; iv) R-$C(OEt)_3$, EtOH, TsOH, reflux.



Scheme 2. Synthetic strategy of a 135-membered library of fully substituted purine analogues.

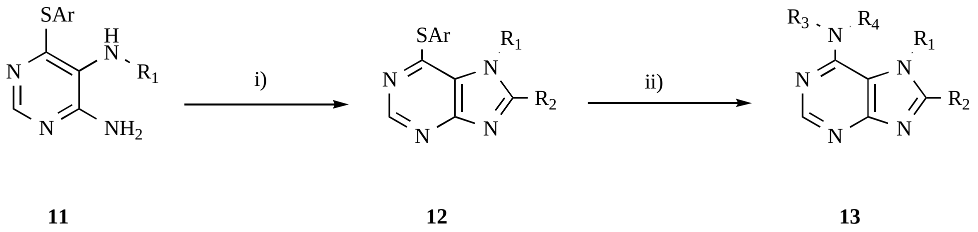
a substituted pyrimidine nucleus followed by imidazole ring construction [15,16]; b) preparations that start from the corresponding imidazole ring, and then construction of the pyrimidine nucleus (Fig. (**1**)) [17-20]; c) direct substitution of the preformed purine ring [21-25].

2. SYNTHESES STARTING FROM A SUBSTITUTED PYRIMIDINE NUCLEUS FOLLOWED BY THE IMIDAZOLE RING BUILDING

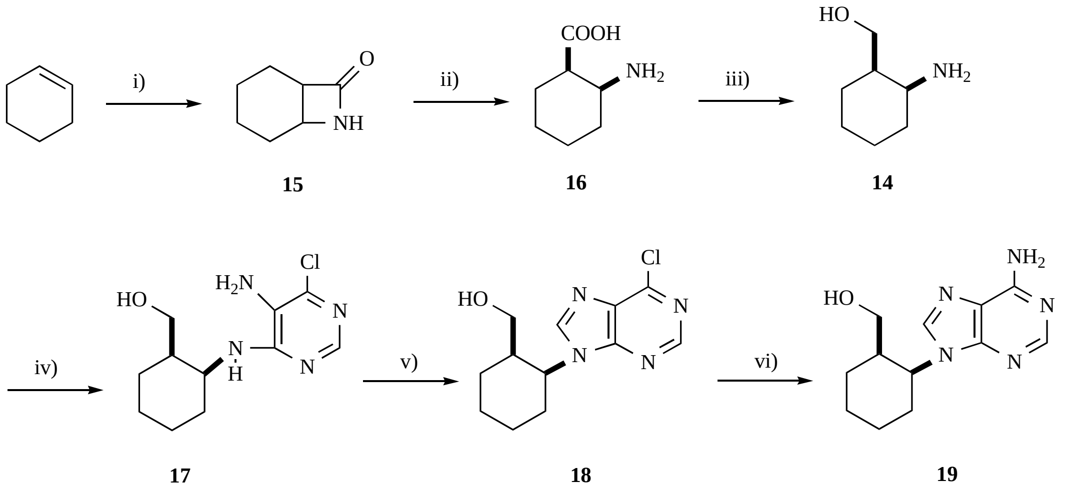
Laufer *et al.* [15] reported the syntheses of the 6-phenyl-substituted purines **1** and **2**, and the 6,8-diphenyl-substituted purine **3** as shown in Scheme **1**. Suzuki coupling of benzeneboronic acid with 4,6-dichloro-5-nitropyrimidine [26] provided the arylpyrimidines **4** or **5**, which were treated with methylamine to deliver the 4-amino-5-nitro compounds **6** or **7**. Subsequent catalytic reduction of the 5-nitro group afforded the diamines **8** or **9**, which permitted the acid-catalyzed ring closure with the suitable ortho esters (ethyl orthoformate and ethyl orthobenzoate).

Although many methodologies have been developed for the synthesis of various trisubstituted purines, few examples exist for the synthesis of fully substituted purine analogues. Bai *et al.* [27] proposed an efficient strategy that leads to a 135-membered library in good yields and high purity of fully substituted purine analogues **10** (Scheme **2**).

*N*9-Substituted purine derivatives are among the most commonly studied compounds, which is not too surprising since natural purine nucleosides are *N*9-substituted. Despite the abundance of work reported on purine derivatives, few studies report libraries of *N*7-substituted purine derivatives [28]. Traditionally, *N*7-substituted purines are made via alkylation reactions of purines, which often produce both *N*7- and *N*9-substituted purines as a mixture of regioisomers [29]. It has been recently reported that the cyclization reaction of 5-alkylamino-4-amino-6-arylthiopyrimidine **11** leads to the *N*7-substituted purines **12** regiospecifically, and the 6-arylthio group allows further elaboration of the *N*7-substituted purine system to produce a 40-member library of 6,7,8-substituted purines (Scheme **3**) [30].



Scheme 3. Synthetic strategy of a 40-membered library of 6,7,8-trisubstituted purines. *Reagents*: i) R_2COOH or R_2CHO; ii) 1. *m*-CPBA; 2. R_3R_4NH.



Scheme 4. *Reagents and conditions*: i) CSI, -78 ºC, 43%; ii) HCl, 12 M, rt, 99%; iii) $LiAlH_4$, THF, reflux, 72 h, 55%; iv) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux, 24 h, 71%; v) $CH(OEt)_3$, 12 M HCl, reflux, 12 h, 71%; vi) NH_4OH, reflux, 4 h, 99%.

The final step shown in Scheme **3** is the introduction of two additional diversity points, R_3 and R_4, to the *N*7-substituted purines **12**. The activation of a sulphide group at the 6-position of a purine toward nucleophilic substitutions has often been reported and applied to the preparation of purine libraries using either solution-phase [31] or solid-phase methodologies [32]. Therefore, *m*-CPBA oxidation of compounds **12** gives their corresponding 6-phenylsulfonyl purines in excellent yields and are sufficiently pure for the next reaction without further purification. Substitution of the 6-phenylsulfonyl group by various amines is achieved using an excess of primary or secondary amines in *n*-butanol at 100 ºC in sealed tubes to give the final target *N*7-substituted purines **13** (Scheme **3**).

Viña *et al.* [33] have reported novel cyclohexyl nucleosides, in which the purine base and the hydroxymethyl group have a 1,2-relationship. Following the route shown in Scheme **4**, β-amino acid **16** was obtained by a [2 + 2] cycloaddition between cyclohexene and chlorosulfonyl isocyanate (CSI) followed by hydrolysis of the resulting lactam **15**. The β-amino acid **16** was reduced with $LiAlH_4$ to afford **14** [34]. A sequence of three steps produces the target molecule **19**: the condensation of **14** with 5-amino-4,6-dichloropyrimidine gives the substituted pyrimidine **17**, the reaction of this product with ethyl orthoformate in an acidic medium produces **18** and finally, nucleophilic exchange of the 6-chloro atom affords the amino group (Scheme **4**).

3. SYNTHESIS STARTING FROM A SUBSTITUTED IMIDAZOLE NUCLEUS FOLLOWED BY THE PYRIMIDINE BUILDING

As the purine ring system is a fusion of two aromatic heterocycles, pyrimidine and imidazole, another logical starting point for the preparation of the bicyclic system is an appropriately substituted imidazole from which the second ring can be constructed by a cyclization process. 9-Phenyl-9*H*-purin-6-amines **20** and **21** have been recently prepared [35] via a multistep procedure from ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **22**, by treatment with a phenylamine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of aniline hydrochloride to give the corresponding formamidines **23** and **24** [36,37]. Cyclization of the formamidines in the presence of an aqueous KOH solution provides the corresponding 5-amino-1-phenyl-1*H*-imidazole-4-carbonitriles **25** and **26** [38], which are readily converted to **20** and **21** by treatment with ethyl orthoformate and acetic anhydride (Ac_2O) followed by reaction with ammonia (Scheme **5**).

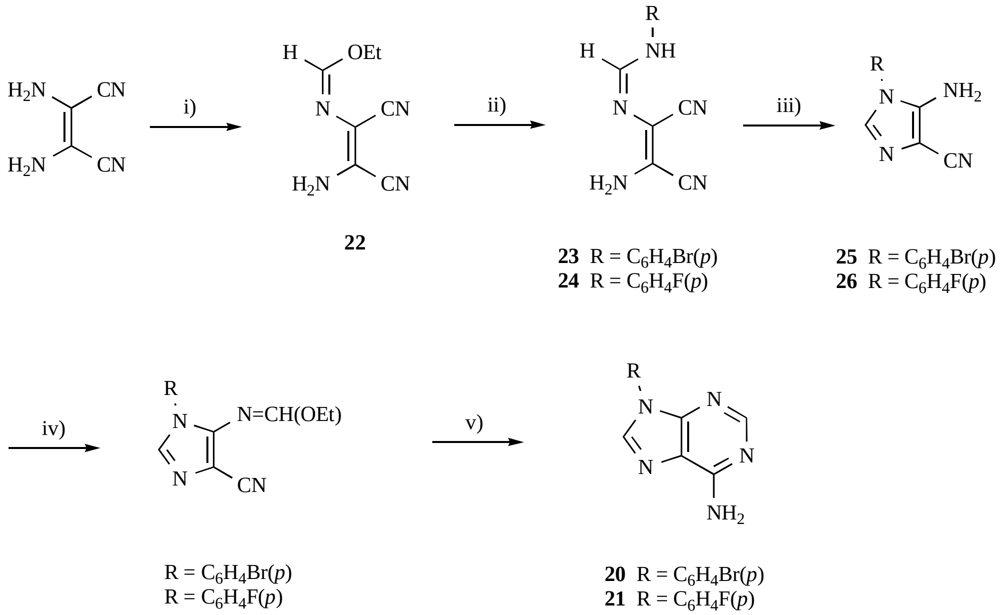
Preparations of the purine ring from various imidazoles [39-45] are available.

4. SYNTHESIS BY DIRECT SUBSTITUTION OF THE PREFORMED PURINE RING

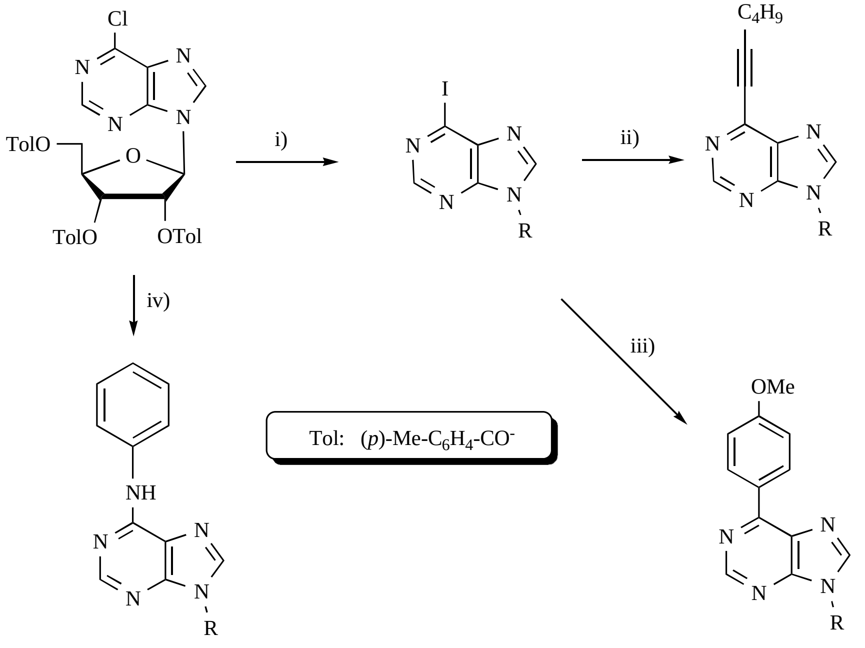
4.1. Funtionalization at 6-position

Advances in the synthesis of C6 modified purines have employed Sonogashira [46,47], Suzuki-Miyaura [48,49], and S_NAr [50] reactions, and the area of organometallic cross-coupling with purine and purine nucleoside derivatives has been reviewed [12].

Highly efficient transformations of 6-chloropurine nucleoside and 2'-deoxynucleoside derivatives into their 6-iodo analogues via a trifluoroacetic (TFA)-catalyzed aromatic Finkelstein reaction at temperatures below -40 ºC in methyl ethyl ketone (MEK) have been reported [51]. Robins *et al.* state that 6-iodo purines are efficient substrates for S_NAr, Sonogashira, and Suzuki-Miyaura reactions, in contrast with the 6-chloro analogues, and give high yields of C-C and C-N coupled products (Scheme **6**) [51].



Scheme 5. *Reagents and conditions*: i) $HC(OEt)_3$, dioxane, Δ; ii) RNH_2, $PhNH_3^+Cl^-$, rt, 3-4 h; iii) 1 M KOH (aq), rt; iv) $HC(OEt)_3$, Ac_2O, Δ; v) NH_3, MeOH, Δ (67-83%).

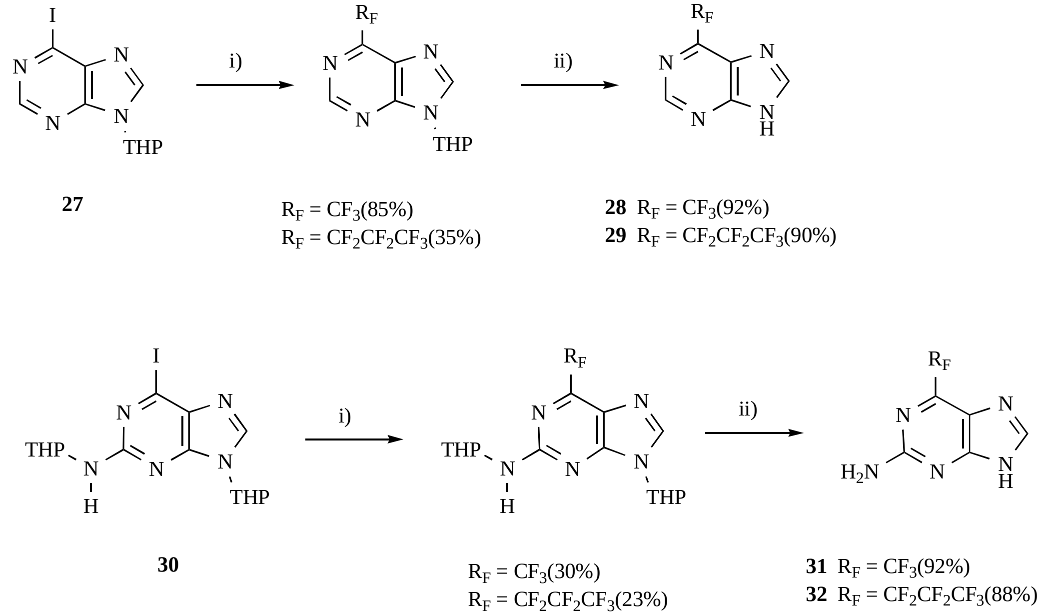


R = 2',3',5'-tri-*O*-(4-methylbenzoyl)-β-D-ribofuranosyl

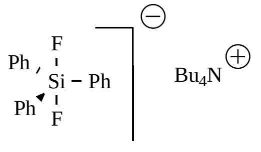
Scheme 6. *Reagents and conditions*: i) NaI, TFA, MEK, -50 to -40 ºC (73%); ii) $C_4H_9C{\equiv}CH$, $Pd(PPh_3)_4$, CuI (92%); iii) (*p*)-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3 (83%); iv) $PhNH_2$ (80%).

Keeping in mind that fluorinated analogues of natural compounds exert interesting biological activities [52], Hocek and Holý have described a CuI/KF-mediated perfluoroalkylation reaction of various 9-substituted 6-iodopurines **27** and **30** with trimethyl (trifluoromethyl)silane or heptafluoropropyl(trimethyl)silane to prepare the corresponding 6-(trifluoromethyl)- and 6-(heptafluoropropyl)purine derivatives (**28** and **29** and **31** and **32**, respectively) (Scheme **7**) [53].

Tetrabutylammonium triphenyldifluorosilicate **33** {TBAT, (Fig. (**2**))} has been found to be a useful reagent for the conversion of 6-chloropurine nucleosides to 6-fluoro purine derivatives. The 6-chloropurine nucleosides were reacted with trimethylamine to form quaternary trimethylammonium salts which were treated *in situ* with TBAT in DMF to effect conversion to the 6-fluoro derivatives in yields of 59-72% [54]. TBAT is an easily handled crystalline solid that has several advantages over tetrabutylammonium fluoride (TBAF) as a fluoride source; it is anhydrous, non-hygroscopic, soluble in most commonly used organic solvents, and less basic than TBAF [55].



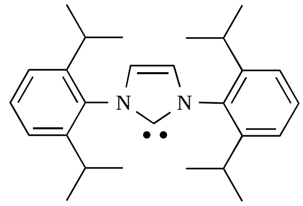
Scheme 7. Synthesis of 6-perfluoroalkyl)purines. *Reagents and conditions*: i) R_FSiMe_3, KF, CuI, DMF, NMP, 60 ºC, 20 h; ii) Dowex 50 (H^+), H_2O, reflux, 1 h.



TBAT, **33**

Fig. (2). Structure of tetrabutylammonium triphenyldifluorosilicate (TBAT).

Robins and Liu [56, 57] have reported reactions involving the use of nickel- and palladium-based systems with the carbene 1,3-bis(2,6-di*iso*propylphenyl)imidazolin-2-ylidene **34** {IPr, [Fig. (**3**)]}.

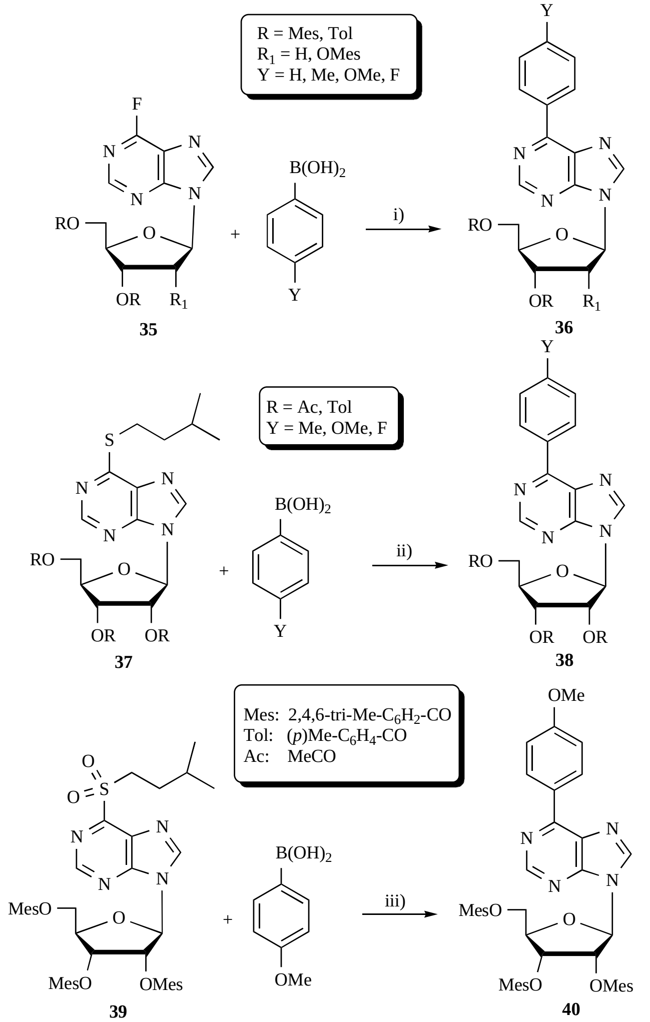


IPr (**34**)

Fig. (3). Structure of the imidazolium-carbene ligand IPr.

This imidazolium-carbene ligand catalyzes efficiently Suzuki cross-couplings of arylboronic acids and the 6-fluoropurine- **35**, the 6-[(3-methylbutyl)sulfanyl]- **37**, and the 6-[(3-methylbutyl) sulfonyl]purine nucleoside derivative **39** to give the corresponding 6-arylpurines **36**, **38** and **40**, respectively (Scheme **8**) [56].

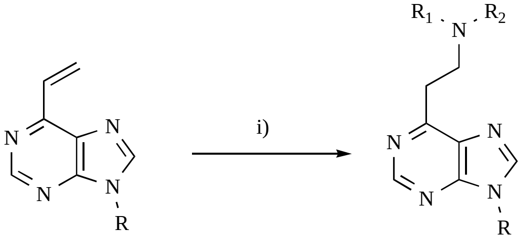
S_NAr reactions with 6-(fluoro, chloro, bromo, iodo, and alkylsulfonyl)purine nucleosides and nitrogen, oxygen, and sulfur nucleophiles have been studied [57]. There is no global general rule that can be deduced. Nevertheless, the authors state the following: a) 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (compound **35**, R = Mes, R_1 = OMes, Scheme **8**) is the most reactive substrate for S_NAr reactions among the four 6-halopurine analogues with an aliphatic amine, an arylamine plus TFA, and with oxygen and sulfur nucleophiles; b) however, 6-iodo-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine



Scheme 8. *Reagents and conditions*: i) 10 mol% $Ni(COD)_2$, 10 mol% IPr·HCl, K_3PO_4/THF/60 ºC, 3h (60-84%); ii) 10 mol% $Pd(OAc)_2$, 10 mol% IPr·HCl, K_3PO_4/toluene/90 ºC, 8h (69-78%); iii) 10 mol% $Pd(OAc)_2$, 10 mol% IPr·HCl, K_3PO_4/THF/60 ºC, 8h (81%).

[60] is the best substrate for the aromatic amine (autocatalysis by generated HI) in the absence of an external acid catalyst; and c) 6-(3-methylbutylsulfonyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine **39** (Scheme **8**) is even more reactive than its 6-iodopurine analogue with oxygen and sulfur nucleophiles [56].

Purine is an electron-withdrawing substituent and, thus, vinylpurines easily undergo conjugate additions. Hocek *et al.* [58] first studied conjugate additions to 9-benzyl-6-vinylpurine **41** and 6-vinyl-9-(tetrahydropyran-2-yl)purine **42**, both of which are easily available [59] from the corresponding 6-chloropurines by a Stille cross-coupling with vinyl(tributyl)tin. A series of experiments with several amines was performed (Scheme **9**).



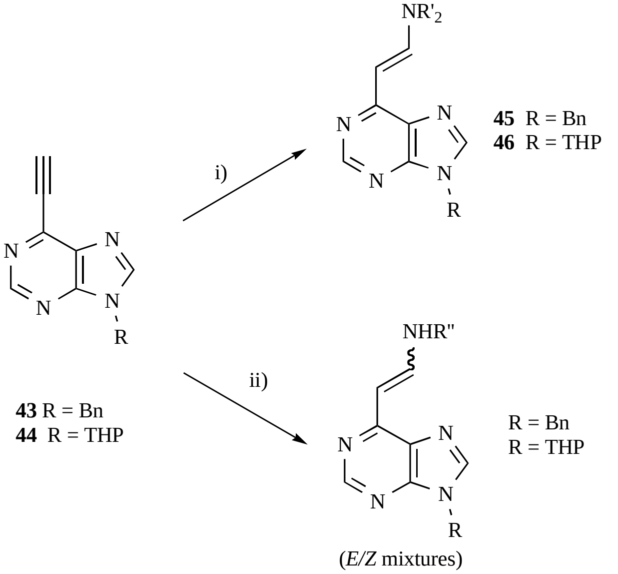
41 R = Bn
42 R = THP

R = Bn
R = THP

Scheme 9. *Reagents and conditions*: i) R_1R_2NH ($-NR_1R_2$ = piperidine, morpholine, dibutylamine, diethylamine, dimethylamine, cyclohexylamine, benzylamine, methylamine, NH_3, THF or EtOH, rt (40-94%).

Analogous additions to 6-ethynylpurines **43** and **44** [58], which are easily available [60] by the Sonogashira cross-coupling of the corresponding 6-chloropurines and TMS-acetylene, followed by desilylation by methanolic ammonia. Secondary amines react slowly to give (*E*)-configured 9-benzylated enamines **45** and 9-THP-substituted enamines **46** in lower yields than **45** (Scheme **10**).

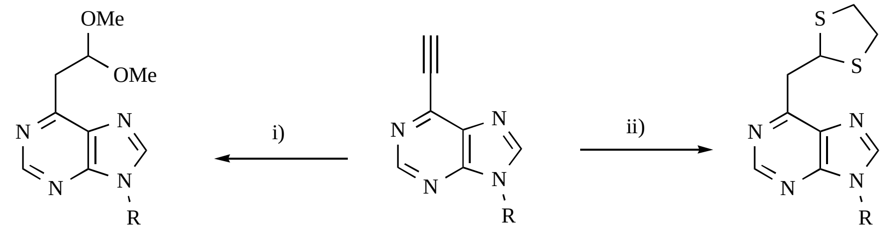
On the other hand, the addition of two equivalents of alcoholates and thiolates to 9-substituted 6-ethynylpurines gives acetals **47** and **48** and dithioacetals **49** and **50** (Scheme **11**) [58-60].



Scheme 10. *Reagents and conditions*: i) R'_2NH ($-NR'_2$ = piperidine, morpholine, dibutylamine, diethylamine, dimethylamine) (45-97%); ii) $R''NH_2$ ($-NHR''$ = cyclohexylamine, benzylamine, methylamine) (76-94%).

Phosphonated azaheterocycles are an important class of compounds with high biological potential as conformationally restricted bioisosteres of amino acids [61]. Very recently, heterocycles bearing the phosphorus functionalities have been synthesized, which would serve in further functionalizations to produce molecular diversity and produce biologically active compounds [62].

Guo *et al.* [63] have reported C6-phosphonated purine nucleosides in excellent yields by the simple and catalyst-free S_NAr-Arbuzov reaction of trialkyl phosphate with 6-chloropurine nucleosides, including non-sugar carbon nucleosides (Scheme **12**). Microwave irradiation leads to a dramatic reduction of reaction times and substantial increase of the yields.

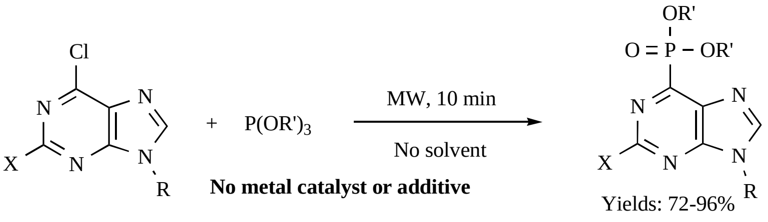


47 R = Bn (86%)
48 R = THP (91%)

43 R = Bn
44 R = THP

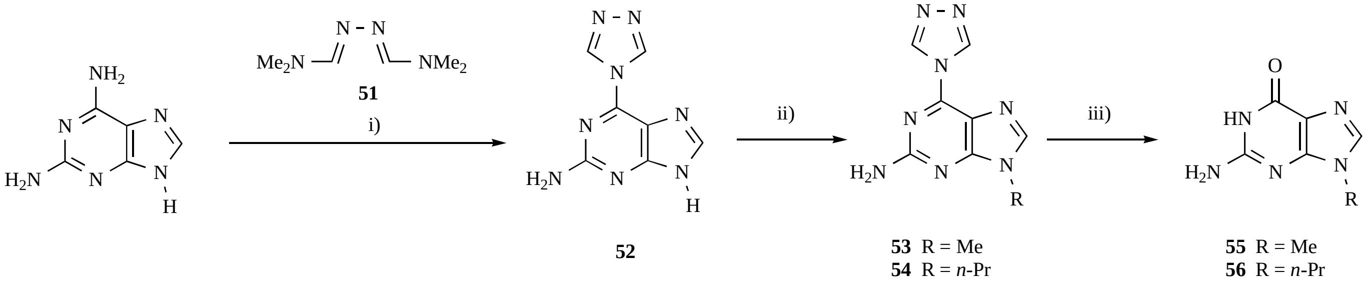
49 R = Bn (85%)
50 R = THP (83%)

Scheme 11. Addition of *O*- and *S*-nucleophiles to ethynylpurines **43** and **44**. *Reagents and conditions*: i) NaOMe, MeOH; ii) 1,2-ethanedithiol, NaH, THF.

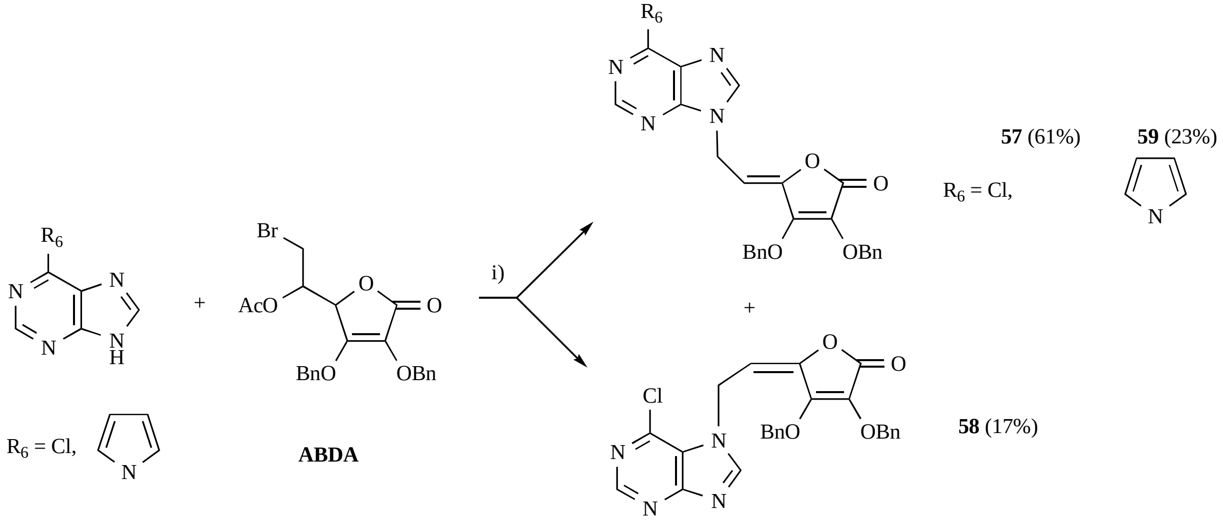


X = Cl, H, NH_2
R = sugar and non-sugar carbon substituents
R' = Et, *i*-Pr

Scheme 12. Synthesis of C6-phosphonated purine nucleosides under microwave irradiation by SNAr-Arbuzov reaction.



Scheme 13. *Reagents and conditions*: i) DMF, 180 ºC, 18 h (85%); ii) methyliodide or 3-bromopropane, NaH, DMF, rt, 1 h (78% with MeI, and 93% with BrC$_3$H$_7$; iii) 1 N NaOH, 100 ºC (67% of **55**, and 85% of **56**).



Scheme 14. *Reagents and conditions*: i) Et$_3$N/dry DMF, 70 ºC, 11 h.

4.2. Functionalization at *N*7 and *N*9 Positions

2-Amino-6-(1,2,4-triazol-4-yl)purine **52**, prepared from 2,6-diaminopurine and 1,2-bis[(dimethylamino)methylene]hydrazine **51**, was regioselectively alkylated at position 9 to give **53** and **54**, and the subsequent alkaline hydrolysis afforded 9-alkylguanines **55** and **56** in high yield (Scheme **13**) [64]. The selective alkylation at 9-position of 2-amino-6-(1,2,4-triazol-4-yl)purine **52** may be due to steric hindrance introduced by the triazole that precludes alkylation at 7-position [64].

The regioselective *N*9 arylation of purines employing arylboronic acids in the presence of Cu(II) acetate has been reported [65]. Later on, 6-(substituted-imidazol-1-yl)purines were used as versatile substrates for their regiospecific alkylation and glycosylation at *N*9 [66].

L-Ascorbic acid and its derivatives have been of manifold biological and pharmacological interest. Thus, some derivatives of L-ascorbic acid, e.g., 6-bromo-, 6-amino-, and *N*,*N*-dimethyl-6-amino-6-deoxy-L-ascorbic acid, have been found to inhibit the growth of certain human malignant tumour cell lines: cervical carcinoma (HeLa), laryngeal carcinoma (Hep2), and pancreatic carcinoma (MiaPaCa2) [67]. Searching for pharmacologically active molecules, Raić-Malić *et al.* [68] prepared new types of molecules containing purine moieties connected via an acyclic chain to 2,3-dibenzyl-4,5-didehydro-5,6-dideoxy-L-ascorbic acid.

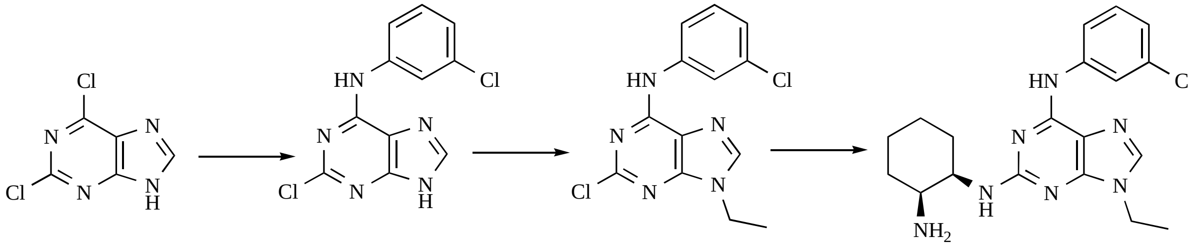
Compounds **57**-**59** are obtained by the direct condensation of 6-chloropurine with 5-acetyl-6-bromo-2,3-dibenzyl-L-ascorbic acid (ABDA) [69,70] using a modified procedure for the preparation of purine and pyrimidine trihydroxyacyclonucleosides [71] (Scheme **14**). Reaction affords both *N*9 (**57**) and *N*7 (**58**) regioisomers in a ratio of 4:1. In contrast, reaction of 6-(*N*-pyrrolyl)purine with ABDA gives only the *N*9 isomer (**59**).

Compound **59** showed the most selective inhibitory activity against human Molt4/C8 and CEM/0 cell proliferation as compared to normal fibroblast Hef522 cell proliferation [68].

4.3. Synthesis of Disubstituted Purines

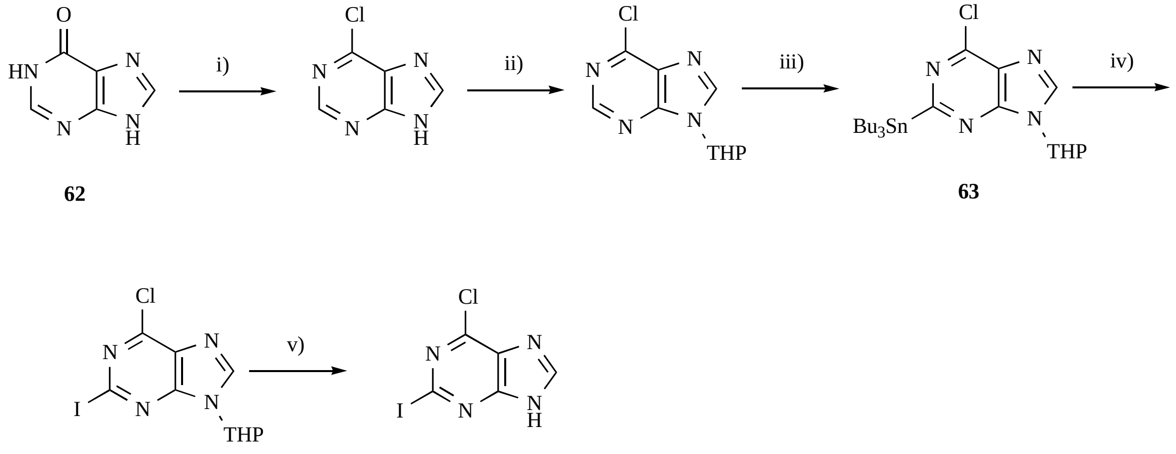
4.3.1. 2,6-Disubstituted Purines

The introduction of substituents on the 2- and 6-position of purines is generally achieved via the nucleophilic displacement of 2,6-dihalogenated purine derivatives. The introduction of a nitro group at the 2-position by nitration with tetrabutylammonium nitrate (TBAN) and trifluoroacetic anhydride (TFAA) has been described [72]. The 2-nitro group greatly enhances the electrophilicity of the purine C6 position. The introduction of a trifluoromethyl group on purine C6 is greatly facilitated by the C2 nitro substituent. The reaction can be achieved at -20 ºC, while other protocols need highly elevated temperature and catalysts [53]. The functionalization of C2 with nucleophiles is highly enhanced by the C6 CF$_3$-substituent. The introduction of nucleophiles can proceed at temperatures varying from 0 º to 40 ºC [73]. The *N*9 position is functionalized with different alkyl or arylalkyl groups via standard alkylation or Mitsunobu conditions [73]. After the introduction of a halogen (I, Br) substituent at position C8 of the purine system, these compounds can be further functionalized by adding nucleophiles. Palladium-catalyzed coupling procedures (Sonogashira, Stille, Suzuki, Buchwald-Hartwig) allow for a broad range of carbon and



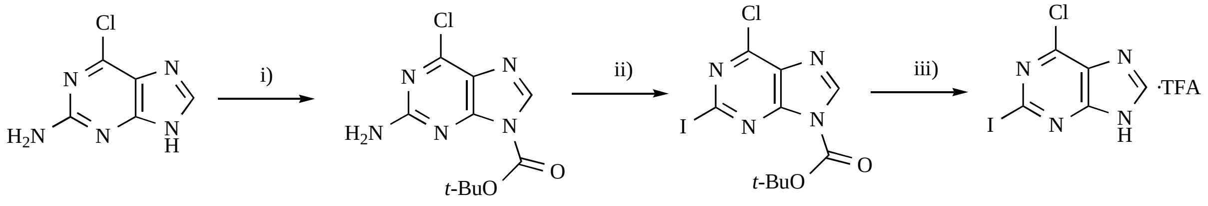
100% **60** (78-85%) **61** (yield not indicated in the original paper)

Scheme 15. General synthesis of 2,6,9-trisubstituted purine derivatives.



62 **63** **64** **65**

Scheme 16. *Reagents and conditions*: i) $POCl_3$, DMA, 120 ºC (86%); ii) dihydropyrane, cat. TsOH, THF, 80 ºC (68%); iii) LiTMP, THF, -78 ºC, then Bu_3SnCl (100%); iv) I_2, THF (95%); v) 0.1 equiv. $CuCl_2$, aqueous EtOH (98%).



65·TFA

Scheme 17. *Reagents and conditions*: i) Boc_2O, K_2CO_3, DMF (87%); ii) CH_2I_2, isoamyl nitrite, 4 Å molecular sieves, THF, 50 ºC (37%); iii) TFA, CH_2Cl_2 (96%).

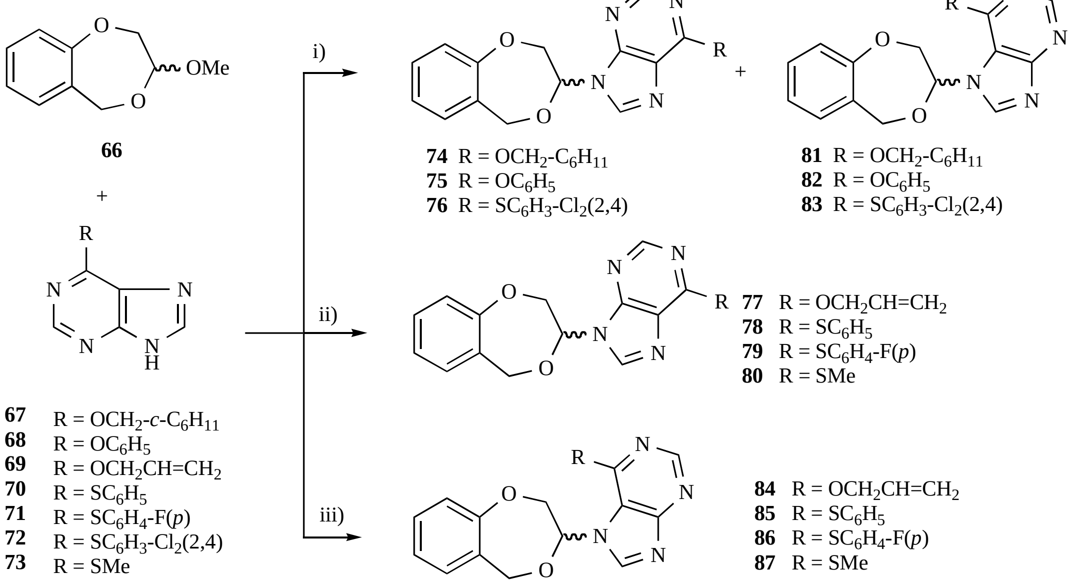
heteroatom nucleophiles that can be introduced at the 8-position of the halo-purines [73].

2,6-Dichloropurine is a commercially available, albeit expensive, starting material for the preparation of 2,6-diaminopurine analogues as shown on Scheme **15**. Following the displacement of the 6-chloro substituent with *m*-chloroaniline and selective *N*9-alkylation with an alkyl iodide is carried out to give **60**. Finally, nucleophilic displacement at C2 is achievable at a higher temperature (150 ºC) with *cis*-2-aminocyclohexylamine to produce **61** [74].

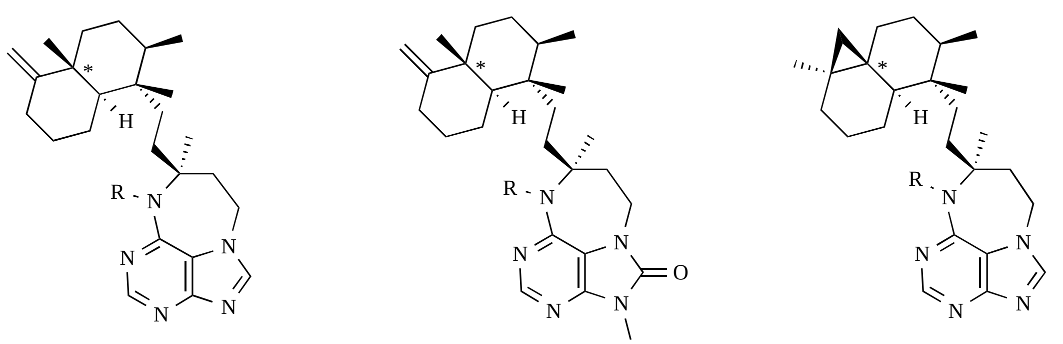
Due to the higher reactivity of the 2-iodide [75], milder conditions for the nucleophilic displacement with amines with respect to the 2-chloride of 2,6-dichloropurine are possible. Woollins *et al.* [76] have prepared 6-chloro-2-iodopurine **65** as a template for the preparation of purine cyclin-dependent kinase (CDK) inhibitors (Scheme **16**).

The most modern synthesis starts with hypoxanthine **62** and its most important step is the regiospecific lithiation-quenching process with the harpoon's base (lithium 2,2,6,6-tetramethylpiperidide, LiTMP) and tributyltin chloride. The 2-stannulated purine **63** was subsequently reacted with iodine to afford the 2-iodo derivative **64** in high yield. Finally, refluxing the 9-THP purine **64** with 10 mol% of copper(II) dichloride in ethanol/water (95:5) [76] was a highly efficient deprotection. The molecular structures of the final dihalogenopurine **65** and its 9-protected precursor **64** were determined by single crystal X-ray diffraction. Nevertheless, the preparation of **64** was previously reported seven years before by Kato *et al.* [77] following the same lithiation-mediated stannyl transfer process followed by 2-tributyl-stannyl-iodine exchange. Legraverend *et al.* [78] stated that the presence of the THP protecting group was required in order to obtain the 2-stannylated purine intermediate in high yield. In this way the 6-chloro-2-iodopurine derivative **64** was obtained in high yield from inexpensive 6-chloropurine (in contrast to 2,6-dichloropurine which although frequently employed in purine synthesis [74,79-81], its cost is prohibitive).

Alternately, Al-Obeidi *et al.* [82] reported the preparation of multi-gramme quantities of **65** in three steps from 2-amino-6-chloropurine (Scheme **17**).



Scheme 18. *Reagents and conditions:* Purine bases (**67-73**), TMSCl, HMDS, $SnCl_4$, anhydrous MeCN. Methods i), ii) or iii): i) 45 ºC, 24-72 ºC (**74-76** and **81-83**, average yield: 20%); ii) MW, 130 ºC, 5 min (**77-80**, average yield: 30%); iii) MW, 100 ºC, 5 min (**84-87**, average yield: 28%).



Asmarine A: R = OH
Asmarine B: R = OH, *epi
Asmarine G: R = OMe
Asmarine H: R = H
Asmarine K; R = H, *epi

Asmarine C: R = H, *epi
Asmarine D: R = H,
Asmarine E: R = OMe, *epi
Asmarine F: R = OMe

Asmarine I: R = OH,
Asmarine J: R = H

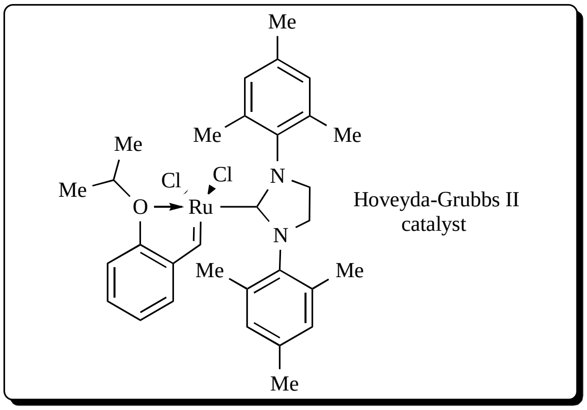
Fig. (4). Structures of known asmarines.

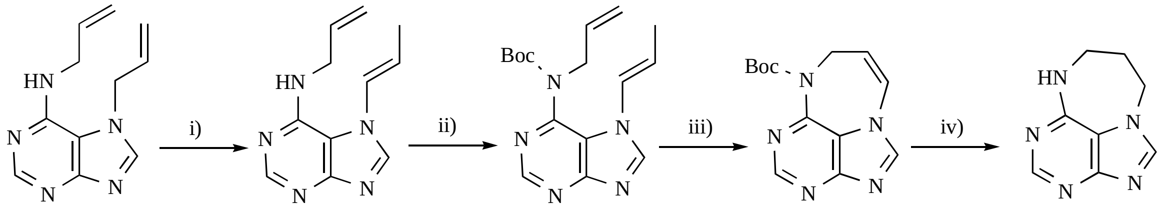
4.3.2. 6,7 and 6,9-disubstituted Purines

Campos *et al.* [83] have published extended studies on the synthesis and pharmacological evaluation of (*RS*)-6-substituted 7- or 9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*- or -9*H*-purines. The preparation of the target molecules **74-87** was achieved by the Vorbrüggen [84] one-pot condensation of the cyclic acetal **66** [85] and the purine bases **67-73** [15,86] using trimethylsilyl chloride (TMSCl), 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and tin(IV) chloride as Lewis acid in anhydrous acetonitrile. When the reaction was carried out at 45 ºC for 24-72 hours (Scheme **18**, method i)), the *N*9 and the *N*7 cyclic alkylated purine regioisomers (**74-76** and **81-83** respectively) were produced and separated by flash chromatography. As an alternative method the reaction mixture was microwave-irradiated at a temperature of 130 ºC for 5 min. The most important feature is that only the *N*9 isomer was isolated in the reaction (Scheme **18**, method ii)), **77-80**]. Surprisingly and interestingly, when the microwave reaction was carried out at 100 ºC, only the *N*7 isomers **84-87** were isolated (Scheme **18**), method iii)). In short, the regiospecificity of this methodology can be controlled. Depending on the temperature of the microwave activation only one of the isomers is obtained in better yield than the ones produced by conventional heating making the purification process easier. From a biological point of view, it must be highlighted that compounds **77** and **82** are more potent as apoptotic inductors against the MCF-7 human breast cancer cells (73.37 ± 0.12 % and 65.28 ± 1.92 %, respectively) than paclitaxel (Taxol®), which induced programmed cell death up to 43% of cell population [87]. This is a remarkable property because the demonstration of apoptosis in MCF-7 breast cancer cells by known apoptosis-inducing agents has proved to be difficult [83].

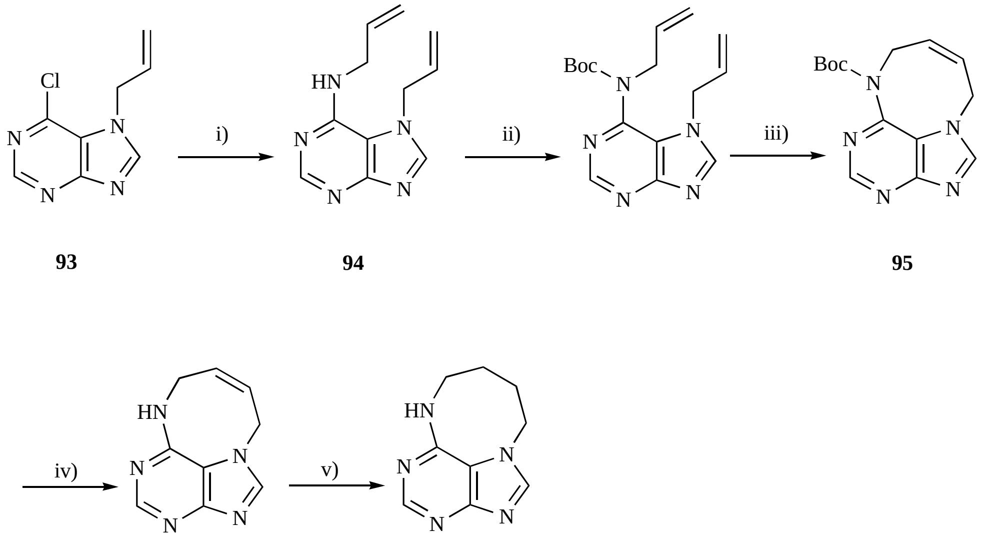
Asmarines are tetrahydro[1,4]diazepino[1,2,3-*g,h*]purine derivatives isolated from marine sponges (*Raspailia* sponges). Currently eleven asmarines [asmarine A-K, Fig. (**4**)] are known [88], and asmarines A and B are reported to possess significant cytotoxic activity against various human cancer cell lines [88a].

To date, no total synthesis of an asmarine has been published and a major challenge in any synthesis of these natural products will be the construction of the tetrahydrodiazepine ring. In order to




88 **89** **90** **91** **92**

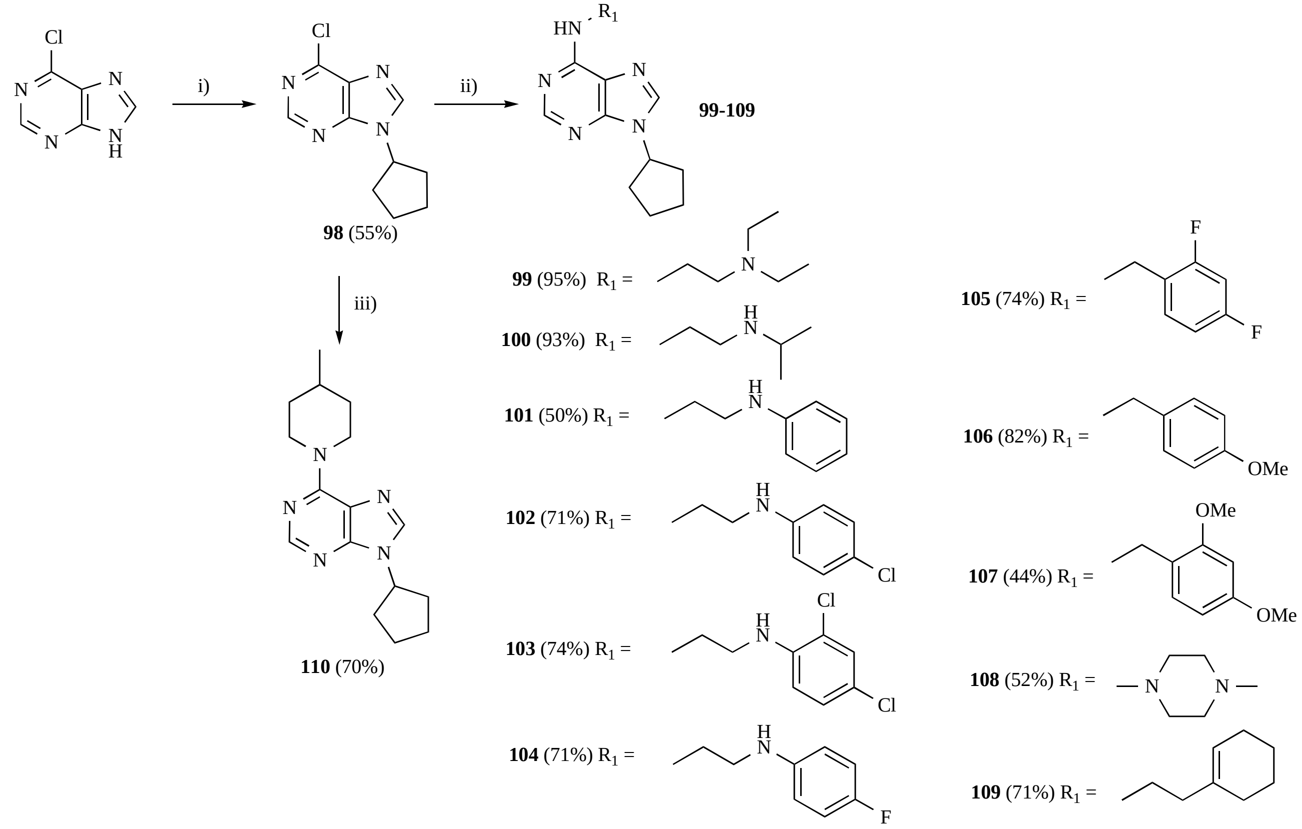
Scheme 19. *Reagents and conditions:* i) K_2CO_3, MeCN or *n*-BuOH, Δ (100%); ii) $(Boc)_2O$, DMAP, MeCN (68%); iii) Hoveyda-Grubbs II, DCE, Δ (95%); iv) 1. H_2, Pd/C, EtOAc, 2. HCl, MeOH (70%).


93 **94** **95** **96** **97**

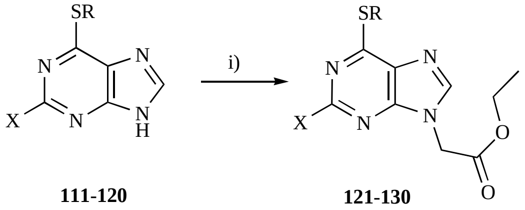
Scheme 20. *Reagents and conditions:* i) $H_2NCH_2CH=CH_2$, py, 100 ºC (93%); ii) $(Boc)_2O$, DMAP, MeCN (65%); iii) Hoveyda-Grubbs II, DCE, Δ (73%); iv) HCl, MeOH (81%); v) H_2, Pd/C, H_2SO_4, MeOH (85%).

construct a seven-membered ring by ring-closing metathesis (RCM), a 7-alkenylpurine was needed, and when 7-allyl-6-allylaminopurine **88** was treated with base in refluxing acetonitrile, the double bond in the *N*7 substituent selectively migrated to give 7-propenylpurine **89** in quantitative yield. The Boc-protected 7-propenylpurine **90** was treated with refluxing 1,2-dichloroethane (DCE) for 1.5 h, in the presence of the Hoveyda-Grubbs II catalyst, and dihydrodiazepinopurine **91** was formed (95% yield). Finally, tetrahydro[1,4]diazepino[1,2,3-*g*,*h*]purine **92** was available after hydrogenation prior to the removal of the *N*-protecting group [89] (Scheme **19**).

The synthesis of compound **97**, with an eight-membered ring was also tried by Gundersen and Vik [89]. It is known that 7-allyl-6-chloropurine **93** (Scheme **20**) is readily available by regioselective *N*-alkylation of 6-chloropurine in the presence of a Co-complex [90]. 7-allyl-6-chloropurine **93** was reacted with allylamine to give **94**. The synthesis of eight-membered rings by RCM reactions has often been a challenge [91,92], even though there are examples of



Scheme 21. *Reagents and conditions:* i) cyclopentyl bromide, K_2CO_3, DMF; ii) the appropriate amine, EtOH; iii) 4-methylpiperidine.



111, **121** X = H, R = 1-decyl (36%)
112, **122** X = H, R = 1-dodecyl (22%)
113, **123** X = H, R = C_6H_4-4-Cl (37%)
114, **124** X = H, R = C_6H_4-3-Me (37%)
115, **125** X = H, R = C_6H_4-4-Me (90%)
116, **126** X = H, R = 2-naphthyl (15%)
117, **127** X = OH, R = $CH_2C_6H_5$ (18%)
118, **128** X = OH, R = $CH_2C_6H_3$-2-Cl-6-F (8%)
119, **129** X = OH, R = $CH_2C_6H_3$-2-Me-3-NO_2 (9%)
120, **130** X = OH, R = $CH_2C_6H_4$-2-F (9%)

Scheme 22. *Reagents and conditions:* i) ethyl bromoacetate, K_2CO_3, DMAc.

such rings formed in excellent yields by RCM [92d,93]. Furthermore, in the construction of azacyclooctenes by RCM, the yield is often highly dependent on the nature of the *N*-substituent [92,94]. Dihydrodiazocinopurine **95** was isolated in 73% yield employing the Hoveyda-Grubbs II complex, the Boc group was readily removed and the double bond of **96** was hydrogenated at atmospheric pressure to afford **97**.

Tunçbilek *et al.* [95] have reported the synthesis and antimicrobial activity of several 6,9-disubstituted purines (Scheme **21**).

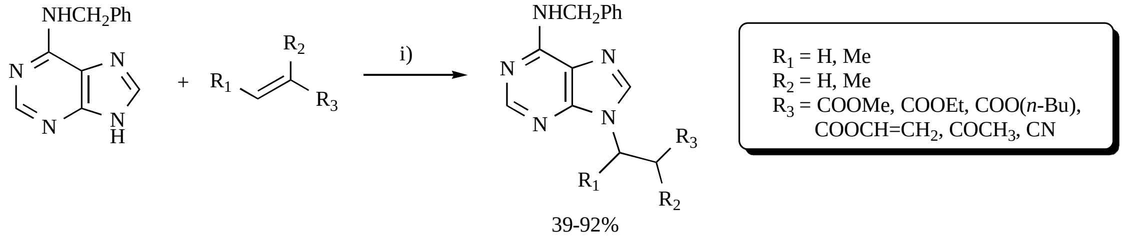
Compounds **99-109** have been synthesized via *N*9 alkylation of 6-chloropurine with cyclopentyl bromide, and subsequent amination of 6-chloro-9-cyclopentylpurine **98** with substituted amines. The alkylation reaction occurred only at the *N*9 atom. Compound **110** was obtained by treating **98** with 4-methylpiperidine.

Compound **102** exhibits comparable antibacterial activity with that of the clinically used drug ciprofloxacin, and **104** displays better antifungal efficacy than that of the standard drug oxiconazole [95].

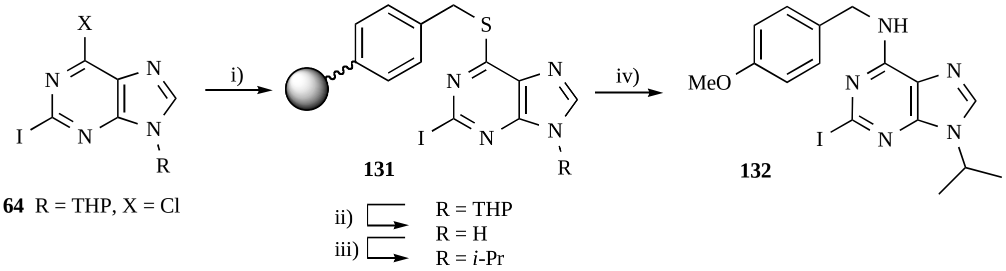
The purine ring system is a key structural element of substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins including cellular kinases, G proteins, and polymerases [96,97]. Very little work has been done to explore the potential of purine analogues as antitubercular agents. Nevertheless, syntheses of purine analogues possessing antitubercular activity have been published [98]. Reynolds *et al.* [99] carried out the synthesis of several 6-thioaryl/alkyl purines for screening against *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium avium* complex (MAC) strains.

Compounds **111-130** are obtained by reactions of 6-chloropurine with the corresponding alkyl/aryl thiols in 2-propanol using potassium *tert*-butoxy after heating at 50 ºC. The 2-hydroxy purine analogues **117-120** are prepared by the treatment of 6-thioxanthine with alkyl/benzyl halides in 0.1 N NaOH. To evaluate the effect of *N*9-substitution on inhibitory activity, *N*9-alkylation of a small number of active 6-thio-substituted purines was performed. The alkylation was carried out with ethyl bromoacetate in the presence of K_2CO_3 using DMAc (*N,N*-dimethylacetamide) as solvent and resulted in 6,9-disubstituted **121-126** and 2,6,9-trisubstituted **127-130** purine analogues (Scheme **22**).

Compounds **121** and **122** exhibit antimycobacterial activity in the preliminary screening against Mtb $H_{37}Rv$ [99].



Scheme 23. *Reagents and conditions*: i) 5 mg DA, 1 mL DMSO, 50 ºC, 72 h.



Scheme 24. *Reagents and conditions*: i) Merrifield resin-SH, *t*-BuOK, DMF, 80 ºC; ii) TFA (20 equiv) in CH_2Cl_2, rt; iii) PPh_3 (1 equiv), DIAD 1 equiv, THF, -50 ºC, *i*-PrOH (1 equiv); iv) 1. *m*-CPBA (2.2 equiv), CH_2Cl_2, 20 ºC; 2. *p*-$MeOC_6H_4CH_2NH_2$, THF, 65 ºC (The yield for product **132** was in the 70-90% range).

Enzymes are efficient catalysts in organic and bioorganic synthesis. Lin *et al.* [100] have reported the regioselective Michael addition of purine derivatives to α,β-unsaturated carbonyl compounds catalyzed by D-aminoacylase (DA) in DMSO. This methodology was extended to diverse purine derivatives and a variety of α,β-unsaturated carbonyl compounds (Scheme **23**) [100]. It is the first report on enzyme-catalyzed Michael addition for the preparation of purine derivatives.

4. SYNTHESIS OF 2,6,9-TRISUBSTITUTED PURINES

The basic tenet for the construction of 2,6,9-trisubstituted purine libraries is that the low reactivity of the C6-*S* bond provides the possibility to introduce a wide variety of functionality at the *N*9 and C2 positions prior the reaction at C6. Subsequent activation of the sulfur atom (oxidation, alkylation, etc.) then opens the way to concomitant introduction of a substituent (nucleophile) at C6 and cleavage of the trisubstituted purine product from the resin. In this sense, full advantage is taken of solid-phase synthesis to introduce functionality at all the centres of interest in the purine ring [32b].

To prepare the resin bound purine **131** [78], the reaction of 6-chloropurine **64** with Merrifield-SH resin was carried out. The efficiency of the release of the purine form resin **131** was then evaluated following the two-step protocol developed in solution (*S*-oxidation/nucleophilic displacement). The yield for product **132** was in the 70-90% range (approximately 50% overall yield for loading and release operations) (Scheme **24**).

A small library of 2,6,9-trisubstituted purines was prepared via solid-phase organic synthesis using the 6-thiopurine-bound Merrifield resin **133** (Scheme **25**).

Schultz *et al.* [32a] have developed an approach for making combinatorial 2,6,9-trisubstituted purine libraries **136** by capturing an *N*9-substituted 2-fluoro-6-chloropurine at the C6 position via a thioether linkage; subsequently the polymer-bound purine intermediate was modified at the C2 position and followed by substitution at the C6 position with concomitant release (Scheme **26**).

According to Lagraverend *et al.* [78] compound **137**, a versatile intermediate for the synthesis of 2,6,9-trisubstituted purines, was obtained from **64**. The 2-iodo purine derivative **137** was subjected to Sonogashira cross-coupling reactions, with acetylene derivatives (Scheme **27**). Finally, Pd(0) catalyzed Suzuki cross-coupling reactions of iodopurine **137** with boronic acids provided a further means for introducing aromatic substituents at C2 (Scheme **27**).

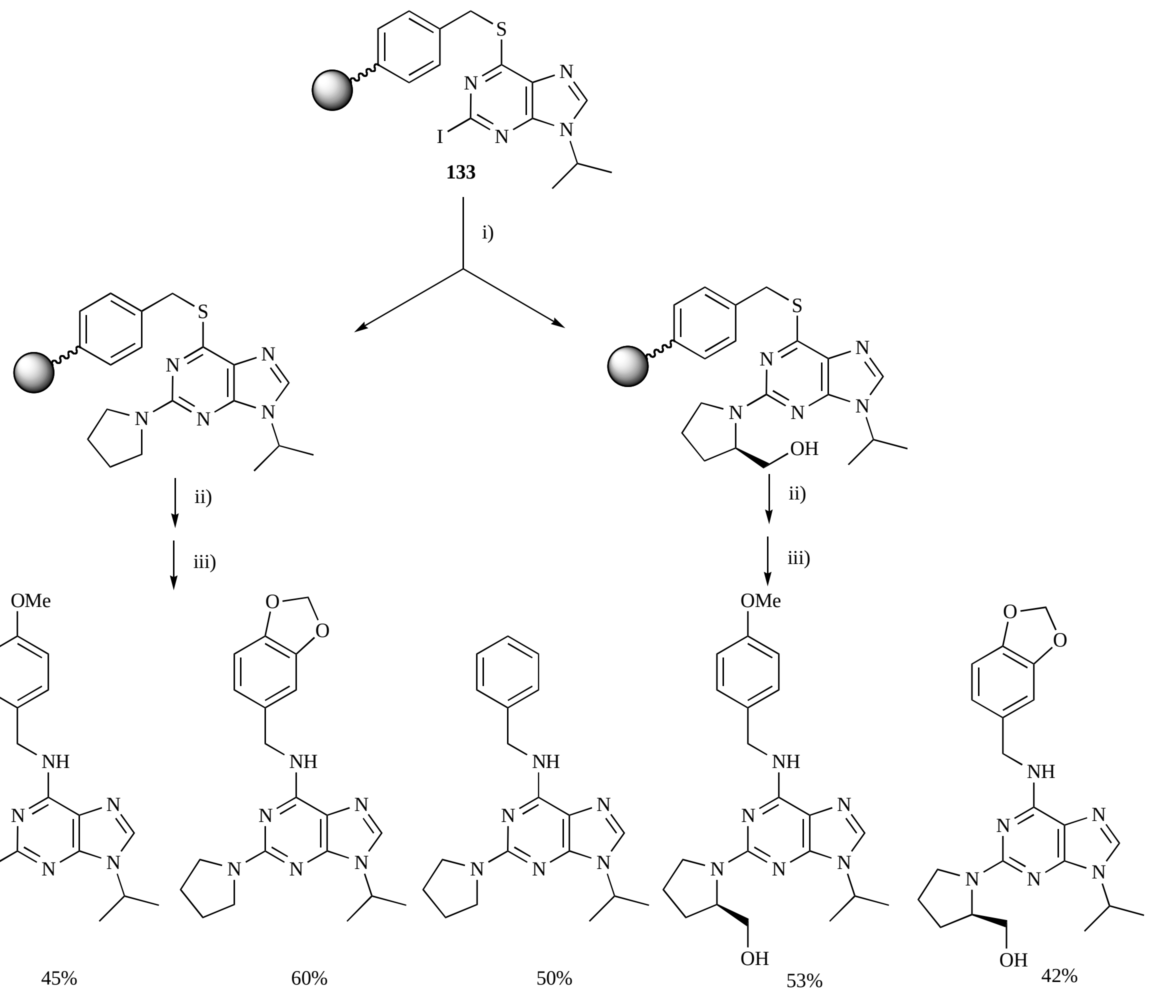
In an attempt to discover a high-throughput method Al-Obeidi *et al.* [82] described a method for microwave-assisted solid-phase synthesis (MASS) of 2,6,9-trisubstituted purines.

Microwave-assisted S_N2Ar conditions were optimized using minivials to efficiently incorporate a diverse collection of sterically hindered and non-nucleophilic amines at the C2 position of the purine scaffold. These minivials permit the minimization of reaction times and dramatically increase yields of this S_N2Ar reaction by increasing reaction concentrations with limited amounts of scaffolds and reagents [101].

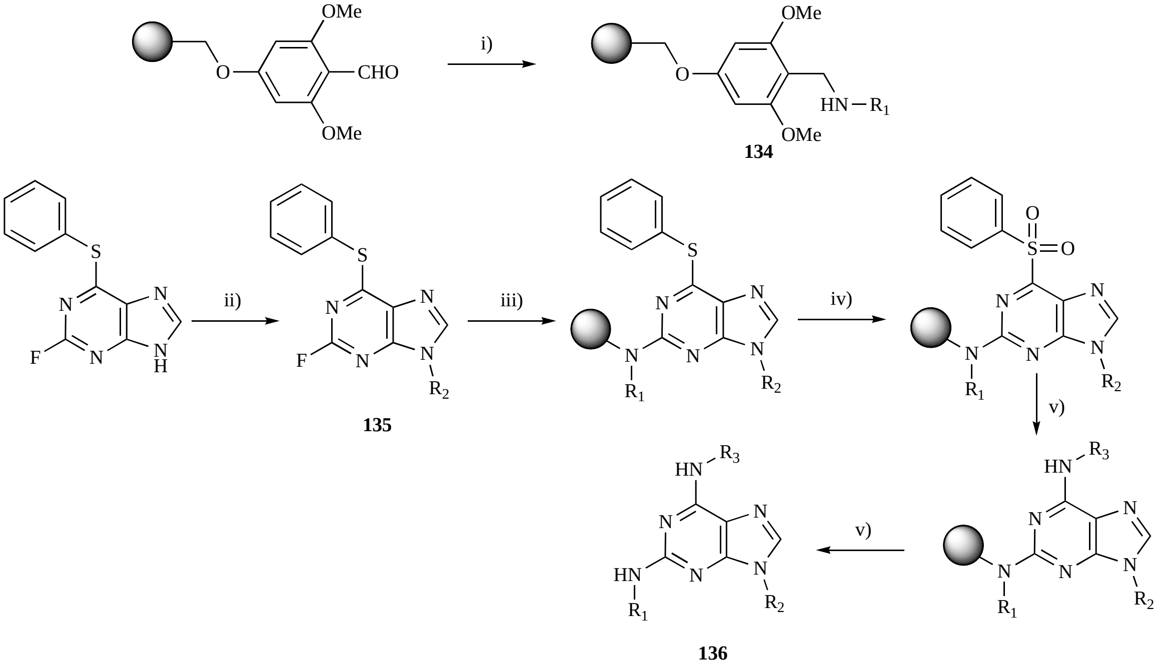
Metzler-Nolte and van Staveren [102] have reviewed the impressive development of ferrocene chemistry. Nevertheless, the first manuscript on ferrocene nucleoside derivatives is only about 18 years old [103]. The stability of the ferrocenyl group in aqueous, aerobic media, the accessibility of a large variety of derivatives, and its favourable electrochemical properties have made ferrocene and its derivatives very popular molecules for biological applications and for conjugation with biomolecules. Sonogashira coupling between ethynylferrocene **138** and 6-chloro-, 6-amino-8-bromo-, 2-chloro-6-amino- 9-benzylpurines **139**-**141** was reported, leading to the corresponding (ferrocenylethynyl)purines **142**,**144**,**146** [105]. Catalytic hydrogenation of these alkynes over Pd/C afforded their [2-(ferrocenyl)ethyl]purines **143**,**145**,**147** (Scheme **28**)[104]. Starting materials **138** [105], **139** [106], **140** [107] and **141** [104] were prepared according to the literature procedures.

The authors claim that each of the three types of ferrocene-purine conjugates (linked via the C2, C6 or C8 purine atoms) has a distinct electrochemical response and thus such compounds may be used in investigations of the modes of binding of some purines to proteins or nucleic acids [104].

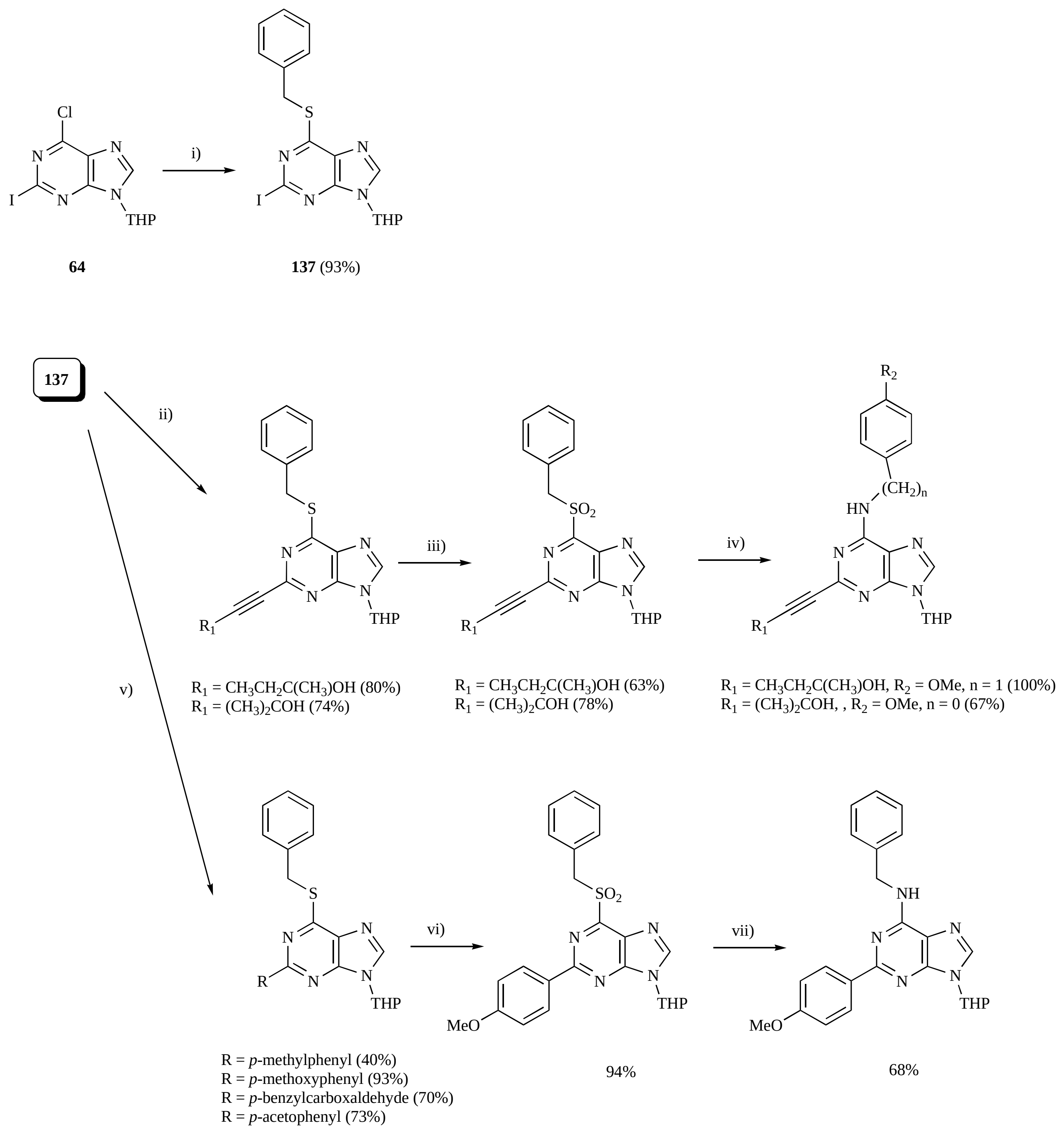
Liu *et al.* [108] have reported an expeditious and efficient method to prepare the 2,6,9-trisubstituted purines **148** in a two-pot reaction using microwave-assisted reactions. The following two aspects need to be highlighted: 1) 2-chloro-6,9-substituted purines



Scheme 25. *Reagents and conditions*: i) RR_1NH (5 equiv), (n-Pr)$_3$N (3 equiv), DMA, 80 ºC, 24 h; ii) m-CPBA (2.2 equiv), rt, 24 h; iii) RNH_2, 65 ºC, 24 h.



Scheme 26. Combinatorial libraries of 2,6,9-substituted purines. *Reagents and conditions*: i) R_1NH_2, $NaBH(OAc)_3$, 1% HOAc, THF; ii) 1.5 equiv of R_2OH, PPh_3 (1.8 equiv), DIAD (1.3 equiv), THF, rt; iii) **135** (0.5 equiv), DiEA (1.5 equiv), BuOH, 80 ºC; iv) m-CPBA (10 equiv), NaOH (1:1), 1,4-dioxane with 10% H_2O; v) 2 equiv of R_3NH_2, anhydrous dioxane, 80 ºC; vi) CH_2Cl_2, TFA, Me_2S, H_2O (45:45:5:5).



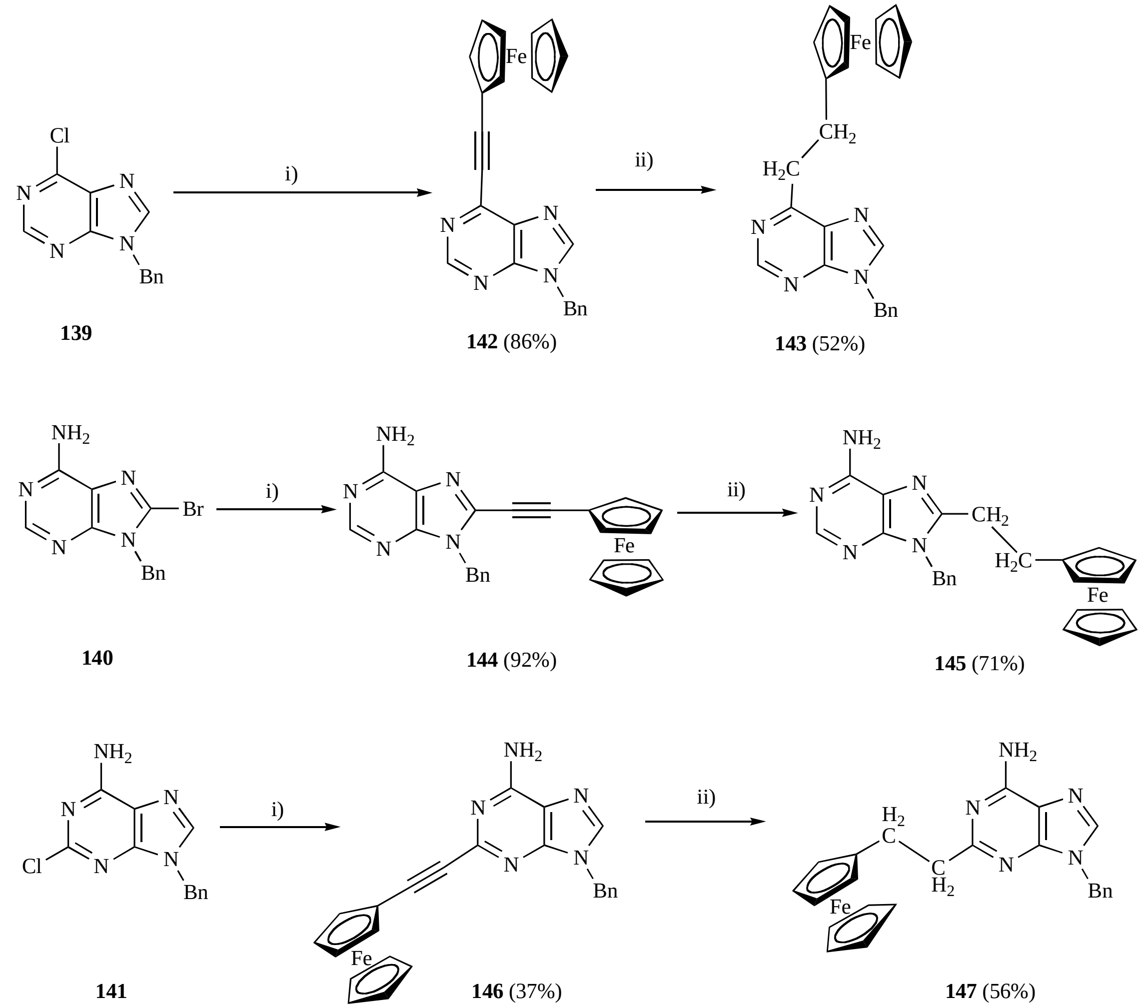
Scheme 27. *Reagents and conditions*: i) benzyl thiol, EtOH, 60 ºC; ii) alkyne, $(PPh_3)_2PdCl_2$, CuI, Et_3N, THF; iii) *m*-CPBA, CH_2Cl_2, 0 ºC or rt, ≤ 10 min; iv) RNH_2, rt or 80 ºC; v) $ArB(OH)_2$, $Pd(PPh_3)_4$ (3 mol%), Na_2CO_3, DMF, Δ, 24 h; vi) *m*-CPBA, CH_2Cl_2, rt; vii) $PhCH_2NH_2$, *t*-BuOH, 60 ºC.

were prepared via a one-pot two-step reaction, which involves a sequential S_NAr displacement of the C6 chloro substituent with various anilines and amines, followed by *N*-alkylation and *N*-arylation at the *N*9 position with different organic halides and boronic acids; 2) $NaBF_4$ catalysis supports a S_NAr substitution of the C2 chloro displacement with high product conversion (Scheme **29**).

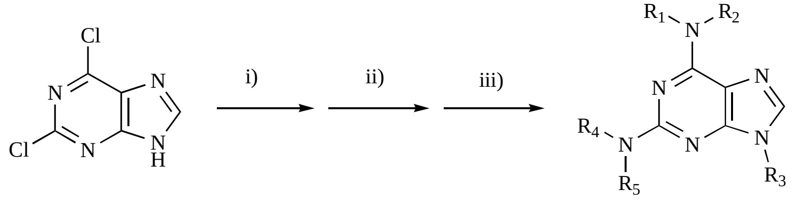
A novel and efficient method for the synthesis of 2-(6-purinyl)acetoacetate ethyl esters **149**, (purin-6-yl)acetates **150** and 6-methylpurines **151** has been recently published through nucleophilic aromatic substitution of 6-halopurines and ethyl acetoacetate without catalyst (Scheme **30**)[109]. Simplicity of this procedure, the absence of expensive catalysts and ligands, and generally satisfactory yields make this method particularly attractive.

5. SYNTHESIS OF 2,6,8,9-TETRASUBSTITUTED PURINES

The purine core consisting of four points of structural diversity is a well-sought scaffold in combinatorial chemistry. Although most of the efforts have been focused on 2,6,9-, 6,8,9-, or 2,8,9-



Scheme 28. *Reagents and conditions*: i) ethynylferrocene (**138**), CuI, [Pd(PPh_3)$_4$], Et_3N, DMF; ii) H_2, Pd/C.



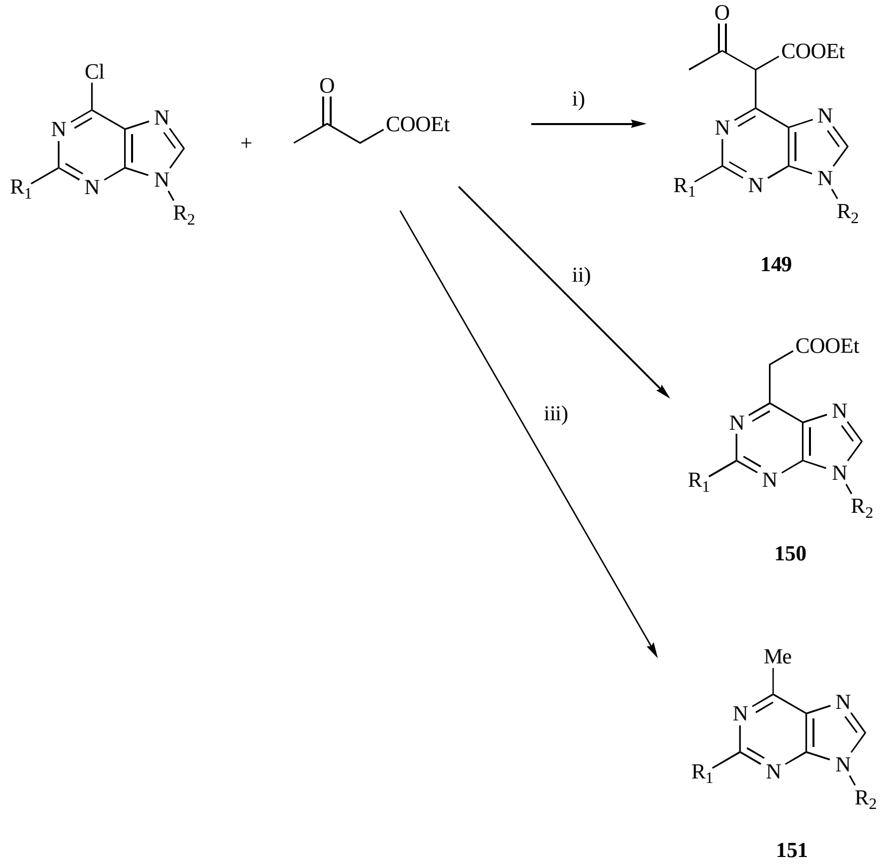
Scheme 29. *Reagents and conditions*: i) aniline/amine, HOAc, dioxane, MW, 10 min; ii) halide/boronic acid, K_2CO_3, DMF, MW, 10 min (17-94%); iii) aniline/amine, $NaBF_4$, DMSO, MW, 5 min (13-99%).

trisubstituted purines, syntheses of 2,6,8,9-tetrasubstituted purines are rare [27,110]. Bai *et al.* [31] have reported a parallel-solution phase 216-member library of fully substituted purines **155**, which should allow systematic exploration of all four positions of the purine ring (Scheme **31**). This strategy is very similar to one previous published [27], with the only difference that the pathways illustrated in Scheme **31** take advantage of the fact that an alkylthio group RS- at the 6-position of purine is relatively reactive toward oxidation to yield its corresponding sulfone, which can be easily displaced by various amines.

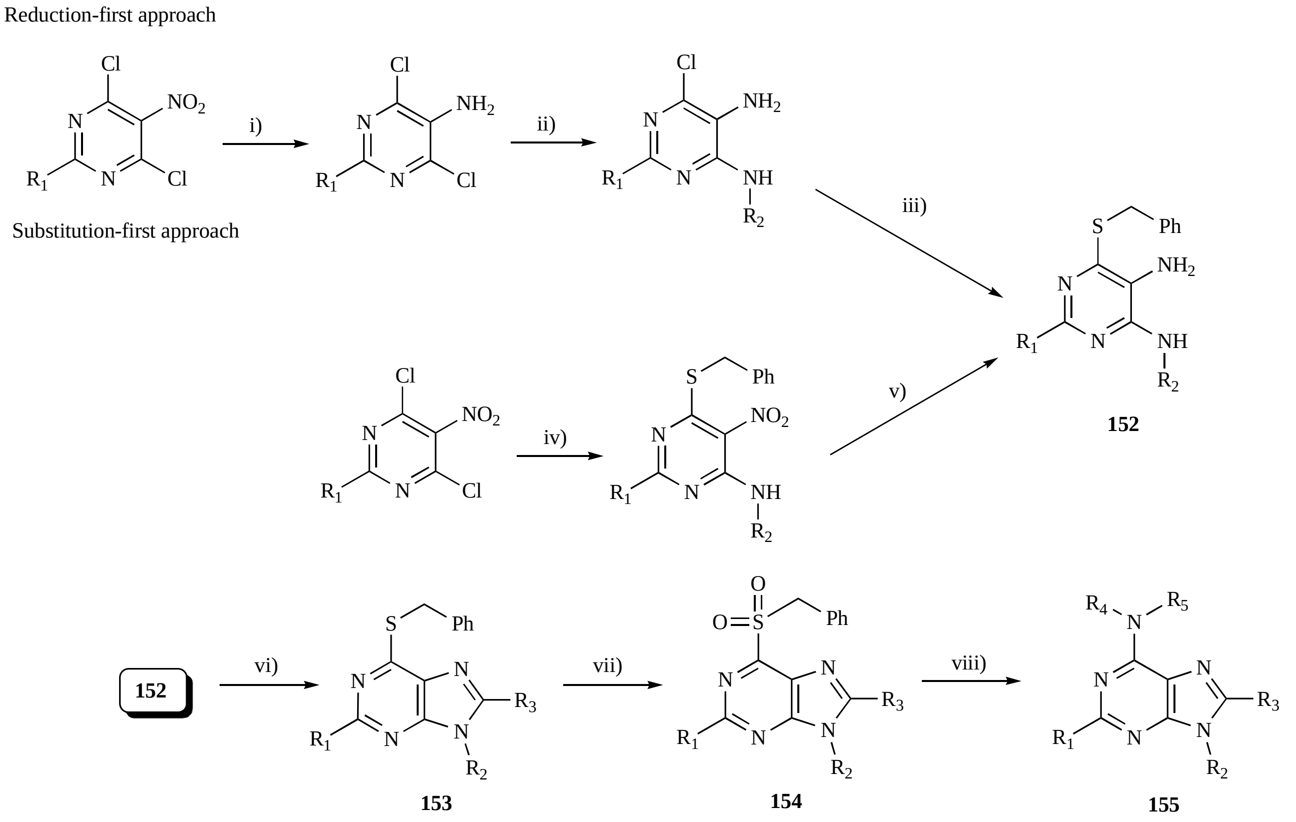
Preparation of diaminopyrimidine **152** is depicted in Scheme **31**. Compound **152** can be synthesized by either reduction of the nitro to amino group, followed by the substitution of a chlorine atom by an amine (reduction first), or the substitution of chlorine atoms, followed by reduction (substitution first). The diaminopyrimidine intermediate **152** was cyclized to construct the purine ring with a C8 substituent. Eventual oxidation of sulfur (**153**) to sulfone **154** and subsequent displacement by a primary or secondary amine provided the desired 2,6,8,9-tetrasubstituted purine analogues **155**.

6. CONCLUSION

The metal-mediated C-C and C-N coupling reaction of purines with boronic acids has been shown to be a powerful synthetic method for introducing aryl or heteroaryl substituents. Several different palladium catalyst-ligand combinations have been used for



Scheme 30. *Reagents and conditions*: i) Cs_2CO_3, DMSO, 60 ºC (68-95%); ii) Cs_2CO_3, DMSO, 80 ºC (23-85%); iii) Cs_2CO_3, DMSO, 120 ºC (69-85%).



Scheme 31. Synthesis of a 216-member purine library. *Reagents and conditions*: i) Fe, HCl; ii) R_2-NH_2, Et_3N, *n*-BuOH, 100 ºC; iii) $PhCH_2SH$, Et_3N, *n*-BuOH, 100 ºC; iv) R_2NH_2, then $PhCH_2SH$, rt; v) Fe, NH_4Cl; vi) R_3-CHO, $FeCl_3/SiO_2$; vii) *m*-CPBA, CH_2Cl_2; viii) R_4R_5NH (excess).

C-C coupling at the 6-position. This reactivity has been demonstrated using fluoro-, chloro-, bromo-, iodo-, sulfanyl, sulfonyl, and azole-substrates. Examples of combinatorial approaches employing coupling reactions with solid-supported purine substrates or parallel solution-phase approaches have also been reported. These methods provide convenient access to structurally unique arylpurine derivatives with applications in drug discovery and chemical biology. Although most of the efforts have been devoted to mono-, di-, and tri-substituted purines, preparation of fully substituted purines are very scarce.

This review has not included medicinal applications of purine derivatives, except a few scattered data that were indicated in the respective sections. Finally, we would like to point out that in recent years there has been an increasing number of papers published in high-impact journals written by authors who work in laboratories with less scientific tradition. This is very important for the evolution of Science in general, and for the synthetic development of modified purines in particular, since it makes their foundations more extensive and accordingly more reliable.

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ABBREVIATIONS

ABDA = 5-acetyl-6-bromo-2,3-dibenzyl-L-ascorbic acid
Ac = acetyl
AcCoA = acetyl-coenzyme A
ATP = adenosine 5’-triphosphate
Boc = *tert*-butoxycarbonyl
Boc_2O = *tert*-butoxycarbonyl anhydride
CDK = cyclin-dependent kinase
CSI = chlorosulfonyl isocyanate
DA = D-aminoacylase
DCE = 1,2-dichloroethane
DIAD = di*iso*propyl azodicarboxylate
DiEA = diethylamine
DMA = *N*,*N*-dimethylaniline
DMAc = *N*,*N*-dimethylacetamide
DMF = *N*,*N*-dimethylformamide
DNA = deoxyribonucleic acid
FAD = flavin adenine dinucleotide
HMDS = 1,1,1,3,3,3-hexamethyldisilazane
IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene
LiTMP = lithium 2,2,6,6-tetramethylpiperidide (harppon’s base)
m-CPBA = *meta*-chloroperoxybenzoic acid
MAC = *Mycobacterium avium* complex
MASS = microwave-assisted solid-phase synthesis
MEK = methyl ethyl ketone
Mes = 2,4,6-trimethylbenzoyl
Mtb = *Mycobacterium tuberculosis*
MW = microwave
NADH = nicotinamide adenine dinucleotide
$Ni(COD)_2$ = bis(1,5-cyclooctadiene)nickel(0)
NMP = *N*-methylpyrrolidin-2-one
Ph = phenyl
py = pyridine
R_F = a perfluoroalkyl group
RNA = ribonucleic acid
rt = room temperature
SAM = 5’-*S*-adenosyl methionine
S_NAr = aromatic nucleophilic substitution
TBAF = tetrabutylammonium fluoride
TBAN = tetrabutylammonium nitrateand
TBAT = tetrabutylammonium triphenyldifluorosilicate
THF = tetrahydrofurane
THP = 9-(tetrahydropyran-2-yl)-
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride
Tol = *p*-tolylbenzoyl
tRNA = transfer ribonucleic acid
Ts = tosyl = *p*-toluenesulfonyl
TMS = trimethylsilyl

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