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Recent advances in the synthesis of purine derivatives and their precursors

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Abbreviations: ATP, adenosine 5′-triphosphate; GTP, guanosine 5′-triphosphate; GDP, guanosine 5′-diphosphate; cAMP, cyclic adenosine 3′,5′-monophosphate; cGMP, cyclic guanosine 3′,5′-monophosphate; AcCoA, acetyl-coenzyme A; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; FAD, flavin adenine dinucleotide; PAPS, 3′-phosphoadenosine 5′-phosphosulfate; SAM, 5′-*S*-adenosyl methionine.

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1. Introduction

The purine ring is the most ubiquitous nitrogen-containing heterocycle in nature,[1] since, besides the numerous purine derivatives found in various marine organisms and plants, it is the core structure of adenine and guanine in nucleic acids (RNA and DNA). In addition, purines are involved in many metabolic processes as cofactors associated with a great number of enzymes and receptors, notably ATP, GTP, GDP, cAMP, cGMP, AcCoA, NAD, NADP, FAD, PAPS and SAM,[1,2] which play key roles at different phases of the cell cycle, in cell signalling and other fundamental biological processes.[3] It should be noted that all of these associated proteins contain a purine recognition pocket and, consequently, purine derivatives have long been developed to selectively inhibit or antagonise each of these enzymes and receptors. Indeed, a great variety of di-, tri- or tetrasubstituted purines described in the literature have been found to be potent inhibitors of chaperone HSP90, protein kinases (MAP, Src and Cdk), sulfotransferases, phosphodiesterases and microtubule assembly, inducers of interferon and dedifferentiation and antagonists of adenosine receptors and corticotropin-releasing hormone receptors.[2] This wide range of biological activities displayed by purines is conferred by a judicious choice of the nature of the substituents that can be combined on the N-1, C-2, N-3, C-6, N-7, C-8 and N-9 centres (Fig. 1).

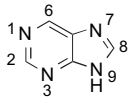


Figure 1. Purine (imidazo[4,5-*d*]pyrimidine) ring.

With such an easy access to so much structural diversity, the purine core has become a privileged structure in medicinal chemistry,[4] and an important scaffold in the preparation of combinatorial libraries. In general, two strategies are applied for the preparation of purine libraries. In the first procedure, a preformed purine ring loaded with various reactive functionalities is directly modified, which allows good regiocontrol at C-2, C-6, C-8 and N-9. Alternatively, substituted pyrimidine or imidazole precursors are functionalised, generating the second heterocycle of the purine core in the process with better regiocontrol at N-1, N-3, N-7 and N-9.

Following a previous article, which highlights the interest in purines as inhibitors and modulators of key biological targets,[2] the goal of the present article is to review recent advances in the synthesis of purine derivatives, with particular emphasis on methods that can lead to purine libraries.

2. Functionalisation at position 6

6-Aminopurines are traditionally obtained in four steps from a nucleoside precursor in a process, which requires protection of the sugar moiety followed by halide formation, often under harsh conditions. Interestingly, Wan and co-workers[5] have recently described the synthesis of several 6-aminopurine derivatives **2** in one step and high yield from unprotected inosine **1** (X=OH) (Scheme 1), by BOP-mediated amination.

Polycyclic aromatic hydrocarbons (PAH) are potent mutagens and carcinogens that are challenging synthetic targets. This method also allowed the synthesis of PAH derivative **3** from 2′-deoxyinosine **1** (X=H) as well as the rare DNA constituent **4** in almost quantitative yield.

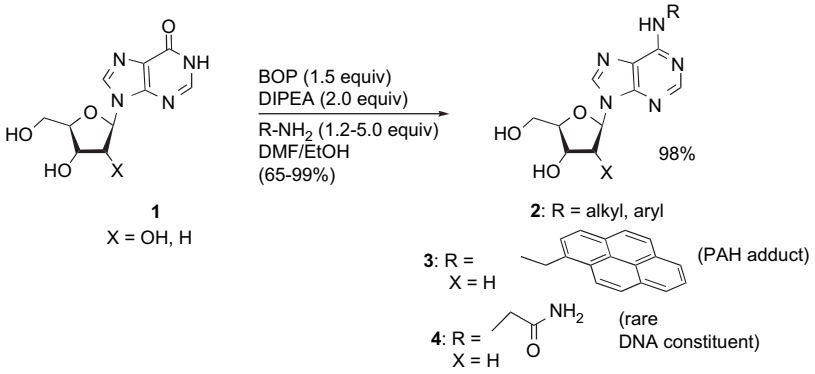
Under these conditions, several 6-substituted purines **2a**–**h** (Table 1, entries 1–8) were prepared from unprotected inosine in high yield from various aryl- or benzylamines.

Using similar reaction conditions, the acetyl-protected inosine **5** led to the corresponding 6-substituted-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purines **6a**–**g** (Scheme 2, Table 2, entries 1–7).

2.1. Functionalisation of the purine ring from guanosine, via a 6-arylsulfonate intermediate

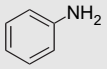
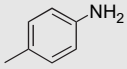
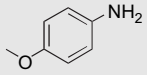
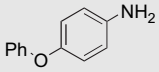
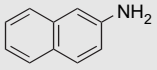
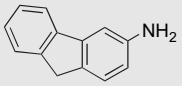
The use of a 6-arylsulfonate for C–C bond formation with boronic acids at room temperature on the purine ring was reported for the first time in 2005.[6] This palladium-catalysed cross-coupling reaction of nucleoside arylsulfonates and arylboronic acids required the use of a ligand and could be generalised to various boronic acids (Scheme 3).

The starting compound, 6-arylsulfonyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **7**, was synthesised from 2′-deoxyguanosine in high yield, in the presence of Et_3N and DMAP, with 2,4,6-trimethylphenylsulfonyl chloride.

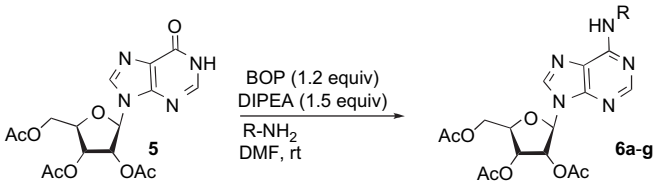


Scheme 1.

Table 1
Amination of sugar-unprotected inosine and 2′-deoxyinosine

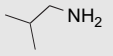
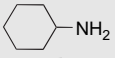
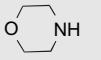
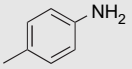
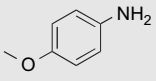
Entry	X	Amine	Method[a]	Product	Yield (%)
1	OH	Bn–NH_2	A	**2a**	99
2	H	Bn–NH_2	A	**2b**	99
3	OH		B	**2c**	91
4	OH		B	**2d**	74
5	OH		B	**2e**	81
6	OH		B	**2f**	85
7	OH		B	**2g**	65
8	OH		B	**2h**	72

[a] A: BOP (1.2 equiv), DIPEA (1.5 equiv), RNH_2 (1.2 equiv), rt; B: BOP (1.5 equiv), DIPEA (2 equiv), RNH_2 (5 equiv), rt, overnight, then 60 or 80 °C.



Scheme 2.

Table 2
Amination of sugar-protected inosine

Entry	Amine	Reaction conditions	Product (%)	Yield (%)
1	Bn-NH_2	rt, <1 h	**6a**	98
2		rt, overnight	**6b**	99
3		rt, overnight	**6c**	99
4		rt, overnight	**6d**	87
5		rt, overnight	**6e**	70
6		rt, overnight then 80 °C, 10 h	**6f**	78
7		rt, 48 h	**6g**	74

Of the nucleoside arylsulfonates evaluated, the *O*-6-(2,4,6-trimethylphenyl)sulfonate **7** proved to be optimal in cross-coupling reactions with tetrahydropyran (THP) as the best solvent, to form **8**.

2.2. Preparation of *C*-6-arylpurines

It has been proposed that DNA containing *C*-6-arylpurines could exhibit unusual properties,[7] prompting a number of studies on the introduction of substituted aryl moieties at the C-6 position of the purine ring in recent years. For example, Lakshman and co-workers have synthesised a wide variety of *C*-6-arylpurine 2′-deoxyribosides **10a–g** via the Pd-mediated Suzuki–Miyaura cross-coupling of arylboronic acids with *C*-6 halonucleosides **9** (Scheme 4 and Table 3).

For several C-6 arylations, the chloronucleoside gave higher coupling yields than the bromo analogue (see Table 3). With arylboronic acids containing electron-withdrawing groups performing less well, several ligands were tested, but the system $Pd(OAc)_2$/K_3PO_4/2-(dicyclohexylphosphino)biphenyl was found to be superior.[7]

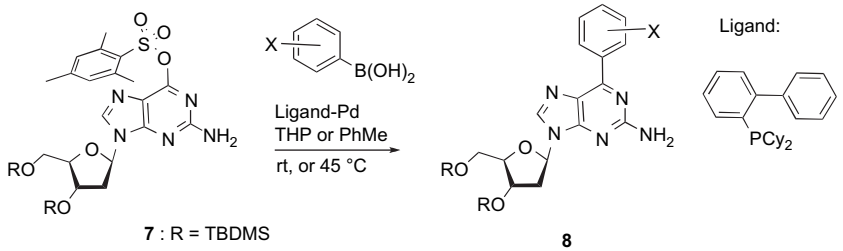
Hocek and co-workers have reported[8] that the regioselectivity of the Suzuki–Miyaura cross-coupling of 2,6-dihalopurines (**11** and **14**) with 1 equiv of phenylboronic acid is dependent on the halogen at position 2. Thus, 9-benzyl-2,6-dichloropurine **11** gave **12**, the product of cross-coupling at position 6, whereas the corresponding iodopurine **14** gave the 2-arylpurine derivative **15**. In the presence of 3 equiv of phenylboronic acid, both halogenopurines led to 9-benzyl-2,6-diphenylpurine **13** in high yield (Scheme 5).

The scope of this reaction was extended to substituted phenyl- and heteroarylboronic acids.[9,10] A high yield (70%) of 2-chloro-6-(3-pyridyl)purine **17d** was obtained from 2,6-dichloropurine **16** with 1 equiv of 3-pyridylboronic acid in an aqueous phase (H_2O/MeCN 2:1). It is interesting to note that no protection at N-9 was necessary (Scheme 6 and Table 4),[9] although the regioselectivities and yields at position 6 (**17a–d**) were inferior to those under the previously described conditions (toluene, K_2CO_3, $Pd(PPh_3)_4$, 100 °C, 8–20 h; Scheme 5) as the unwanted 2,6-disubstituted products **18a,b** were also observed.

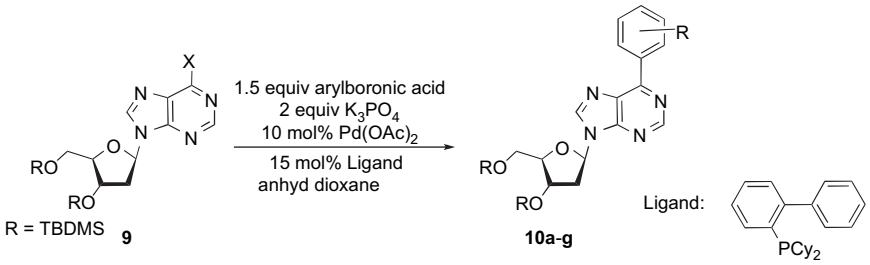
Various 6-aryl-, 6-heteroaryl-, 6-phenylethynyl- or 6-styrylpurines **20a–e** have also been prepared by Stille couplings on the parent halopurine **19a,b**, and were found to be antimycobacterial agents (Scheme 7, and Table 5).[11]

2.3. Synthesis of 6-amidopurines

Olomoucine, roscovitine and purvalanol A and B are well-known representatives of the 2,6-diaminopurine class of molecules that exhibit a great variety of biological activities against CDKs and other enzymes and receptors.[2] Large libraries of 2,6,9-trisubstituted purines bearing an amino substituent at positions 2 and 6 have been synthesised.[12–20] These derivatives are easily obtained from various 2,6-dihalogenopurines, the halogen at position 6 (Cl or Br) being more reactive than that at position 2 (F, Cl, Br or I) under S_NAr conditions.



Scheme 3.

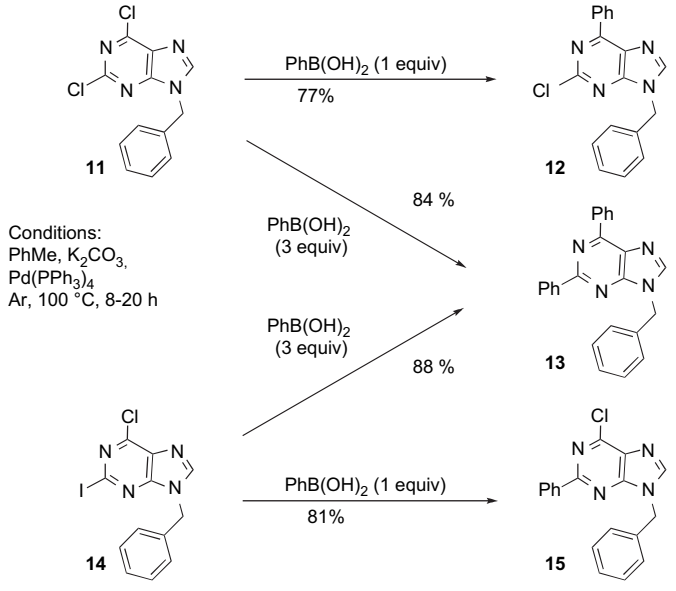


Scheme 4.

Table 3
Synthesis of *C*-6 aryl 2′-deoxynebularine derivatives

Arylboronic acid	Time (h)	Product	Yield (%)	Arylboronic acid	Time (h)	Product	Yield (%)
Phenylboronic acid	1[a]	**10a**	91	Phenylboronic acid	1.5[b]	**10a**	91
4-Methoxyphenylboronic acid	1.5[a]	**10b**	69	4-Methoxyphenylboronic acid	1.5[b]	**10b**	69
3-Methoxyphenylboronic acid	1[a]	**10c**	73	3-Nitrophenylboronic acid	1.5[b]	**10e**	73
2-Ethoxyphenyboronic acid	19.5[a]	**10d**	62	4-Acetylphenylboronic acid	1.5[b]	**10f**	62
3-Nitrophenylboronic acid	1.5[a]	**10e**	59	3-Thiopheneboronic acid	8[b]	**10g**	59
4-Acetylphenylboronic acid	8.5[a]	**10f**	49				
3-Thiopheneboronic acid	6[a]	**10g**	58				

[a] X=Br.
[b] X=Cl.



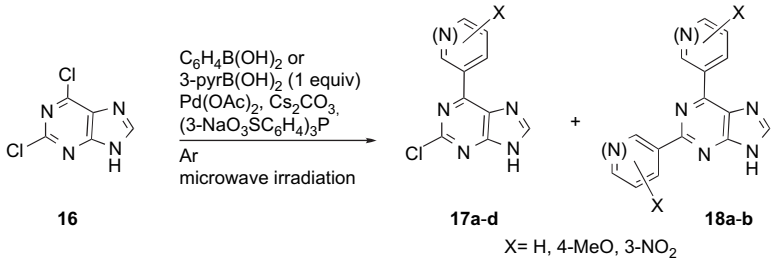
Scheme 5.

On the contrary, 6-amido-2-aminopurines are not so easily obtained and this perhaps explains why the biological activities of such derivatives have not been explored to date. Recently, the regioselective syntheses of 6-amidopurine derivatives **22** and **24** from 2,6-dihalogenopurines **21** and **23**, respectively, have appeared, which give convenient access to this type of derivative (Scheme 8).[21]

Furthermore, the halogen at position 2 can then be substituted by amines under S_NAr conditions from fluoropurine **22** or Pd(0)-mediated coupling from the corresponding iodo derivative **24**. A further Pd(0)-catalysed cross-coupling at position 2 in **24** is also possible with boronic acids or alkynes.

2.4. Substitution reactions of 6-chloropurine and 2-amino-6-chloropurine with nucleophiles

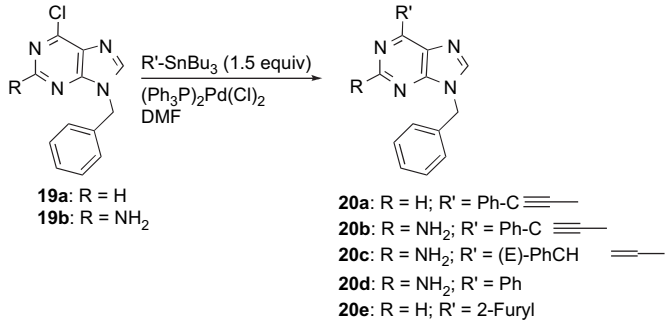
Substitution reactions of 6-halogenopurines with nucleophiles, particularly amines, have been widely exploited in medicinal chemistry, for example, in the synthesis of ATP analogues.[22] A library of 6-*O*-alkylguanine derivatives has been synthesised as cyclin-dependent kinase 1 and 2 inhibitors.[23,24] Recently, a rapid, high-yielding nucleophilic displacement reaction of 6-chloropurine **25** and 2-amino-6-chloropurine **26** with various nucleophiles under microwave irradiation has been described (Scheme 9 and



Scheme 6.

Table 4
The Suzuki–Miyaura reactions of 2,6-dichloro-9*H*-purine

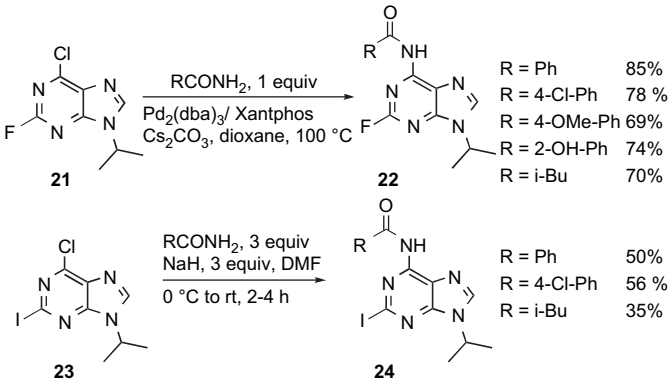
Boronic acid	Equiv	Product	Yield (%)
Phenyl	1	**17a**	55
		18a	5
4-Methoxyphenyl	1	**17b**	57
		18b	6
3-Nitrophenyl	1	**17c**	26
3-Pyridyl	1	**17d**	70



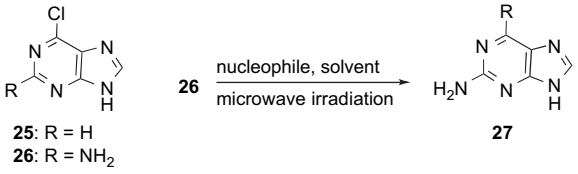
Scheme 7.

Table 5
Pd-catalysed coupling between purines **19a**,**b** and organotin reagents

Starting material	Product	Temperature (°C)	Time (h)	Yield (%)
19a	**20a**	75	2.5	77
19b	**20b**	80	21	64
19b	**20c**	100	21	77
19b	**20d**	110	24	30
19a	**20e**	95	17	93



Scheme 8.



Scheme 9.

Table 6
Reaction of 2-amino-6-chloropurine with nucleophiles

Nucleophile	Solvent	Molar proportion of nucleophile	Temperature (°C)	Time (min)	R (**27**)	Yield (%)
NH_2Bn	No solvent	10	110	15	NHBn	93
$NH_2(CH_2)_3Me$	No solvent	20	80	15	$NH(CH_2)_3Me$	84
$CyNH_2$	No solvent	30	130	1	NHCy	94
$PhNH_2$	No solvent	10	130	5	NHPh	96
$PhNH_2$	No solvent	10	130	5	NHPh	48
Morpholine	No solvent	10	90	1	*N*-Morpholyl	99
Piperidine	No solvent	10	90	1	Piperidyl	93
MeONa	NMP	3	100	1	OMe	99
EtONa	DMSO	3	100	2	OEt	83
EtONa	NMP	3	100	3	OEt	98
BnOH	DMSO	3	100	1	OBn	74
PhONa	DMSO	4	150	10	OPh	96
MeSNa	DMF	2.2	90	1	SMe	91
MeSNa	NMP	3	90	1	SMe	99
PhSNa	DMF	2	80	1	SPh	99

Table 6).[25] This method is particularly suitable for the rapid construction of libraries of purines with a high diversity at position 6. In a few minutes, 6-substituted purines **27** were obtained from **26** and primary amines, including anilines, and secondary amines, as well as *O*- and *S*-nucleophiles, including MeONa, EtONa, PhONa, MeSNa and PhSNa.

In 2007, Liu and Robins[26] reported a complete study of S_NAr reactions between 6-fluoro-, 6-chloro-, 6-bromo-, 6-iodo- and 6-alkylsufonylpurine nucleosides and nitrogen, oxygen and sulfur nucleophiles. In several cases, 6-halogenopurines do not follow the classical order of reactivity for S_NAr reactions of 1-halogeno-2,4-dinitrobenzenes (F>Cl>Br>I); the reactivity at C-6 in purines clearly depends on the leaving group and the nucleophile. For example, the relative ease of displacement with a weakly basic arylamine (aniline) was inverted (I>Br>Cl>>F), as compared to benzylamine (F>Br>Cl>I) (Table 7).

Table 7
Orders of leaving group reactivities with various 6-substituted purines

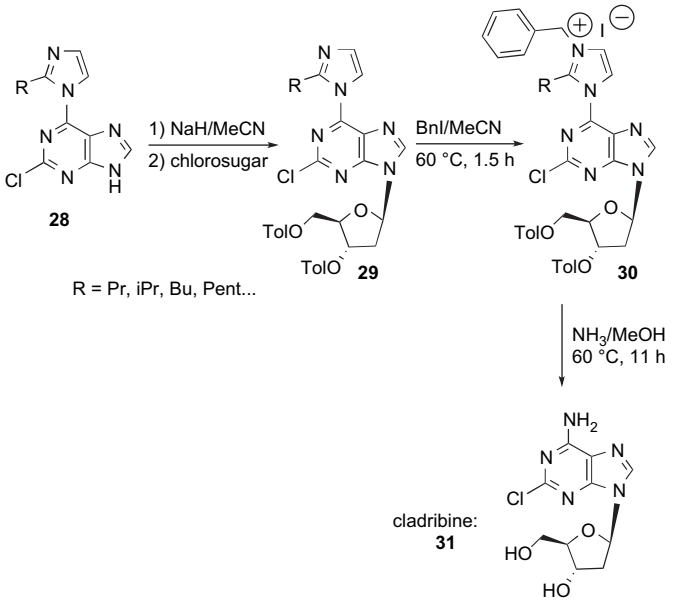
Nucleophile	Reactivity
$BuNH_2$	F>RSO_2>Br>Cl>I
MeOH/DBU	RSO_2>F>Br≈Cl>I
i-PentSH/DBU	RSO_2>F>Br≈I>Cl
$PhNH_2$	I>Br>RSO_2>Cl>F
$PhNH_2$/TFA	F>RSO_2>I>Br>Cl

3. Functionalisation at position 9: preparation of 9-substituted purine derivatives

3.1. Regioselective and stereoselective coupling of 6-(substituted-imidazol-1-yl)purines with 1-chloro-2′-deoxyribose

Alkylation of purines usually results in the formation of regioisomeric mixtures of *N*-7- and *N*-9-alkylpurines. The desired N-9 compound is normally the major product, but the formation of significant amounts of the N-7 isomer, as well as other alkylation products, is often observed.[27] Glycosylation of purines suffers from a similar lack of regioselectivity with the additional problem that complex diastereomeric mixtures may be encountered.

This traditional problem in purine chemistry was recently solved by Robins and co-workers.[27–29] Unsubstituted heteroaryl rings appended at C-6 of purines adopt essentially coplanar ring alignments, and it was reasoned that the proton above the N-7 atom would prevent any N-7 alkylation. Indeed, the N-9 regiospecific glycosylation of purine acceptors with furanosyl and pyranosyl sugar donors was improved by the presence of an imidazole substituent at position 6 of the purine ring (**28**). Such purines undergo regiospecific N-9 glycosylation, but the stereoselectivity of glycosylation (α or β) was still dependent on the solvent used for the glycosylation reaction. Such derivatives (**28**) were readily prepared, improving the solubility and solvation of the purine in mixed solvents. Glycosylation of the 6-sodium salts of (imidazol-1-yl)purines **28** with a protected chlorosugar proceeded with high regioselectivity (100%) and stereoselectivity (98%) in high yield (>90%) to afford exclusively the β anomer-N-9 regioisomers **29** (Scheme 10).[29] Ammonolysis of the imidazolium salts **30**, generated in situ from **29** with BnCl and NaI, gave high yields of the adenine derivative, Cladribine **31**, a clinical anticancer drug.



Scheme 10.

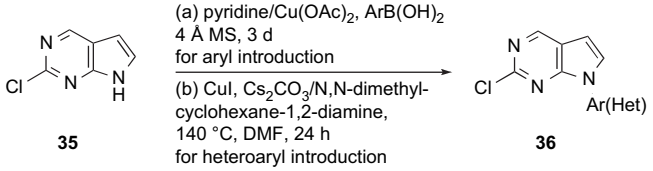
3.2. Michael addition of adenine

Highly efficient Michael addition reactions of adenine **32** to α,β-unsaturated esters **33** under microwave irradiation to form **34a–d** have been reported (Scheme 11),[30] where it was unnecessary to protect the exocyclic amino group, due to its relatively weak nucleophilic character. Similarly, coupling of 6-chloropurine (**25**) with benzyl acrylate in DMF, in the presence of base (DIEA) at room temperature, gave the 9-substituted product in 74% yield.[31] Furthermore, methyl, ethyl, or *tert*-butylacrylate also react regioselectively with 6-chloropurine under microwave irradiation in water to give the 9-substituted products in good yield.[32]

These authors noted that, again, no protection was necessary if amino or hydroxy groups were present in the molecule, and that the purine was exclusively alkylated at N-9.[32]

3.3. Arylation at N-9 of 7-deazapurines

Lam–Chan[33] or Buchwald[34] coupling conditions can be applied to perform N-arylation of the N-7 atom of pyrrolo[2,3-*d*]pyrimidines such as **35** to form **36** (Scheme 12). The Lam–Chan protocol was applicable for the introduction of *meta*- and *para*-substituted aryl rings, but it could not be extended to *ortho*-substituted aryl rings or heterocyclic systems. In these cases, the transformation was carried out using the Buchwald procedure. The pyridine/$Cu(OAc)_2$ combination was found to be optimal for the Lam–Chan reaction, while the use of Cs_2CO_3/*N*,*N*-dimethylcyclohexane-1,2-diamine at 140 °C in DMF gave superior results for the Buchwald procedure.[35]

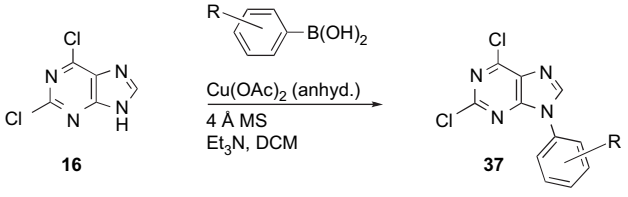


Scheme 12.

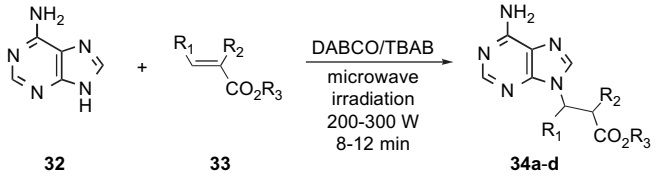
3.4. Arylation at N-9 of purines

In 2001, Ding and co-workers[36] described one of the first N-9 arylations of purines such as **16** via boronic acid/cupric acetate/NEt_3 in dichloromethane to form **37** (Scheme 13 and Table 8).

Bakkestuen and Gundersen later described[37] a regioselective N-9 arylation of purines **38** using arylboronic acids **39** in the presence of Cu(II) and an organic base. Trials revealed phenanthroline to give



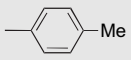
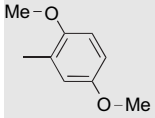
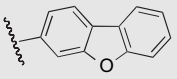
Scheme 13.



34	R^1	R^2	R^3
a	H	H	Et
b	H	H	*n*-Bu
c	H	Me	Et
d	Me	H	Et

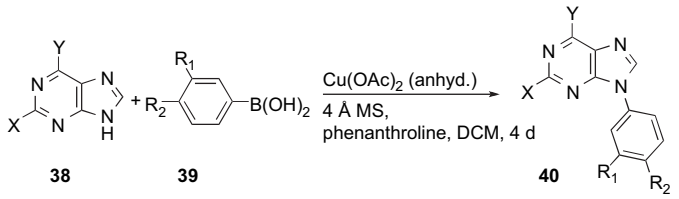
Scheme 11.

Table 8
N-9 Arylation of purine

N-9 Aryl substituent	Yield (%)	*N*-9 Aryl substituent	Yield (%)
	45		47
	43		44

significantly higher yields of **40** than triethylamine or pyridine (Scheme 14 and Table 9).

Under these conditions, 2-amino-6-chloropurine **26** did not react, due to solubility problems. N-9 Arylation was, however, possible with various boronic acids in comparable conditions



Scheme 14.

Table 9
Cu-mediated reaction between purines **38** and arylboronic acids **39**

X	Y	R_1	R_2	Yield (%)
H	Cl	H	H	71
H	Cl	H	CH_3	68
H	Cl	H	OCH_3	52
H	Cl	H	Cl	41
H	Cl	Cl	H	73
Cl	Cl	H	H	52
Cl	Cl	H	CH_3	48
NH_2	Cl	H	H	42
H	NH_2	H	H	No reaction
H	SCH_3	H	H	76
H	SH/SPh	H	H	81
H	2-Thienyl	H	H	68

($Cu(OAc)_2$/pyridine/molecular sieves/CH_2Cl_2) and with good yields (41–81%) on condition that the reaction was carried out on the bis-Boc-amino 6-chloropurine derivative.[38]

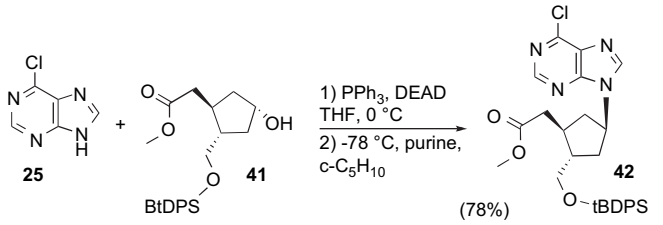
At present, these arylations have been achieved with phenyl- and substituted phenylboronic acids (Table 9). Other conditions may be needed to generalise this reaction with heteroarylboronic acids. The use of Cs_2CO_3/*N*,*N*-dimethylcyclohexane-1,2-diamine/Het-X at 140 °C in DMF was, however, recently found to be the optimum conditions to introduce heterocyclic systems on the pyrrole nitrogen of various pyrrolo[2,3-*d*]pyrimidines (7-deazapurines).[35]

It is noteworthy that this copper(II)-mediated N-9 arylation methodology greatly enhances the structural diversity of possible purine libraries, since other methods, such as anionic alkylation with an alkyl halide, Mitsunobu alkylation and various glycosylation reactions, do not allow regioselective N-9 arylation.

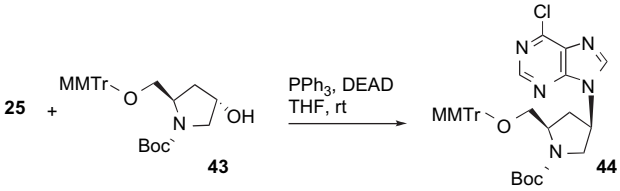
3.5. Mitsunobu alkylation at N-9 position with either primary or secondary alcohols

Nucleoside analogues are generally prepared either by direct coupling of a base with a carbon substrate or by construction of purines and pyrimidines from aminoalkanes. The first route usually involves fewer steps and gives higher overall yields. All of the reported approaches, however, do not work efficiently with electron-rich purines, such as guanine, due to side reactions.

The triphenylphosphine-diethyl (or -diisopropyl) azodicarboxylate Mitsunobu inversion procedure has become very useful to synthesise nucleoside analogues.[39–44] Thus analogues **42** and **44** have been synthesised from 6-chloropurine **25** and alcohols **41** and **43**, respectively (Schemes 15 and 16).



Scheme 15.

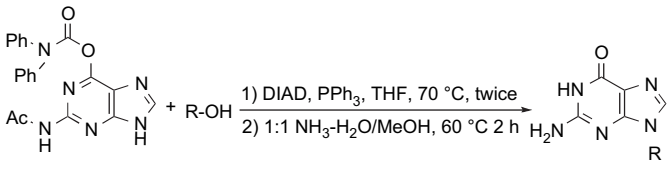


Scheme 16.

This alkylation reaction tolerates virtually any alcohol without additional acidic hydrogens (pK_a<10–12).[12] The large number of commercially available alcohols offers a considerable diversity in libraries of *N*-9 substituted purine derivatives.[45]

Coupling of unprotected guanine with alcohols under Mitsunobu conditions has, however, been reported to be impossible, probably due to a solubility problem with THF, the best solvent for the Mitsunobu reaction.[46,47]

Although successful coupling of various alcohols with 2-amino-6-chloropurine was reported by Toyota and co-workers in 1993,[46] it was only recently that a general method for highly N-9 regioselective and high-yield coupling of a series of alcohols with a protected guanine (**45**) to form **46a–j** was reported (Scheme 17 and Table 10).[47] This method was applied to various 2- or 6-(di)chloropurines.



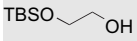
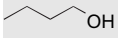
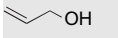
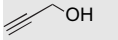
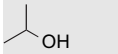
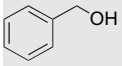
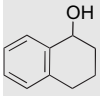
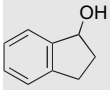
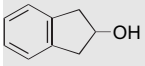
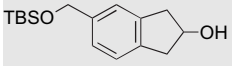
Scheme 17.

This method is compatible with a very large range of substrates and allows stereochemical control of the couplings, as shown by the isolation of a single diastereoisomer when a diastereoisomeric alcohol was employed.[47]

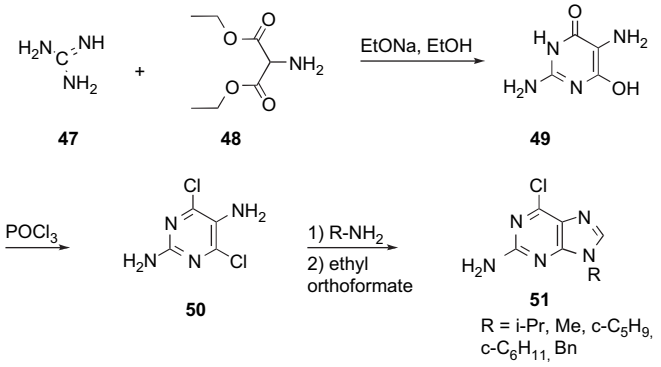
3.6. Use of an aminoalkane and pyrimidine precursors

Condensation of guanidine **47** and ethyl aminomalonate **48** under basic conditions led to 2,5-diamino-4,6-dihydroxypyrimidine

Table 10
Reaction substrate scope in the guanine–alcohol coupling

Alcohol	Product	Yield (%)
	**46a**	86
	**46b**	85
	**46c**	83
	**46d**	85
	**46e**	76
	**46f**	81
	**46g**	72
	**46h**	78
	**46i**	74
	**46j**	84

49, which is a precursor of 2-amino-6-chloropurines **51**, via the 2,5-diamino-4,6-dichloropyrimidine **50**[48,49] (Scheme 18) bearing an *N*-9 substituent arising from substitution of one chlorine atom in **50** by a primary amine.[16,19,48]



Scheme 18.

The synthesis of pyrimidine **49** was performed on a 37-g scale in 65% yield, while the subsequent chlorination was achieved in a $POCl_3$/benzyltriethylammonium chloride/PCl_5/MeCN mixture in only 32% yield.[48] An improvement of this chlorination was reported in 2000[49] using the Vilsmeier reagent, which gave the bis[(dimethylamino)methylene]amino derivative of **50**. This derivative had to be carefully hydrolysed in acidic conditions to give **50** in 42% yield from **49**.

4. Functionalisation at N-1, N-3, N-7 and C-8

4.1. Preparation of xanthine derivatives from 6-aminouracils (Traube synthesis)

Xanthines constitute an important class of pharmacologically active compounds, which are commonly used for their effects as mild stimulants, bronchodilators, phosphodiesterase inhibitors, CFTR chloride-channel activators and adenosine receptor antagonists.[50]

The syntheses of xanthines from 6-aminouracils, such as **52**, generally involve multistep reactions and require tedious chromatographic separations, which limit the synthesis of a large number of compounds. In addition, the Traube synthesis is generally incompatible with the introduction of complex *N*-substituents,[51] although interesting xanthine derivatives have been prepared from 5-bromo-6-aminouracil **53** (Scheme 19), 5,6-diaminouracil such as **56** (Scheme 20),[52,53] and *N*-1(or *N*-3) monosubstituted-5,6-diaminouracil (Scheme 19).[54]

In the present example, the cyclisation step (**54a**–**f** to **55a**–**f**) was carried out under microwave irradiation (Scheme 19).

Novel 1,3-dipropyl-8-(1-heteroarylmethyl-1*H*-pyrazol-4-yl)-xanthine derivatives such as **59**, **61a**,**b** and CVT-5440 have been synthesised[55,56] as potent and selective A_{2B} adenosine receptor antagonists or inverse agonists[56] (Scheme 20). These targets were synthesised in a similar fashion from **56** by coupling the corresponding carboxylic acids **57**, **60** and 4-benzyloxybenzoic acid in the presence of a coupling agent (EDCI, EDAC). The ring closure of the intermediate pyrimidines (e.g., **58**) was effected by treatment with aqueous NaOH to afford **59**, **61a** or **62**, the CVT-5440 precursor.

CVT-5440 (Scheme 20) is a high-affinity A_{2B} adenosine receptor antagonist for the potential treatment of asthma.[57]

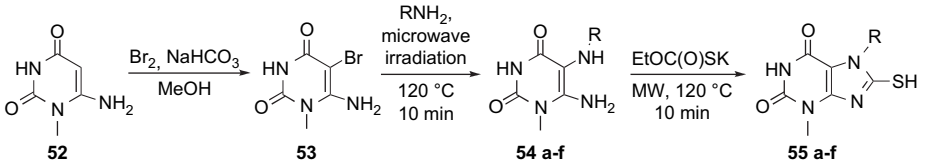
4.2. Synthesis of purines from an imidazole precursor

An alternative approach to the synthesis of xanthines from aminouracils is to use an imidazole starting material. A solution-phase synthesis of a xanthine substituted at the N-1 and N-7 positions was achieved from benzyl alcohol **63** as a substitute for Wang resin (Scheme 21).[50] The *N*-substituted glycine benzyl ester **65** was obtained by reacting **63** with bromoacetic acid to give **64**, which in turn, could be treated with butylamine in THF to provide **65**. Treatment of **65** with ethoxymethylene cyanamide gave intermediate **66**, which upon reaction with a strong base underwent imidazole ring formation to afford **67**. Imidazole **67** was treated with an isocyanate to provide **68** in 90% yield before subsequent ring closure with NaOEt to give the 1,7-disubstituted xanthine **69** in 90% yield.

The new synthetic procedure summarised in Scheme 21 allowed the preparation on solid support of di-, tri-, or tetrasubstituted xanthines **75** (Scheme 22).[50]

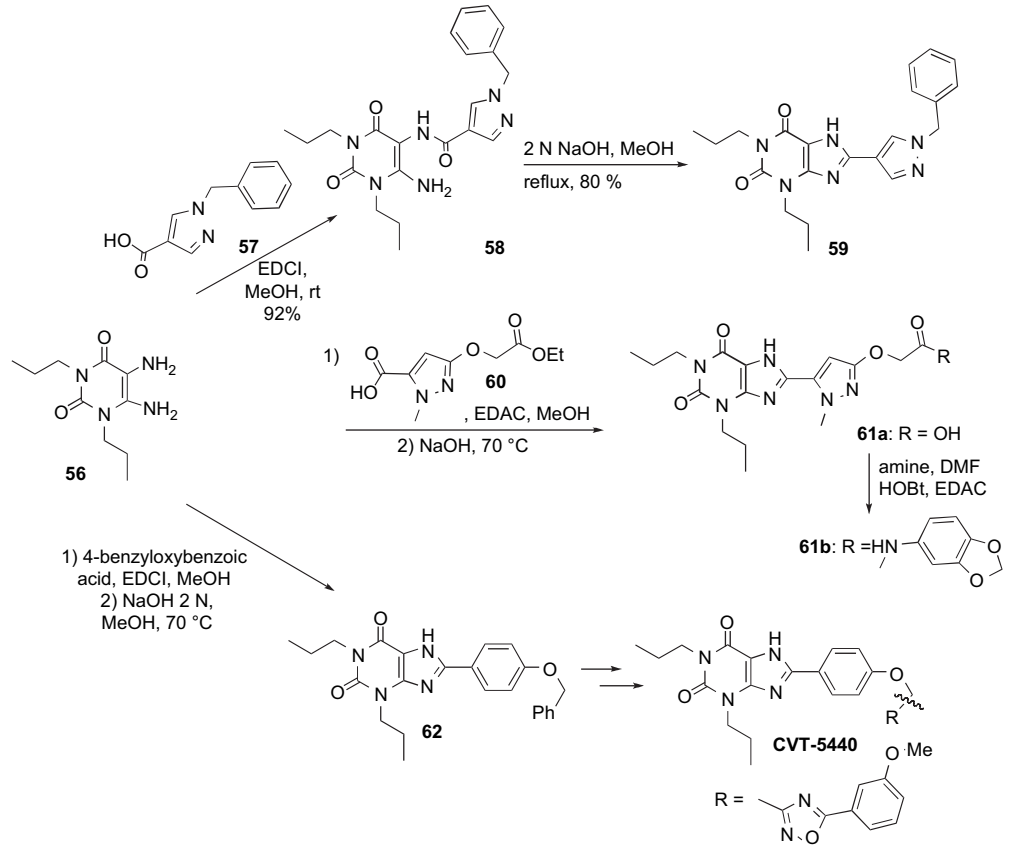
4.3. Solid-phase synthesis of xanthine derivatives

The versatility of this chemistry was illustrated by the preparation of a library of 22 di-, tri- or tetrasubstituted xanthines

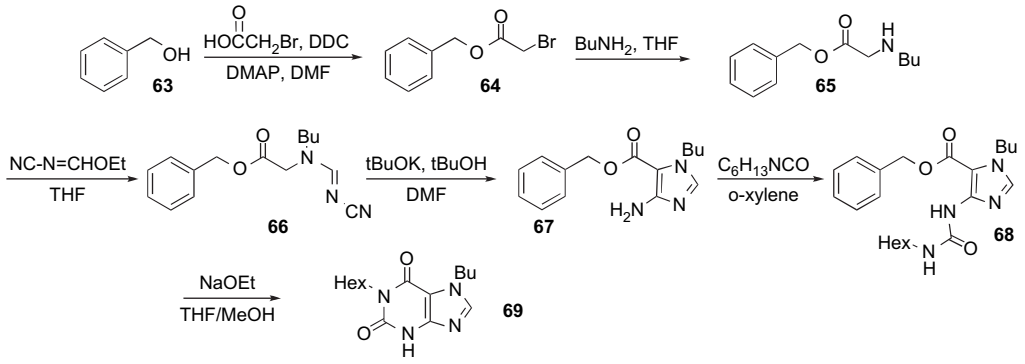


a: R = nBu, b: R = Bn, c: R = $PhCH_2CH_2$, d: R = *p*-F-$PhCH_2CH_2$,
e: *R* = *o*-$PyCH_2$, f: R = *m*-$PyCH_2$

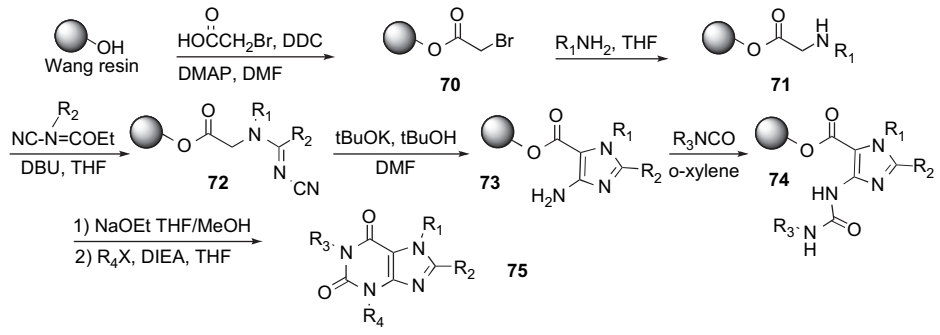
Scheme 19.



Scheme 20.

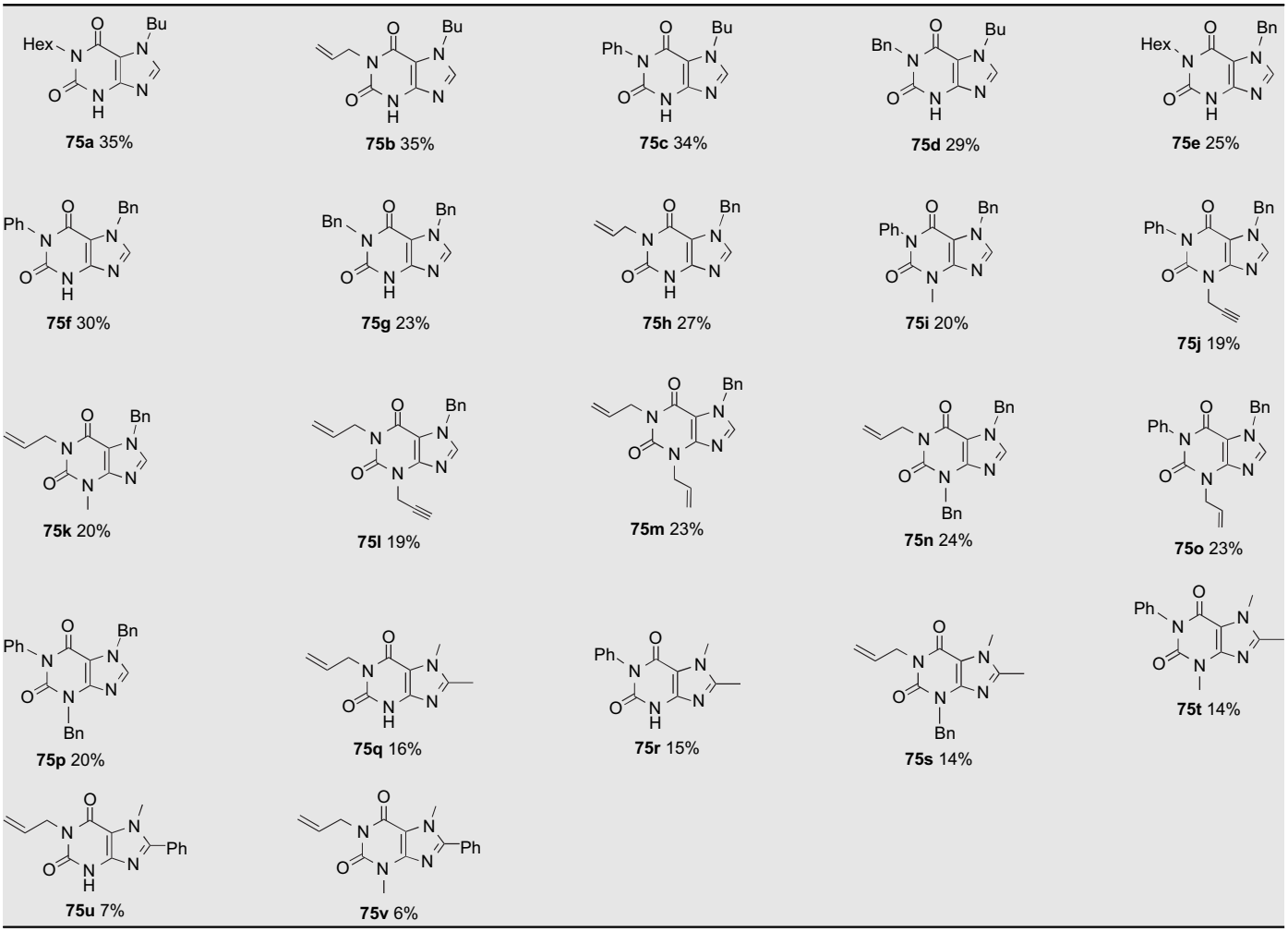


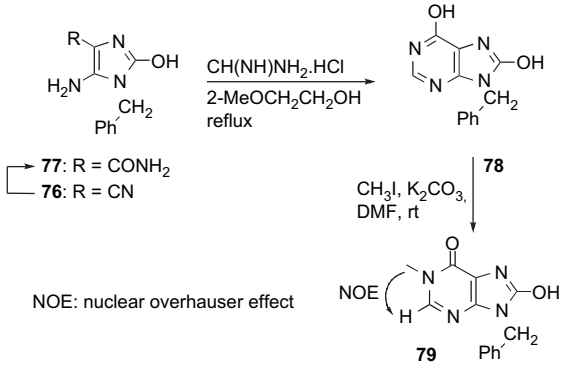
Scheme 21.



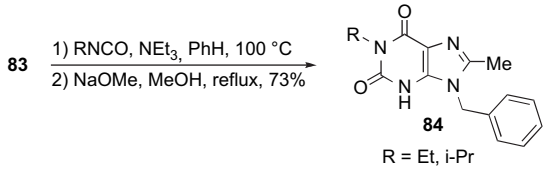
Scheme 22.

Table 11
Library of substituted xanthines





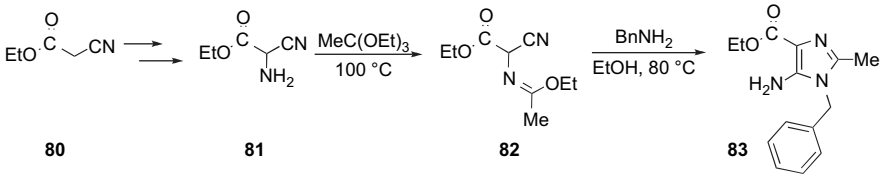
Scheme 23.



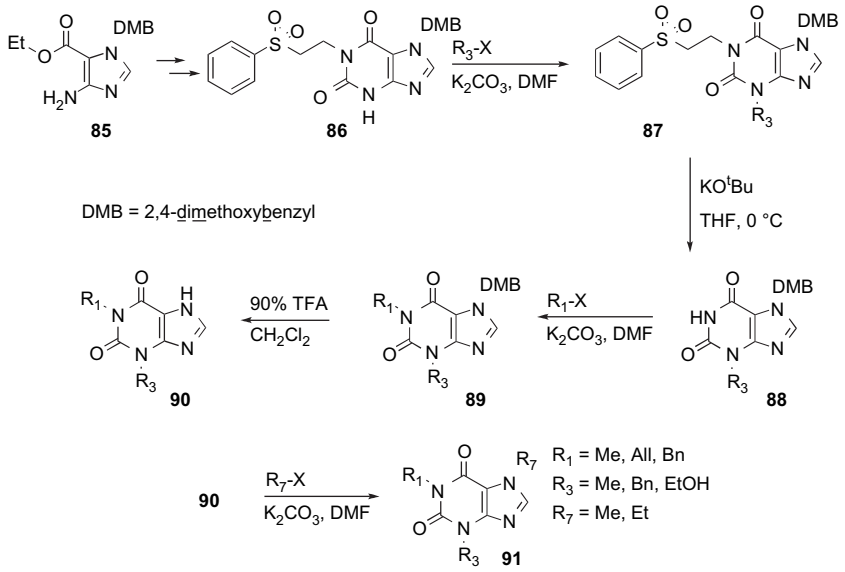
Scheme 25.

(**75a**–**v**) (Table 11). The solid-phase synthesis (**70**–**75**, Scheme 22) was adapted from preliminary solution-phase studies (Scheme 21). The overall yields obtained were 14–35%, indicating an average yield of ≥75% for each step of the solid-phase reaction, for all but the most encumbered analogues (**75u** and **75v**).

Imidazole precursors such as **76**[58] allow the synthesis of purines bearing substituents at N-1, C-8 and N-9 (**77**–**79**), as outlined in Schemes 23–25.



Scheme 24.



Scheme 26.

5-Aminoimidazole derivatives such as **83** can be elaborated in a few steps from **80** and ethyl 2-aminocyanoacetate **81** via **82**, as shown in Scheme 24.[59]

Aminoimidazole **83** was treated with various isocyanates (RNCO), setting the stage for cyclisation step in methanol/MeONa under reflux to afford 1,8,9-trisubstituted xanthines **84** (Scheme 25).[59,60]

Recently, an elegant synthesis from aminoimidazole **85** of a key precursor (**86**) of functionalised xanthines was reported[51] that does not need to use isocyanates to introduce the *N*-1 substituents (Scheme 26). This method, which allows maximum flexibility for modification at N-1 (**88**→**89**), N-3 (**86**→**87**) and N-7 (**90**→**91**) is based on the selective removal of each *N*-protecting group under mild conditions. This allows efficient access to a range of disubstituted xanthines with the less common 1,7- and 3,7-substitution patterns, as well as 1,3,7-trisubstituted derivatives (**91**) (Scheme 26), from a common precursor **86**. N-3 Protection can be achieved, if required, with allylmethyl chloride in the presence of K_2CO_3, and cleaved under neutral conditions by Pd(0) catalysis.

4.4. Synthesis of *N*-1,*N*-7-disubstituted purines from 6-chloropurine

N-1,*N*-7-Disubstituted purines **97a**–**o** (Table 12) can be synthesised in five steps from 6-chloropurine **25** and **92** via an initial Michael addition. Subsequent acid-catalysed hydrolysis of **93** afforded **94** that was N-1-alkylated with butyl iodide to give **95**. Quaternisation of **95** occurred on heating with further BuI to afford **96**, which gave **97**, the *N*-9 deprotected product, in the presence of ammonia (Scheme 27).[31]

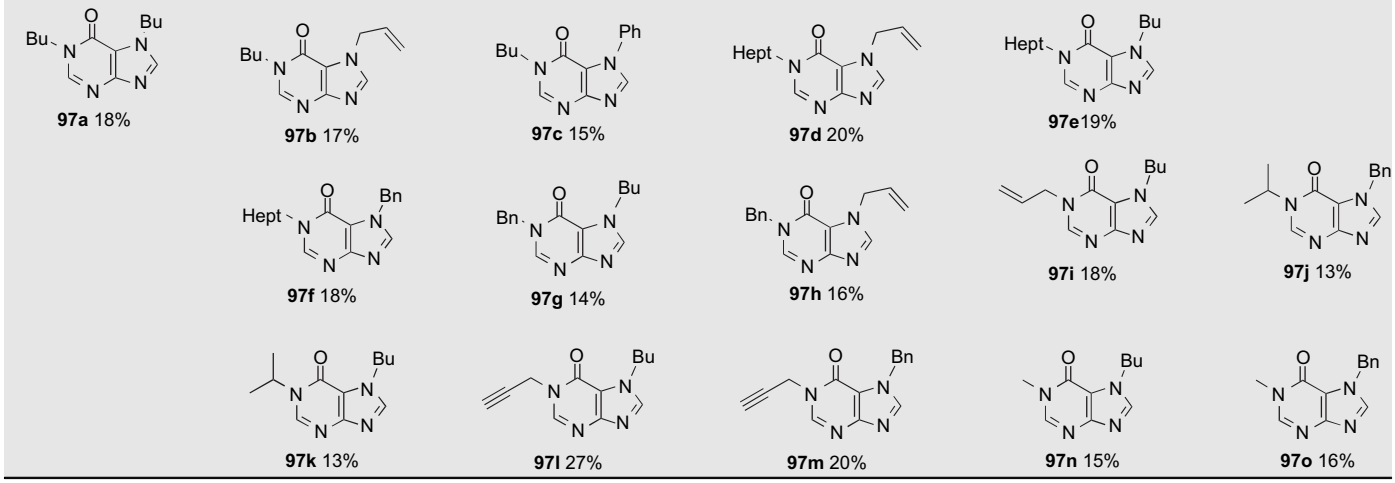
This methodology, developed on solid-phase, has permitted the synthesis of a library of 15*N*-1,*N*-7-disubstituted purines in 13–27% overall yield (average yield of 70% for each step) (Table 12).

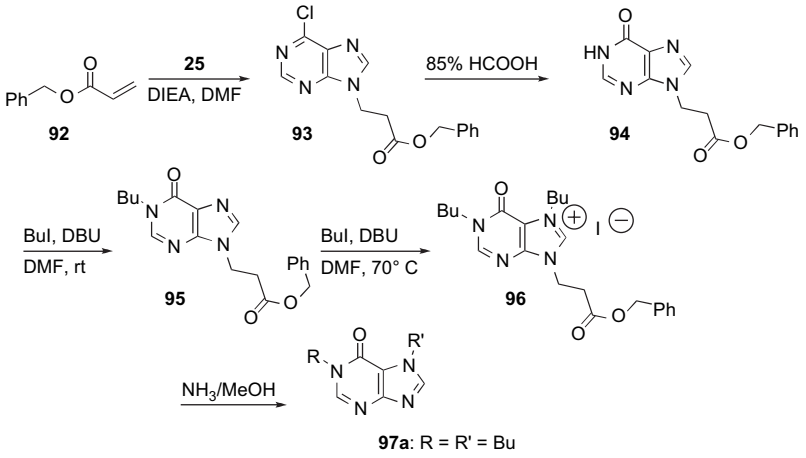
5. Functionalisation at position 2

5.1. Pyrimidine precursors of 2,6,8,9-tetrasubstituted purines

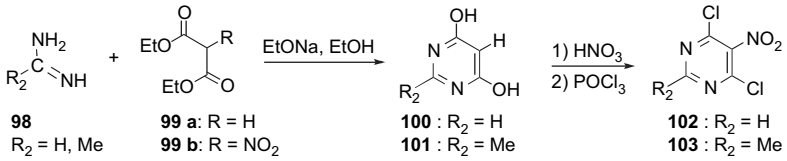
Pyrimidines are versatile substrates for the synthesis of variously substituted purines. Pyrimidine synthesis from amidines

Table 12
Library of *N*-1,*N*-7-disubstituted purines





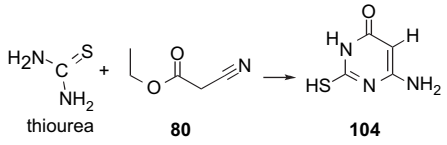
Scheme 27.



Scheme 28.

constitutes a very efficient strategy to prepare 2-substituted purines, due to the great variety of commercially available alkyl, aryl or heterocyclic amidines (Scheme 28),[61,62] which provide the first point of structural diversity.[61,63] For example, amidines **98** were condensed with diethyl malonate (**99a**) in the presence of sodium ethoxide to obtain the 4,6-dihydroxypyrimidines **100** and **101**. Controlled nitration with fuming nitric acid and chlorination with phosphorus oxychloride afforded the corresponding dichloropyrimidines (**102** and **103**) in good yields.[62]

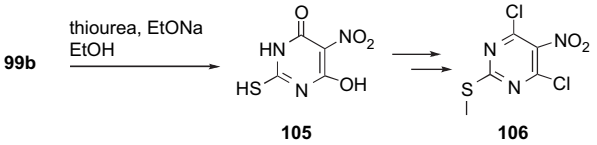
Replacement of diethyl malonate by ethyl cyanoacetate **80** in an alkaline medium provides a 6-aminopyrimidinone **104** (Scheme 29), another interesting purine precursor.[64–67]



Scheme 29.

Diethyl nitromalonate **99b** has not been widely used to synthesise 5-nitropyrimidines, since, as shown above, good yields for the nitration of dioxopyrimidines **102** or **103** are obtained.

In the case of the 2-thiopyrimidine derivative **105**, however, Harnden and Hurst have observed that the use of commercial diethyl nitromalonate might be a better strategy than the nitration of 2-methylthiopyrimidine-4,6-diol.[68] The 5-nitropyrimidine-2-thiol (**105**) was obtained in 41% yield, the low yield being the result of the effect of the 5-nitro group on the hydrolytic stability of the 2-mercapto substituent (Scheme 30). A methylation of **105** gave the 2-methylthio derivative in 64% yield, which was chlorinated to give **106** in good yield.



Scheme 30.

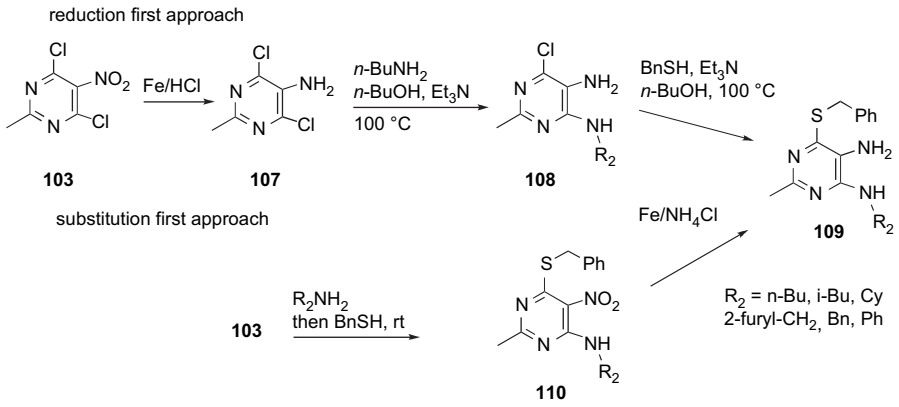
5.2. Synthesis of 2,6,8,9-tetrasubstituted purines

A synthesis of tetrasubstituted purines has been reported from 4,6-dichloro-2-methyl-5-nitropyrimidine (**103**), itself prepared according to a literature procedure.[69,70] The second point of diversity is introduced by the substitution of one chlorine atom of the 5-aminopyrimidine **107** by various amines (see Section 5.1 and Scheme 28 for the first point of diversity).[71] Incorporation of an alkylthio group at the 6-position in **103** or **108** led to **110** or **109**, respectively (Scheme 31). Cyclisation with aldehydes in the presence of $FeCl_3$ afforded **111**, which was oxidised to the corresponding sulfone **112** for displacement by various amines to give the third point of diversity (**113**) (Scheme 32). The fourth point of diversity at position C-8 can be introduced with aldehydes (Scheme 32).

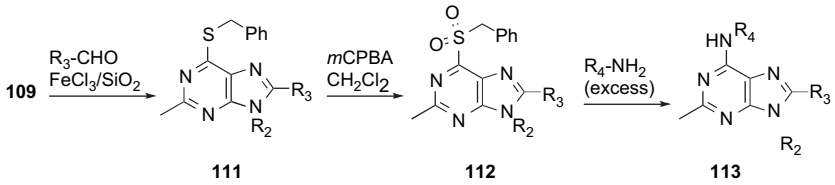
The 2-methylthiopyrimidine **106** (Scheme 30) constitutes an interesting starting material towards libraries of 2,6,8,9-tetrasubstituted purines with complete regiospecificity at every step, including a wide variety of substituents at the 9 position.[72,73]

This liquid-phase methodology (Schemes 31 and 32) was validated by the synthesis of a 216-member 2,6,8,9-tetrasusbstituted purine library (**113**) (Scheme 32),[74] and was applied recently on solid support[75] (**114**–**119**) to build a library of 24 purines (**120**) (Scheme 33).

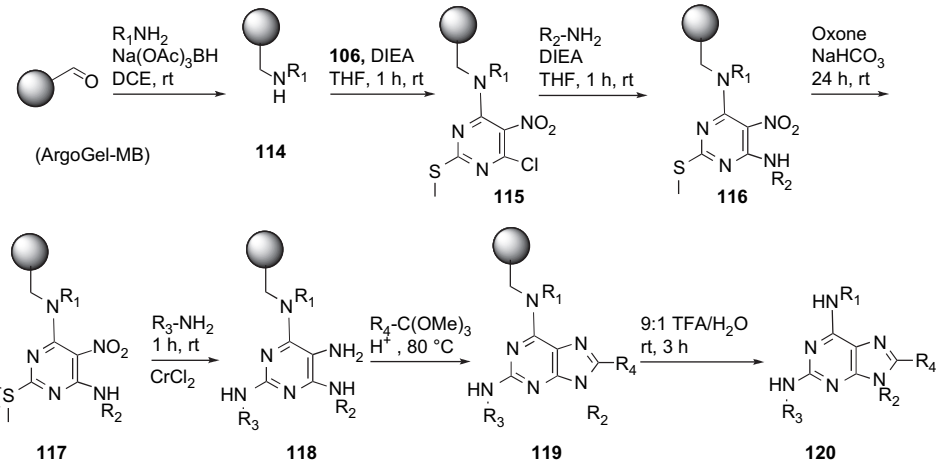
Substitution of the methyl sulfone at position 2 can be achieved easily on the pyrimidines **117**, which leads to 2-amino-substituted pyrimidines **118**. On the contrary, it should be noted that substitution by amine nucleophiles of 2-methyl- or 2-phenylsulfonylpurines is considered to be difficult.[73,75–77] Functionalisations at position 2 in purines are otherwise carried out from 2-halogenopurines, since 2-halogens (F, Cl, Br, I) are generally less reactive than the 6-halogen in S_NAr. Whitfield and co-workers noted in 2003 that S_NAr displacement reactions of 6-*O*-alkyl-2-fluoropurine with various weak



Scheme 31.



Scheme 32.



Scheme 33.

nucleophiles (anilines) were dramatically accelerated in the presence of trifluoroacetic acid and 2,2,2-trifluoroethanol as solvent.[78]

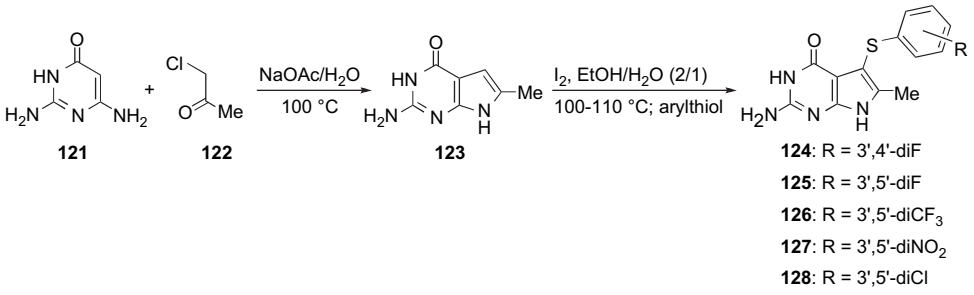
5.3. Synthesis of 7-deazapurines (pyrrolo[2,3-*d*]pyrimidines) from pyrimidine precursors

7-Deazapurines (pyrrolo[2,3-*d*]pyrimidines)[79] are among the most intensively studied purine analogues and display various biological activities. A number of synthetic strategies are available including their preparation from various pyrimidine precursors.[80,81]

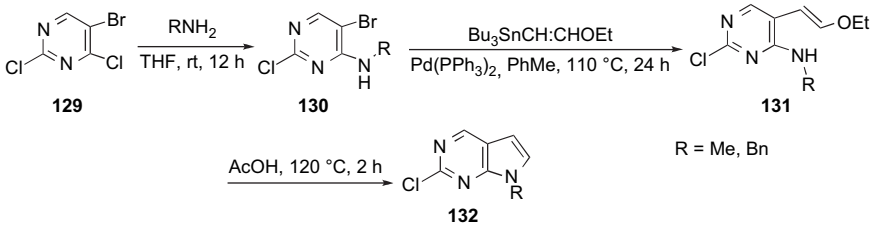
Compounds **124**–**128** (Scheme 34) were synthesised as potential thymidylate synthase inhibitors, from the key intermediate, 2-amino-4-oxo-6-substituted-pyrrolo[2,3-*d*]pyrimidine **123**,[82,83] (itself prepared from diaminopyrimidin-4-one **121** and chloroacetone **122**) to which various arylthiols were conveniently attached at the 5-position via a modification of an oxidative thiolation procedure reported by Gangjee and co-workers (Scheme 34).[79,82]

Similarly, 7-deazapurines may be obtained from pyrimidines bearing adjacent amino and vinyl functionalities, e.g., **131**. The different reactivities of the three halogens of the pyrimidine **129** allow a regioselective amination to give **130**, followed by a regioselective Stille coupling to yield the intermediates **131**. A thermal cyclisation step in acetic acid affords the desired pyrrolo[2,3-*d*]pyrimidines **132** (Scheme 35).[35]

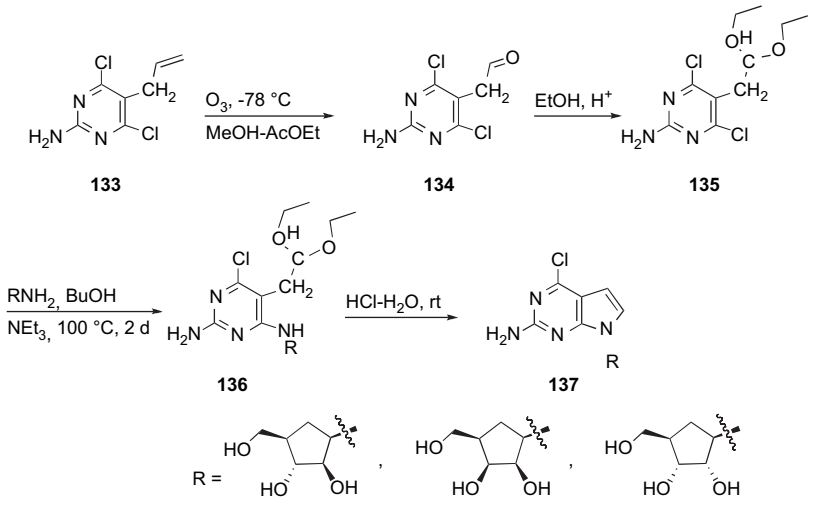
Pyrrolo[2,3-*d*]pyrimidines have also been prepared from 5-allyl-2-amino-4,6-dichloropyrimidine **133**, itself obtained from guanidine and ethyl allylmalonate in two steps.[84] An ozonolysis of **133** leads to the aldehyde **134**, which is protected as the diethylacetal derivative **135**. A monosubstitution by a primary amine gives **136**, which is cyclised to the 7-deazapurines **137** in dilute aqueous hydrochloric acid (Scheme 36).[84]



Scheme 34.



Scheme 35.



Scheme 36.

6. Functionalisation at position 8

6.1. Synthesis of 8,9-disubstituted adenines

The highly potent water-soluble protein chaperone HSP90 inhibitor **138** (R=*t*-BuCH_2) (Fig. 2) is an 8,9-disubstituted adenine, which induced inhibition of tumour growth.[85] It is synthesised in three steps from adenine by alkylation at position 9 followed by bromination at position 8 with Br_2 in a mixture of THF, AcOH and H_2O. Exchange of the bromo atom of **139** for a sulfur and substitution of the thionoadenine **140** (Scheme 37) by the phenyldiazo derivative **141** gave intermediates **142**.

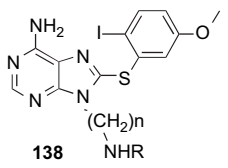


Figure 2.

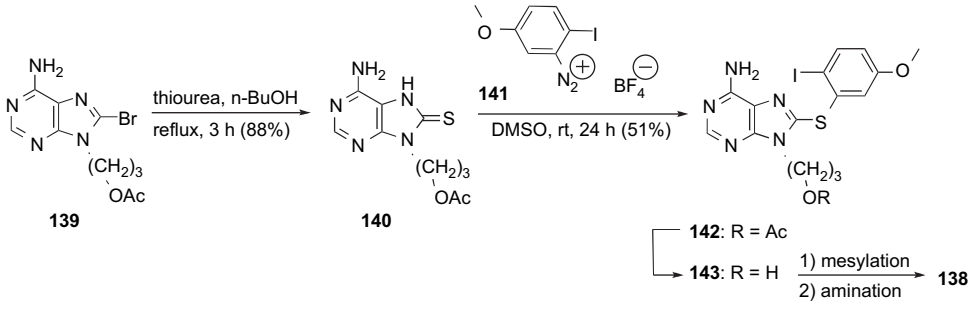
The alcohol function of **143** is then revealed to create the mesyl leaving group required for subsequent amination.

Further HSP90 inhibitors **146** and **149** can be synthesised according to two related strategies starting from di- or triaminopyrimidines **144** or **147** (Schemes 38 and 39). In the first sequence, the butyl substituent of **146** is introduced prior to the cyclisation of **145** and before amination at C-6 with NH_3 (Scheme 38). Alternatively, the butyl substituent of **149** can be introduced at the last step from the 4,5,6-triaminopyrimidine precursor **147** (Scheme 39),[85] via cyclisation of the amido intermediate **148**.

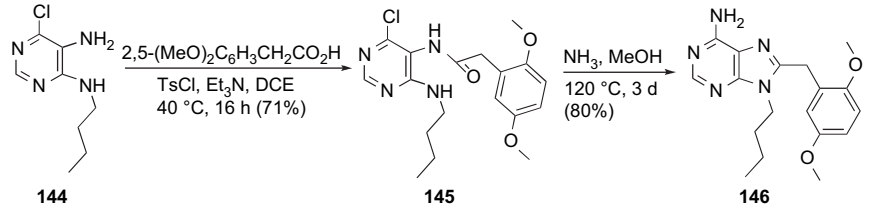
6.2. Synthesis of 2,8,9-trisubstituted adenines

6.2.1. Synthesis of 2,8,9-trisubstituted adenine inhibitors of HSP90

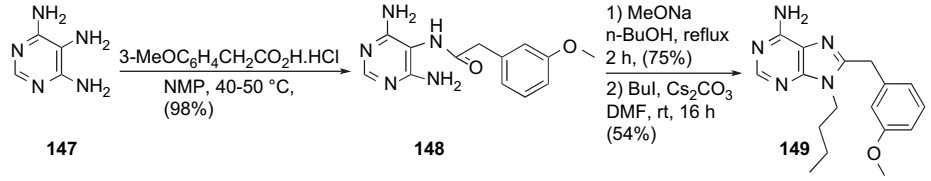
Commercially available 2,4,5,6-tetraaminopyrimidine **150** (Scheme 40) and 2-fluoroadenine **152** (Scheme 40) have been featured in strategies towards the preparation of libraries of functionalised 2-fluorinated purines, from which very potent 8-arylsulfanyl-adenine inhibitors of HSP90 were synthesised.[86] Interestingly, the fluorine atom at C-2 increased the solubility and



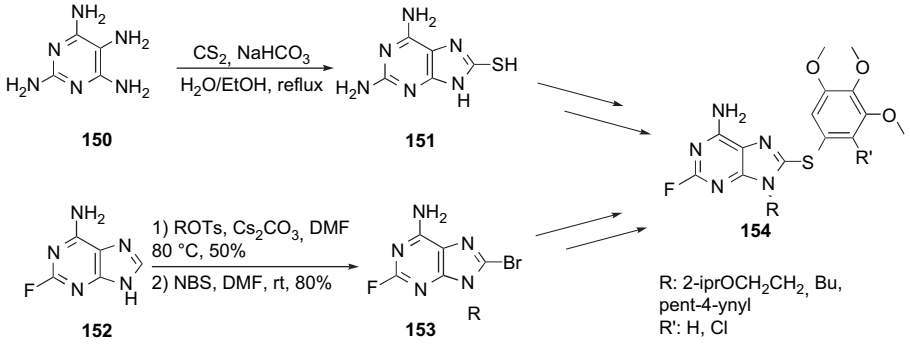
Scheme 37.



Scheme 38.



Scheme 39.



Scheme 40.

potency of the resulting inhibitors. Cyclisation of **150** in CS_2 gave the purinethiol **151** before reaction with aryl iodides and alkylation at N-9 afforded the 8-arylsulfanyl-adenines **154**. Transformation of the *C*-2-amino group to fluorine in **151** with HF/pyridine in the presence of sodium nitrite[86] gave the 2-fluoroadenines **154**. Similarly, the target 2-fluoroadenines **154** were synthesised from 2-fluoroadenine **152** after alkylation at N-9 with tosylates, bromination at C-8 with *N*-bromosuccinimide giving **153** and thioarylation at C-8 in DMF/K_2CO_3.

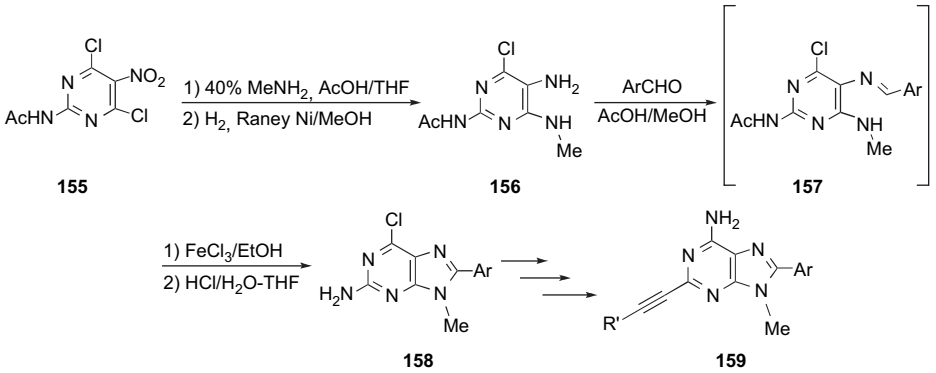
6.2.2. 8-Aryl-9-methyladenine derivatives from a 4,6-dichloropyrimidine precursor

Treatment of *N*-1-(4,6-dichloro-5-nitropyrimidin-2-yl)acetamide **155** with an aqueous solution of methylamine neutralised with acetic acid gave the monomethylamino derivative in good yield before nitro reduction with Raney nickel afforded the diamino derivative **156**. The Schiff base **157**, obtained by condensation of **156** with an aldehyde, was directly converted by oxidative ring closure[87] into 2-amino-8-aryl-6-chloropurine **158**, which was further functionalised to **159** (Scheme 41).[88]

Considerable diversity can thus be introduced at C-8, N-9 and C-2 with aldehydes, amines and alkynes, respectively.

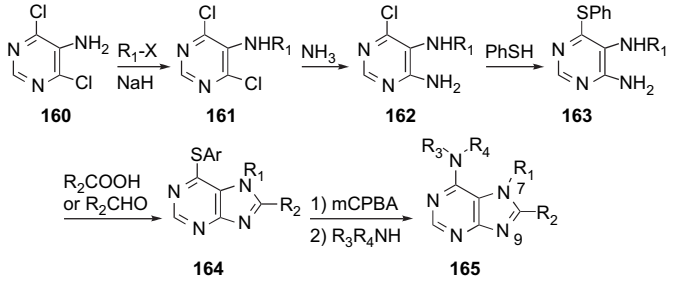
6.3. Synthesis of 6,7,8-trisubstituted purines

N-7-Substituted purines can be synthesised by direct alkylation of 6-chloropurine **25**, but, in this case, *N*-7- and *N*-9-substituted purines are obtained as a mixture of regioisomers (see Section 3.1). Liu and co-workers have recently reported an efficient and regiospecific strategy to prepare *N*-7-substituted purines (Scheme 42).[89]



Scheme 41.

This method is based on the mono-amination of pyrimidines **161** with ethanolic ammonia in a sealed tube at 120 °C, followed by displacement of the second chloro group with an excess of thiophenol in refluxing *n*-butanol, leading to the intermediates **163**. Cyclisation in the presence of a carboxylic acid or an aldehyde gave 7,8-disubstituted purines **164**. The strong electron-donating effect of the newly introduced amino group in pyrimidines **162** prevents a second amination.



Scheme 42.

A 40-membered library of 6,7,8-trisubstituted purines (**165**) was constructed, demonstrating the potential utility of this regiospecific strategy.

6.4. Preparation of 6,8-disubstituted purine analogues: thiazolopyrimidines

Thiazolopyrimidines are widely used bioisosteres of the purine base (Scheme 43) and this heterocycle can be obtained in one step by the reaction of a purine precursor, 4-chloro-5,6-diaminopyrimidine (**166**), with isothiocyanates or by the reaction of 5-amino-4,6-dichloropyrimidine **160** with isothiocyanates (Scheme 43 and Table 13).[90]

Table 13
Reaction of 4,6-dichloro-5-aminopyrimidine with aryl isothiocyanates

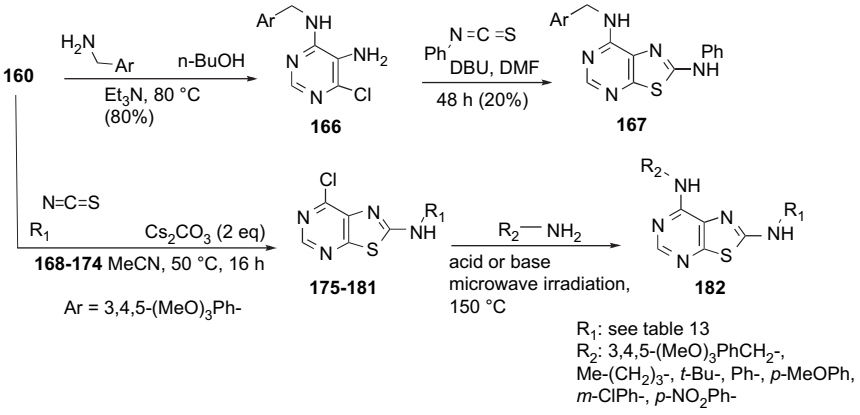
Entry	Isothiocyanate	R_1	Product	Yield (%)
1	**168**	Ph–	**175**	92
2	**169**	2,6-Me_2Ph–	**176**	90
3	**170**	*p*-MePh–	**177**	93
4	**171**	*p*-MeOPh–	**178**	95
5	**172**	*p*-CF_3Ph–	**179**	82
6	**173**	*p*-NO_2Ph–	**180**	50
7	**174**	3-Pyridyl–	**181**	80

These compounds (**175**–**181**) are interesting 6,8-disubstituted purine analogues that can be obtained in one or two steps from a readily available pyrimidine precursor (**160**).

The thiazolopyrimidines **175**–**181** can be aminated at the last step under microwave irradiation to give the disubstituted thiazolopyrimidine derivatives **182**.

7. Conclusions

The purine motif is a privileged substructure, which is recognised by an enormous number of proteins.[91] This biological relevance and the occurrence of the purine heterocycle in nature make it an attractive target for chemical modification. Being one of the most studied heterocycles in medicinal chemistry, a wide range of



Scheme 43.

chemical reactions can now be applied, opening up the possibility of building large libraries of new molecules bearing a great diversity of functions in seven directions around its small core. Recent advances in purine chemistry have been illustrated in this review, either by new synthetic routes or by improvements of known reactions, which widen the scope, and allow better regioselectivity with a higher yield. This article highlights the potential for combinatorial chemistry on the purine ring; for example, with only two non-identical substituents and seven possible points of attachment, as many as 42 different regioisomeric disubstituted purines can be envisaged. Thus, while much of the purine chemical space remains to be explored, the recent advances in purine chemistry should lead to more potent and specific inhibitors of known biological targets and pave the way to new inhibitors or antagonists of targets that have yet to be described. In conclusion, purines offer an exceptional scaffold for the synthesis of relevant tools in biology through a combination of the high level of regio-functionalisation and the diversity of the chemistries that are possible with this heterocycle.

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Biographical sketch

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