Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 5274–5286

Synthesis and reactivity of (*RS*)-6-chloro-7- or 9-(1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)-7*H*- or 9*H*-purines bearing a nitrobenzenesulfonyl group on the nitrogen atom

Mónica Díaz-Gavilán,[a] Duane Choquesillo-Lazarte,[b] Josefa M. González-Pérez,[b] Miguel A. Gallo,[a] Antonio Espinosa[a] and Joaquín M. Campos[a,*]

[a]*Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada, Spain*
[b]*Departamento de Química Inorgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada, Spain*

Received 21 February 2007; revised 23 March 2007; accepted 26 March 2007
Available online 30 March 2007

Abstract—The *O*,*O*-acetalic compounds (*RS*)-3-methoxy-1-[(2)- or (4)-nitrobenzenesulfonyl)]-1,2,3,5-tetrahydro-4,1-benzoxazepine have been studied in the Lewis acid-mediated condensation with 6-chloropurine. 6-Chloropurine leads to the *N*-7″ aminalic bond in the cyclic products and mainly to the *N*-9″ aminalic bond in the acyclic ones. Substitution of the chlorine atom at the 6″ position of the purine moiety is more feasible when the ring is alkylated at *N*-7″ than at *N*-9″. Exchange with a hydroxyl group is performed with water traces in deuterated dimethylsulfoxide at room temperature in a solvent-mediated process. The exchange with strong nucleophiles (e.g., thiophenol) does not need further activation.

1. Introduction

In our effort to prepare antiproliferative agents with an acetalic function, our group has reported the synthesis and characterization of 1,2,3,5-tetrahydro-4,1-benzoxazepines *O*,*O*- and pyrimidine *O*,*N*-acetals of type **I**, **II** and **III** (Fig. 1), which turned out to be moderate antiproliferative agents on MCF-7 human breast cancer cells.[1,2] The synthesis of the *O*,*N*-acetals was accomplished from the corresponding *O*,*O*-acetals[3] in a Lewis acid-mediated process.

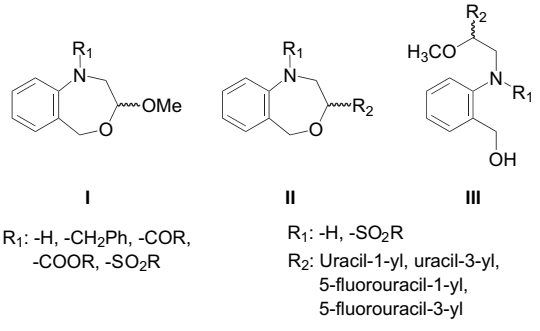


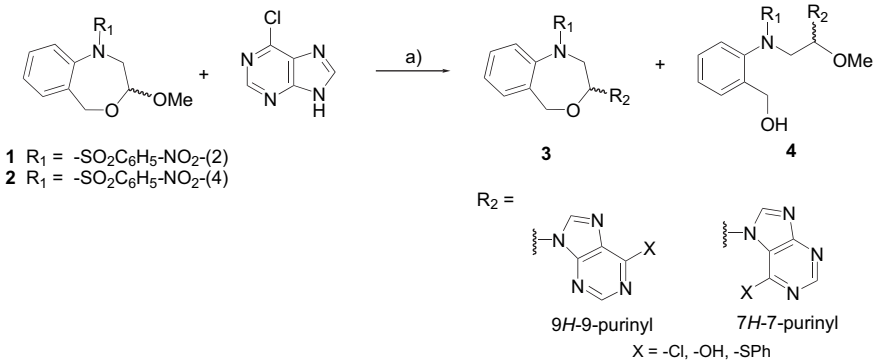
Figure 1. Structures of the previously described *O*,*O*- and *O*,*N*-acetalic compounds type **I**, **II** and **III**.

Both cyclic and acyclic *O*,*N*-acetals (**II** and **III**), in which the pyrimidines are linked to the C-3 atom through their *N*-1″ and *N*-3″ atoms, were products in the reaction between 1-nitrobenzenesulfonyl-1,2,3,5-tetrahydro-4,1-benzoxazepines (**1** and **2**[1]) and the nitrogen bases. After a report on the factors that control the regioselectivity in this reaction,[2] it is our objective to complete the study with a description of the condensation process between the same substrates and a purinic base. In this paper, new data about this mechanism are reported and the stability of the final compounds is discussed. 6-Chloropurine (6-CP) has been used due to its versatility to undergo further modifications. The final *O*,*N*-acetals were evaluated as antiproliferative agents against the MCF-7 cancerous cell line. Comparison of the biological activities found for pyrimidine and purine derivatives has given us further information about the role of the benzoxazepine moiety and the efficiency of this family of compounds to act as drugs endowed with a new anticancer mechanism of action.

The Lewis acid-mediated transformation of *O*,*O*- into *O*,*N*-acetals has been widely described in bibliography and the existence is well known of several factors with regard to the nucleophile, the electrophile and the Lewis acid, that

Keywords: Acetals; Benzoxazepines; Medium ring heterocycles; Purines; X-ray.
* Corresponding author. Tel.: +34 958 243848; fax: +34 958 243845; e-mail: jmcampos@ugr.es

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.155



Scheme 1. Condensation reactions between *O*,*O*-acetals and 6-chloropurine. Reagents and conditions: (a) HMDS (4.0 equiv), TMSCl (4.0 equiv), $SnCl_4$ (4.0 equiv), anhydrous MeCN, 50 °C, more than 48 h.

can influence the velocity and the regioselectivity of this process.[3] Purine alkylation follows different approaches such as nucleophile attack on halides,[4,5] Mitsunobu activated electrophiles,[6,7] or alkylation by modification of the Vorbrüggen reaction, and mainly gives rise to alkylation at the *N*-9″ purine atom. Fewer cases of regioselective *N*-7″ alkylation have been reported.[8,9] The high number of factors affecting the regioselectivity makes it difficult to successfully predict the position of alkylation[3,8–11] and this fact has caused many authors to build up the purine ring from the appropriate synthons.[12]

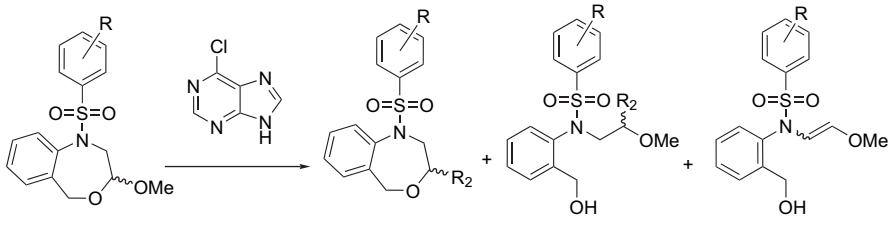
Our aim is to contribute with further data presenting a case of *N*-7″ regioselective alkylation of 6-chloropurine, together with other results obtained in the Lewis acid-mediated alkylation of 6-chloropurine with the sulfonamides **1** and **2**, and the carbamate **3**[1] (Scheme 1). All the *N*-9″ and *N*-7″ purine *O*,*N*-acetals[13] show in vitro antiproliferative activities against the MCF-7 human breast cancer cell line in the submicromolar range (data not shown). This is an outstanding fact that has not being previously reported in bibliography, and these compounds may serve as prototypes for the development of even more potent structures. Conditions reported as optimal in the reaction with pyrimidines[2] have been used in the preparation of the purine derivatives: silylating agents 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 4.0 equiv) and chlorotrimethylsilane (TMSCl, 4.0 equiv), the Lewis acid tin(IV) tetrachloride ($SnCl_4$, 4.0 equiv), anhydrous MeCN at 50 °C under an inert atmosphere.

2. Results and discussion

2.1. Lewis acid-mediated reaction between (*RS*)-3-methoxy-*N*-nitrobenzenesulfonyl-1,2,3,5-tetrahydro-4,1-benzoxazepines (1 and 2) and 6-chloropurine

Condensation of the sulfonyl compounds **1** and **2** with 6-chloropurine produced the cyclic and acyclic *O*,*N*-acetals showed in Table 1.

Table 1. Products of the reaction between the *O*,*O*-acetals **1** and **2**, and 6-chloropurine (50 °C, 69 h)



Substrate	R	R_2	Products (yield, %)		
1	(2)-NO_2	6-Chloropurin-9-yl	**3a** (2)	**3a+3b** (34)	**3a+3b+4a+4b** (47)
1	(2)-NO_2	6-Chloropurin-7-yl	**3b** (32)		
1	(2)-NO_2	6-Chloropurin-9-yl	**4a** (7)	**4a+4b** (13)	
1	(2)-NO_2	6-Chloropurin-7-yl	**4b** (6)		
2	(4)-NO_2	6-Chloropurin-9-yl	**3c** (2)	**3c+3d** (17)	**3c+3d+4c+4d** (39)
2	(4)-NO_2	6-Chloropurin-7-yl	**3d** (15)		
2	(4)-NO_2	6-Chloropurin-9-yl	**4c** (22)	**4c+4d** (22)	
2	(4)-NO_2	6-Chloropurin-7-yl	—		
1	(2)-NO_2	—	**5a**[a] (2)		**5a**[a] (2)
2	(4)-NO_2	—	**5b**[b] (7)		**5b**[b] (7)

[a] (*E*+*Z*) mixture.
[b] *E* isomer.

From these results, the following can be observed:

(1) Substrates **1** and **2** afford similar total yields of the *O*,*N*-acetalic products, a value that is slightly higher for **1** (47% vs 39%).
(2) In both cases, the formation of cyclic *O*,*N*-acetals occurred regioselectively, the purine being linked through its *N*-7″ atom (**3a/3b**=2/32, **3c/3d**=2/15). However, the *O*,*N*-acetalic compound in the acyclic series was selective only when **2** was the substrate, leading exclusively to the *N*-9″ compound (**4a/4b**=7/6, **4c/4d**=22/0). In no case was formation of *N*-3″ alkylated purines detected.
(3) The ratio of cyclic/acyclic *O*,*N*-acetals was different depending on the substrate of the reaction: from **1** the highest yield was found for cyclic products (**3a**,**b/4a**,**b**=34/13), while from **2**, the acyclic derivatives were the main products (**3c**,**d/4c**,**d**=17/22).

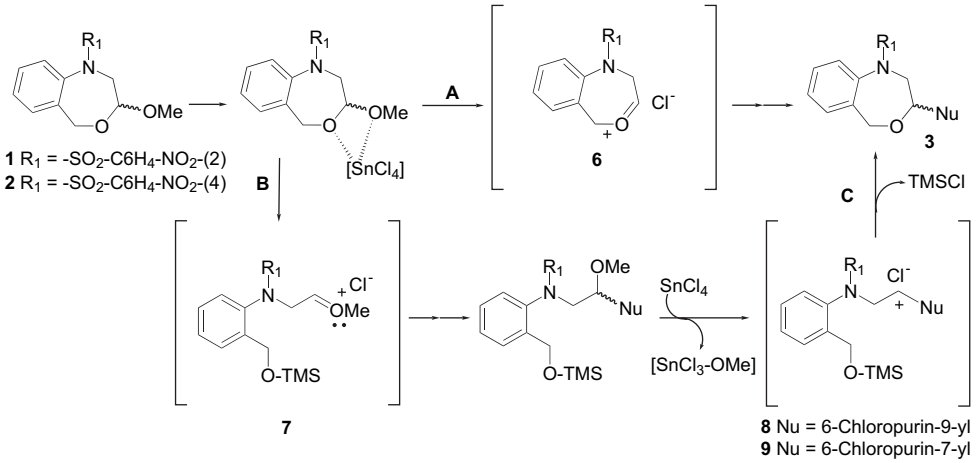
In accordance with what was found in the condensation reaction with pyrimidines, the different cyclic/acyclic and *N*-7″/*N*-9″ product ratios indicate that the change of the nitro group on the benzenesulfonyl moiety from *ortho* to *para* can modify the structural characteristics of the reaction intermediates in such a way as to influence the behaviour of the reaction. Our group has previously reported a S_N1 mechanism explaining the formation of *O*,*N*-acetals from (*RS*)-3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepines[14] or (*RS*)-3-methoxy-1,2,3,5-tetrahydro-4,1-benzoxazepines[2] and pyrimidines, in which cyclic (**6**) and acyclic (**7**) oxocarbenium ions of the substrates are formed (Scheme 2). The formation of the final cyclic or acyclic compounds depended on the rate of formation of both ion types (steps A and B), the affinity of the nucleophile for each ion type and the possibility of a later cyclization of the acyclic products (step C).

Therefore, any stabilizing effect which can increase the population of one of the intermediate ions facilitated the formation of the final type of *O*,*N*-acetal. It has been observed that in the case of **6**, when the nitro group is *ortho*, there is an approximation of the negative oxygen towards the positive charge on the benzoheterocycle (up to 2.67 Å). Therefore stabilization of the cyclic ions occurred.[2] This fact is consistent with the higher yields of cyclic compounds found in the reaction between **1** [R=–SO_2–C_6H_4–NO_2–(2)] and 6-chloropurine when compared to the reaction between **2** [R=–SO_2–C_6H_4–NO_2–(4)] and 6-chloropurine. This approximation has been previously reported as an important factor influencing the regioselectivity of **1** and **2** condensations with pyrimidines.[2]

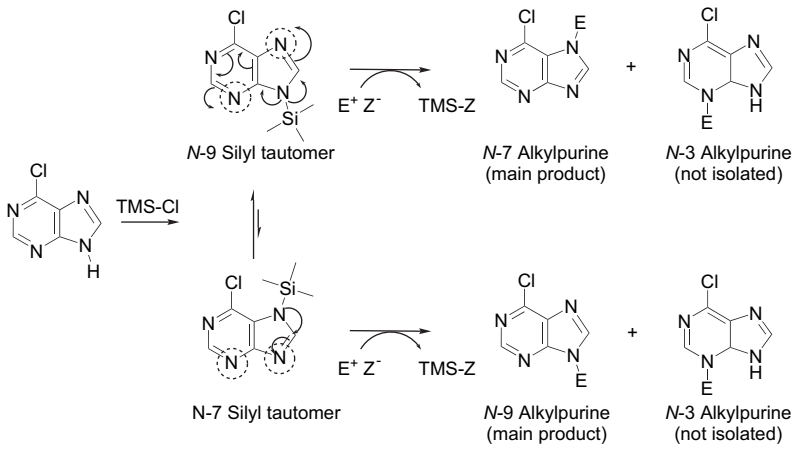
According to that previously described cyclic *O*,*N*-acetals could also be formed by cyclization of carbenium ions type **8** or **9**[2,14] (step C, Scheme 2). Both ions with an *N*-9″ or *N*-7″ alkylated purine (**8** or **9**, respectively) could be subjected to a stabilizing cession of a negative charge towards the cationic position exerted by the sulfonyl group. We have postulated that in ion type **7** one of its oxygen atoms approximated to the positively charged positions (2.19–2.28 Å). The intramolecular attack of the nucleophile benzyl hydroxy group at this point could be easiest in the *N*-7″ alkylated regioisomers due to the −I effect exerted by the chlorine atom on the acetalic position and the less favoured delocalization of the positive charge along the purine ring.

The aminalic bond between the C-3 atom of the seven-membered moiety and the N atom of the purine fragment depends on steric and electronic factors. Once silylation of purines has taken place on the imidazole ring, the equilibrium is settled between the *N*-7″ silyl and the most favoured *N*-9″ silyl tautomers (Scheme 3).[15] Each tautomer reacts with the electrophile or coordinates to the Lewis acid through its free nucleophile position. If there is no coordination to the Lewis acid, i.e., in the case of electron-poor purines or in a nucleophile solvent such as acetonitrile,[3] the main product would be the *N*-7″ alkylated purine, formed from the prevalent silylated tautomer *N*-9 (Scheme 3) (examples can be found from regioselective *N*-7″ isomers in reactions of nucleoside formation carried out in acetonitrile[3,9]).

When the formation of σ complexes between the Lewis acid and the purine takes place, the situation becomes more complex. The transformation is possible from the kinetic product (*N*-7″ alkyl purine) to the thermodynamic one (*N*-9″ alkylpurine).[3,9,16] The velocity of this process depends on the activation energy of the transition state and therefore the ratio of the *N*-7″/*N*-9″ alkyl products is different depending on the structure of the starting material. From the results that have been obtained in our case, this process could take place in



Scheme 2. Proposed mechanism for the Lewis acid-assisted transformation of *O*,*O*- into *O*,*N*-acetals.



Scheme 3. Tautomeric equilibrium of silylated 6-chloropurine and alkylation in the absence of Lewis acid coordination. Nucleophile nitrogen atoms are indicated within dotted lines. E^+Z^-: electrophile (oxocarbenium ion) and counterion.

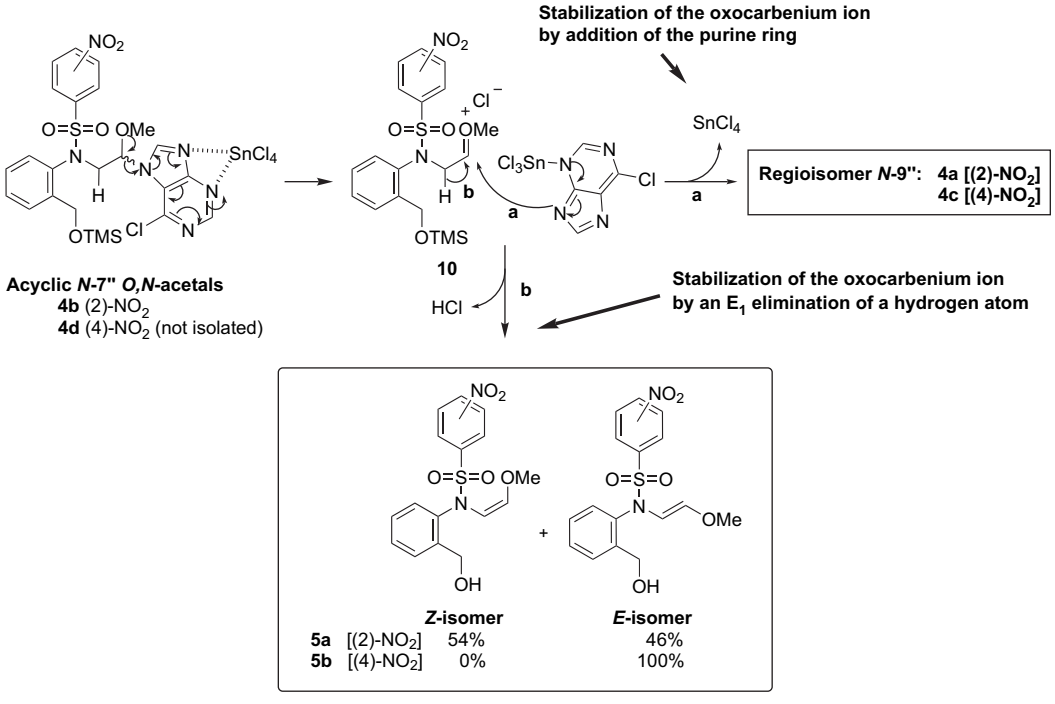
acyclic products but does not seem to happen in the cyclic ones.

2.2. Other products in the reaction of 1 and 2 with 6-chloropurine

Compounds **6a** and **6b** were obtained along with the cyclic and acyclic *O*,*N*-acetals in the reaction of 6-chloropurine with **1** and **2**, respectively. Their yields are low (<10%) but their importance lies in the information that they provide on the mechanism of the reaction with 6-chloropurine as none of these olefins have been isolated in the corresponding reactions with U (uracil) or 5-FU (5-fluorouracil).

These compounds could have been originated in a process, which shared the reaction mechanism with the *N*-7″→*N*-9″ transformation, via elimination of the purine ring after its activation as a leaving group by the coordination of the Lewis acid to one of its electron-rich positions. This elimination could happen in an E_1 or E_2 fashion and it would be easier for the highest energy *N*-7″ regioisomers than for the more stable *N*-9″ ones. The formation of olefins would be justified by the resonance of the final electronic system.

According to an E_1 mechanism, loss of the purine ring would lead to oxocarbenium ions, which could either attack nucleophile positions of the purine giving rise to the formation of the *N*-9″ *O*,*N*-acetals, or eliminate one α proton with the formation of a double bond (Scheme 4). The progress of the cationic intermediate in one way or another would depend on the speed of each process. This mechanism could explain the mixture of *Z*/*E* isomers[17] (54/46) that was obtained from **1**.



Scheme 4. E_1 Mechanism proposed for the formation of olefins from acyclic *O*,*N*-acetals.

In the case of an E_2 process, the purine and one α-hydrogen are eliminated simultaneously and thus would explain the exclusive formation of the *E* isomer observed for **2**.[18] This coordination of the Lewis acid to the purine ring, leading to the elimination of the latter, could also be expected to happen on the cyclic *O*,*N*-acetals. However, no cyclic olefins have been isolated. This result agrees with the apparent absence of *N*-7″→*N*-9″ transformations observed in cyclic compounds.

2.3. Effect of the substituent R_1 on the formation of *O*,*N*-acetals derived from 6-chloropurine

The following three consequences can be drawn:

(1) Compound **1** led to the best yields in the total formation of *O*,*N*-acetals of 6-chloropurine.
(2) The best selectivity in the formation of cyclic compounds was found for substrate **1** (cyclic/acyclic ratio=2.61). This may be the consequence of the stabilization of the cyclic cations (**67**) by approximation of the electron rich (2)-nitro groups.
(3) The highest selectivity for the *N*-7″ *O*,*N*-acetals in cyclic compounds was obtained for sulfonamide compounds (*N*-7″/*N*-9″ ratio=16 for **1** and *N*-7″/*N*-9″ ratio=7.5 for **2**). The highest selectivity for the *N*-9″ *O*,*N*-acetals in acyclic compounds was obtained for substrate **2**.

2.4. Effect of the nucleophile in the formation of *O*,*N*-acetals from 1 and 2: comparison between 6-chloropurine and the pyrimidines uracil (U) and 5-fluorouracil (5-FU)

Comparing the results that have been obtained in the reactions between **1** and **2** and 6-chloropurine with those that were previously reported for the same substrates and the pyrimidines 5-FU and U,[2] it can be observed that the reactivity of 6-chloropurine is similar to the one of 5-FU, both affording lower total yields of the reaction products than those obtained with U in the same experimental conditions (Table 2).

2.5. Substitutions by nucleophiles on 6-chloropurine. Effect of the *N*-7 and *N*-9 purine alkylation on the stability of the 6-chloropurine moiety

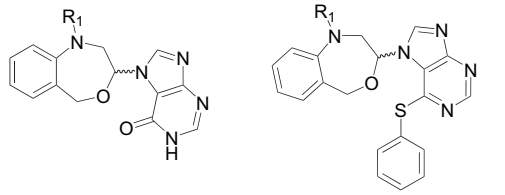
Chlorine substitution by nucleophiles takes place more easily in 7-(benzoxazepin-3-yl)purines than in 9-(benzoxazepin-3-yl)purines. The chloropurine hydrolysis[19,20] and the chlorine substitution by a thiol group[21,22] from chloropurine were previously reported. The substitution products shown in Figure 2 were obtained.

The highest electrophilic character of the C-6″ atom in 7-substituted purines was explained as a consequence of the inductive effect exerted by the benzoxazepine ring. The

Table 2. Comparison of the reactivity shown by chloropurine versus the previously reported one for pyrimidines

	6-Chloropurine (%)	U[a] (%)	5-FU[a] (%)
Total yields from **1**	47	72	53
Total yields from **2**	39	73	44

[a] See Ref. 2.



11 R_1 = -SO_2-C_6H_4-NO_2-(2)
12 R_1 = -SO_2-C_6H_4-NO_2-(4)
13: R_1 = -SO_2-C_6H_4-NO_2-(2)
14: R_1 = -SO_2-C_6H_4-NO_2-(4)
15: R_1 = -H

Figure 2. Products obtained by substitution of the chlorine atom in the 6-chloropurine moiety.

importance of this negative inductive effect (−I) when the benzoxazepine is bound to the *N*-7″ or the *N*-9″ atom of the purine moiety is reflected in the chemical shift of H-8″. This hydrogen, which appears more shielded than H-2″ in the ^{1}H NMR spectrum (DMSO-d_6) of 6-chloropurine (6-CP), shifts to lower fields in the *N*-7″ or *N*-9″ benzoxazepinyl purines. The same effect on H-8″ can be observed in 7-benzoxazepinylhypoxanthines when compared to the single hypoxanthine ring (H) (Table 3).

2.6. Change in DMSO at neutral pH

N-7″ Benzoxazepinyl-6-chloropurines with R_1=nitrobenzenesulfonyl (**3b** and **3d**) resulted unstable in DMSO-d_6 at rt or 4 °C as they underwent substitution of the chlorine atom to the hydroxy group. Neither the *N*-9″ benzoxazepinyl purines with R_1=nitrobenzenesulfonyl (**3a**, **3c**) nor the acyclic *O*,*N*-acetals of *N*-9″ alkyl 6-chloropurine (**4a**, **4c**, **4e**) underwent this transformation. Neither did the non-alkylated 6-chloropurine. No conclusion can be drawn for the acyclic *N*-7′ alkyl-6-chloropurine *O*,*N*-acetal (**4b**), which suffered a different kind of transformation under these conditions (vide infra).

The experimental conditions used are shown in Table 4. A higher proportion of water in the solvent mixture hastens the substitution process. The transformation from 6-chloropurine to 6-oxopurine occurs faster when R_1=(2)-nitrobenzenesulfonyl (**3b**→**11**, entries 6, 7 and 8) than when R_1=(4)-nitrobenzenesulfonyl (**3d**→**12**, entries 2, 3 and 4).

Previous evidence exists of the need to activate the 6-chloropurine ring to perform effective substitution of chlorine with nucleophiles.[23] We propose a mechanism to explain the substitution process in DMSO at neutral pH after having verified the stability of these compounds in other solvents such as CH_2Cl_2 and $CDCl_3$. This is based on the formation of intermediate aryloxysulfonium salts, which would be formed by the displacement of the chlorine atom by a DMSO molecule, as indicated in Scheme 5. Even weak nucleophiles such as water could attack these salts at the carbon 6″ of the purine ring or at the sulfur atom bearing formal positive charge. Both possibilities have been previously described in studies on alcoxysulfonium salts hydrolysis.[24] Despite existing evidence of stable alcoxysulfonium salts that can be isolated, in most cases they have been reported to be unstable and their hydrolysis can be performed by water traces existing in solvents.[24] Water molecules would thus act as an oxygen source for oxidation and DMSO would act as a catalyst that is regenerated in the process. This would explain the

Table 3. Chemical shifts (ppm) for H-8″ and H-2″ in 6-chloropurine (6-CP), hypoxanthine (H) and derived *O*,*N*-acetals (^{1}H NMR, DMSO-d_6, 300 MHz, rt)

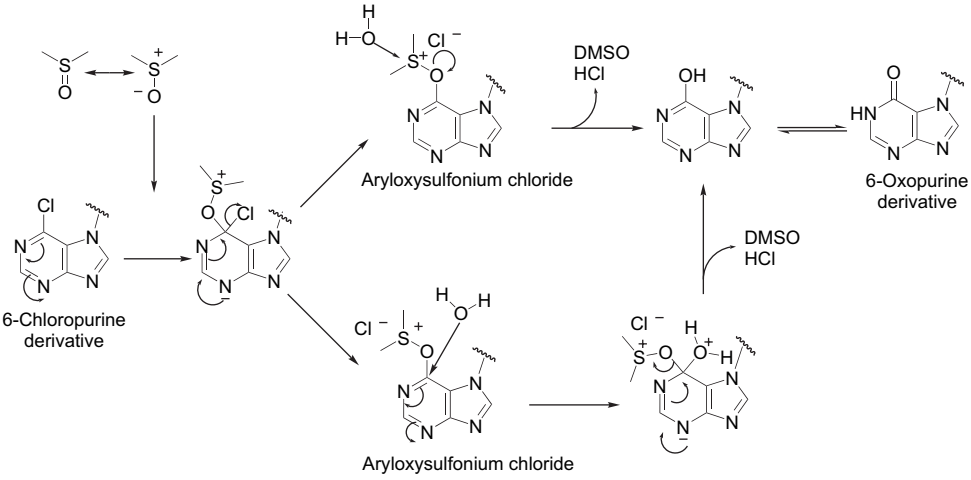
	6-CP[a]	**3c**	**3d**	**3a**[b]	**3b**	**4c**	**4c**[c]	**4a**	**4a**[c]	**H**[a]	**12**	**11**
H-2″	8.80	8.90	8.95	8.81	8.86	8.77	8.72	8.90	8.86	8.03	8.02	8.04
H-8″	8.73	8.95	9.04	8.89	9.00	8.90	8.85	8.99	8.99	8.17	8.45	8.55

Effect of the alkylation on *N*-9″ and *N*-7″ products.
[a] NMR 400 MHz.
[b] It refers to the minor conformer.
[c] See Ref. 18.

Table 4. Experimental conditions for 6-CP chlorine substitution in DMSO at neutral pH

Entry	Substrate (concentration)	Product (yield, %)	Reagents[c,d]	Time	Temperature
1	**3c** (27 mM)	Unchanged, 100[a]	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
2	**3d** (27 mM)	**14**, 100[a]	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
3	**3d** (10 μM)	Unchanged, not determined[b]	DMSO-d_6, H_2O (16 mM)	6 days	rt
4	**3d** (10 μM)	Unchanged, not determined[b]	DMSO-d_6, H_2O (0.71 M)	6 days	rt
5	**3a** (27 mM)	Unchanged, 100[a]	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
6	**3b** (27 mM)	**13**, 100[a]	DMSO-d_6, H_2O (16 mM)	7 days	4 °C
7	**3b** (10 μM)	**13**, not determined[b]	DMSO-d_6, H_2O (16 mM)	5 days	rt
8	**3b** (10 μM)	**13**, not determined[b]	DMSO-d_6, H_2O (0.71 M)	44 h	rt
9	**3e** (27 mM)	Unchanged, 100[a]	DMSO-d_6, H_2O (16 mM)	10 min	60 °C
10	**3f** (27 mM)	Unchanged, 100[a]	DMSO-d_6, H_2O (16 mM)	10 min	60 °C
11	**4a** (38 mM)	Unchanged, 100	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
12	**4b** (38 mM)	**1**, >90	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
13	**4c** (38 mM)	Unchanged, 100	DMSO-d_6, H_2O (16 mM)	30 days	4 °C
14	**4d** (12 mM)	Unchanged, 100	DMSO-d_6, H_2O (16 mM)	10 min	95 °C
15	6-CP (10 μM)	Unchanged, not determined[b]	DMSO-d_6, H_2O (0.71 M)	7 days	rt

[a] Quantitative control by ^{1}H NMR.
[b] Qualitative control by TLC: in entries **7** and **8**, the time indicates the moment when the spot corresponding to the substitution product becomes visible to the naked eye.
[c] A minimum concentration of DMSO (5% v/v) was always added due to solubility reasons.
[d] No substitution took place in $CDCl_3$ at 4 °C or rt.



Scheme 5. DMSO-mediated substitution of chlorine.

hastening of the substitution process with the increase of the proportion of water in the solvent mixture.

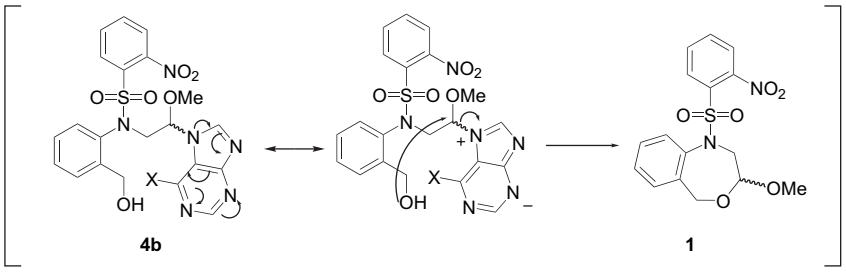
The acyclic *O*,*N*-acetal **4b** (Table 5, entry 12) underwent virtually quantitative transformation to the initial compound **1**, after remaining in DMSO-d_6 (0.03% H_2O/D_2O) at 4 °C for one month. The resonance signals corresponding to **1** can be observed by ^{1}H NMR spectroscopy one week after dissolution of **4b**. The formation of **1** by attack of the benzyl hydroxy group on the acetalic position would be favoured in the polar solvent DMSO and could be aided by protonation of the purine ring after releasing hydrochloric acid during the formation of 6-oxopurine (Scheme 6).

2.7. Change Cl→SPh (from 6-chloropurines to 6-phenylthiopurines 13–15)

N-7″ Alkyl-6-chloropurines **3b** and **3d** underwent substitution of chlorine after treatment with thiophenol and

Table 5. Results of the treatment of **3b** and **3d** with PhSH/K_2CO_3/40 min/rt

Substrate	Product (yield, %)	Equiv of PhSH
3b	**15** (89)	2.0
3d	**14** (36)	0.8
	15 (37)	
3b	**13** (61)	0.8



Scheme 6. Cyclization of **4b** in DMSO.

potassium carbonate in DMF at rt.[7] This process was favoured against the removal of the nitrobenzenesulfonyl group, which was performed in the same conditions.

Table 5 shows the results obtained when **3b** and **3d** were treated with different amounts of the mentioned reagents. A selective substitution of the chlorine atom versus the (2)-nitrobenzenesulfonyl removal can be observed when **3b** is treated with 0.8 equiv of thiophenol. However, both processes compete when (4)-nitrobenzenesulfonyl group is at position 1. The easier removal of the (4)-nitrobenzenesulfonyl group than the (2)-nitrobenzenesulfonyl one could obey to steric reasons as the mechanism described by Fukuyama et al.[25] proposes an intermediate Meisenheimer complex, as a consequence of the thiophenol attack at the adjacent position to the sulfonyl function.

Due to the nucleophile strength, the chlorine substitution by thiophenol needed no further activation of the purine ring.

2.8. Spectroscopic analysis of purine *O*,*N*-acetals

The complete unambiguous assignment of the proton and carbon atoms was confirmed by the heteronuclear multiquantum correlations HMQC (on **3a**, **3b**, **3d**, **4a**, **4c**, **11** and **12**) and heteronuclear multi-bond correlations HMBC (on **3a–c**), in DMSO-d_6.

Compounds containing *N*-7″ alkyl purines have been distinguished from those with *N*-9″ alkyl purines from different interactions that the aminalic hydrogen (see Fig. 3) establishes with the purine ring in each case. *N*-7″ Alkyl purines presented a three-bond interaction between the aminalic hydrogen atoms and the quaternary C-5″ atoms. *N*-9″ Alkyl purines presented a three-bond interaction between the aminalic hydrogen atoms and the quaternary C-4″ atoms.

X-ray diffraction on **3b** crystals confirmed the *N*-7″ aminalic bond (Fig. 4) thus ratifying the spectroscopic identification of the *N*-7″/*N*-9″ regioisomers.

As was observed for pyrimidine derivatives,[2] the ^{1}H and ^{13}C NMR spectra of the acyclic purine *O*,*N*-acetals with sulfonamide functions (**4a**, **4b** and **4c**) appear as a mixture of two structures with the following distribution: **4a**, 53/47; **4b**, 50/50; **4c**, 57/43. The *N*-1-tertiary sulfonamide adopts certain orientations, nonconvertible between each other, in such a way that two conformers may be observed. In all the acyclic *O*,*N*-acetals the benzylic and the R_1N–CH_2– hydrogen atoms appear as diastereotopic.

2.9. X-ray diffraction analysis on 3b

The crystal structure of **3b** (Fig. 4) revealed the following features: (a) The seven-membered ring of benzoxazepine

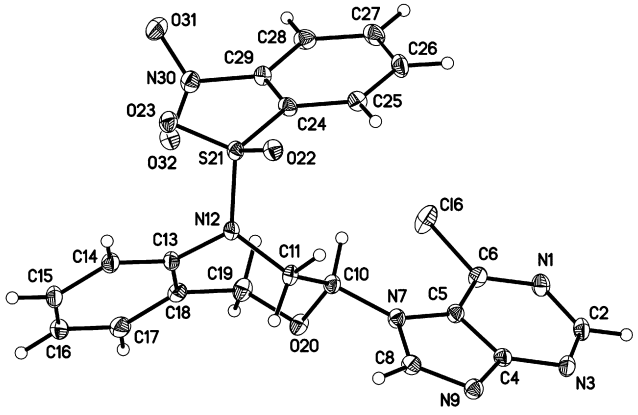


Figure 4. ORTEP drawing of **3b** at 50% probability.

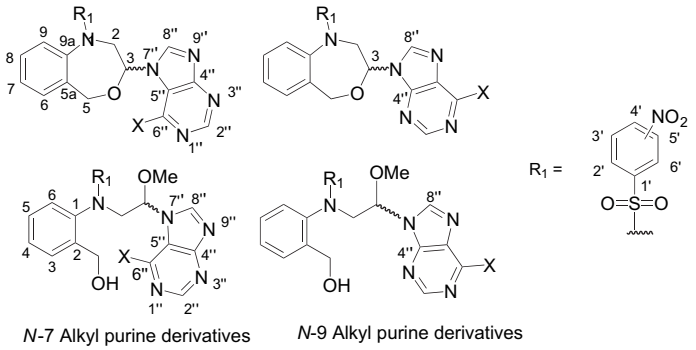


Figure 3. Numbering of cyclic and acyclic purine *O*,*N*-acetals.

adopts a chair-like conformation, (b) the flat ring of purine lies in an equatorial orientation with its six-membered ring orientated towards face α, (c) the 2-nitrobenzenesulfonyl moiety situates in axial disposition, towards the face α of the molecule with its benzene ring tilted to the benzoxazepine ring and (d) the H-2β atom is axial while H-2α is equatorial.

This conformation seems to be the most favourable to enable the building of a 3D-net with the relevant contribution of π/π-stacking and CH–π interactions, involving the purine moiety. The π/π interaction stacks two purine moieties in a nearly antiparallel fashion (dihedral angle between mean planes α=0.46°, slipping angles of approximately 21° and an interplanar distance of 3.28 Å). This interaction builds up pairs of molecules in the crystals (Fig. 5a).

In addition (Fig. 5b), the six-membered ring of each purine (with centroid hereafter named as Cg) acts as acceptor of a C–H/π interaction with the C-28–H-28 bond (H donor) of the nitrobenzene ring. The distance H-28–Cg is 2.95 Å and the angle C-28–H-28–Cg is 119°. Thus each purine ring is involved in a π/π-stacking interaction by one side and in a C–H/π interaction by the other one. The crystal structure of **3b** suggests that among the three aromatic groups of the molecule, the 6-chloropurine moiety is the most suitable to be involved in π/π-stacking interactions.

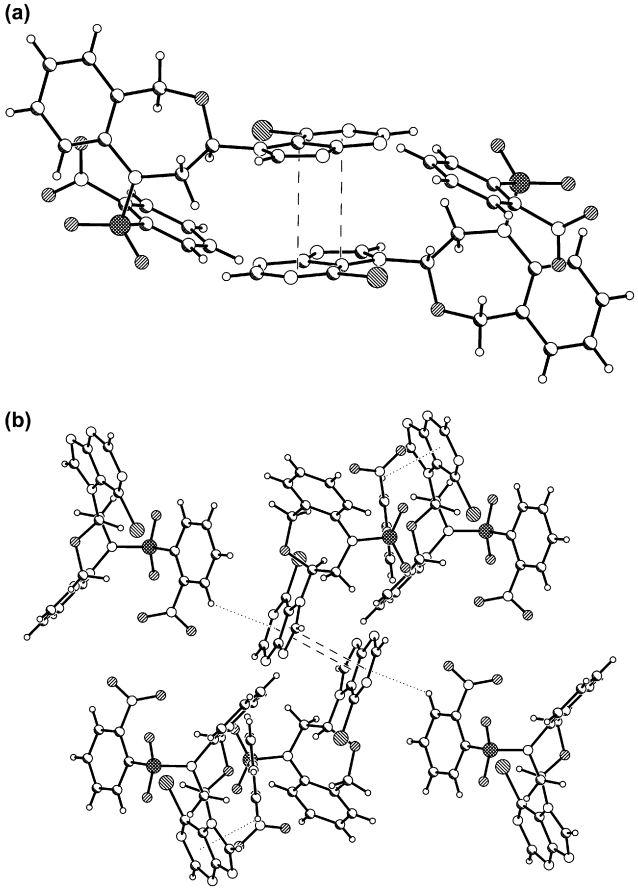


Figure 5. (a) Antiparallel π/π-stacking interaction between the 6-chloropurine moieties of a pair of molecules in the crystal of **3b** (dashed lines link the centroids of the rings). (b) Additional contribution of C–H/π interactions (dotted lines) cooperates with the π/π-stacking to build up the 3D framework molecular crystal of **3b**.

3. Conclusions

The *O*,*O*-acetalic compounds (*RS*)-3-methoxy-1-(2-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine, **1**, and (*RS*)-3-methoxy-1-(4-nitrobenzene sulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepine, **2**, have been studied in the Lewis acid-mediated condensation with 6-chloropurine. When (*RS*)-3-methoxy-4,1-benzoxazepine *O*,*O*-acetals **1** and **2** are condensed with 6-chloropurine in the presence of tin(IV) chloride in acetonitrile, different ratios of the final cyclic and acyclic *O*,*N*-acetals are obtained depending on the starting compound. The presence of the starting compounds of electron-rich groups that can approximate to, and therefore stabilize, the cationic position of the cyclic intermediate carbenium ions [e.g., (2)-NO_2 in **1**] favours the formation of the final cyclic *O*,*N*-acetals. 6-Chloropurine leads to an *N*-7″ aminalic bond in the cyclic products and mainly to the *N*-9″ aminalic bond in the acyclic ones. Substitution of the chlorine atom at the 6″ position of purine is more feasible when the ring is alkylated at the *N*-7″ position than at the *N*-9″ one. Exchange with a hydroxyl group is performed with water traces in deuterated dimethylsulfoxide at rt in a solvent-mediated process. Furthermore, this process takes place in acetonitrile at 50 °C in the presence of a Lewis acid. The exchange with strong nucleophiles (e.g., thiophenol) does not need further activation. Chlorine substitution has been observed in cyclic *O*,*N*-acetals with the *N*-7″ aminalic bond. Coordination of the Lewis acid to the nitrogen bases could cause *N*-7″ → *N*-9″ isomerization, formation of olefins **5a** and **5b** and a Cl → OH exchange.

4. Experimental

4.1. General

The general methods were the same as those previously described.[1,2] The HMBC spectra[26] were measured using a pulse sequence optimized for 10 Hz (inter-pulse delay for the evolution of long-range couplings: 50 ms) and a 5:3:4 gradient combination. In this way, direct responses (^1J couplings) were not completely removed. The HMQC spectra[27] (inv4gs in the standard Bruker software) resulted from 256×1024 data matrix size with 16–64 scans per t_1 depending on the sample concentration and inter-pulse delay of 3.2 ms and a 5:3:4 gradient combination. For numbering of compounds, see Figure 3.

4.2. General procedure for the preparation of 6-chloropurine *O*,*N*-acetals from *O*,*O*-acetalic compounds

A suspension of *O*,*O*-acetalic compound (1.0 equiv) and 6-chloropurine (2.5 equiv) in anhydrous MeCN (5 mL/mmol) was prepared under argon and cooled to 0 °C. At this temperature, TMSCl (4.0 equiv), HMDS (4.0 equiv) and $SnCl_4$ (commercial solution 1.0 M in CH_2Cl_2) were added subsequently. The temperature was allowed to rise to 10 °C before heating up to 50 °C under argon for more than 48 h. The reactions were quenched by cooling

(ice/water bath) and the addition of distilled water. The pH was fixed to 7–8 with $NaHCO_3$ (10%) and the aqueous phases were extracted with EtOAc and CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered and evaporated.

4.2.1. Reaction of 1[1] with 6-chloropurine: 3a, 3b, 4a, 4b, 5a. The general method was followed and the reaction was kept at 50 °C for 69 h.

4.2.1.1. *N*-(2-Hydroxymethylphenyl)-*N*-(2-methoxyvinyl)-2-nitrobenzenesulfonamide 5a. Elution by flash chromatography, 1/2 EtOAc/hexane or CH_2Cl_2; R_f (MeOH/CH_2Cl_2 0.5/10): 0.56; yellow solid; yield 2% [acetone-d_6, rt, isomer *Z* (54%), isomer *E* (46%)]. ^{1}H NMR (acetone-d_6, 300 MHz): δ (ppm) 7.98–7.75 (m, 4H, *4H*), 7.70 (dd, J_1=7.8 Hz, J_2=not det., *1H*), 7.63 (dd, J_1=7.7 Hz, J_2=not det., 1H), 7.43 (ddd, J_1=J_2=7.6 Hz, J_3=1.3 Hz, 1H or *1H*), 7.36 (ddd, J_1=J_2=7.5 Hz, J_3=1.3 Hz, 1H or *1H*), 7.22 (ddd, J_1=J_2=7.6 Hz, J_3=1.6 Hz, 1H or *1H*), 7.16 (ddd, J_1=J_2=7.7 Hz, J_3=1.7 Hz, 1H or *1H*), 7.03 (dd, J_1=7.9 Hz, J_2=1.3 Hz, 1H), 6.90 (dd, J_1=7.9 Hz, J_2=1.2 Hz, *1H*), 6.36 (d, J_{NCH_2CH} = 11.3 Hz, 1H, *NCH_2 or aminalic CH*), 6.22 (d, J_{NCH_2CH} = 11.4 Hz, 1H, *NCH_2 or aminalic CH*), 5.95 (d, J_{NCH_2CH} = 4.5 Hz, 1H, NCH_2 or aminalic CH), 5.61 (d, J_{NCH_2CH} = 4.5 Hz, 1H, NCH_2 or aminalic CH), 4.76 and 4.71 (2s, 2 benzylic H atoms, 2 *benzylic H atoms*), 3.58 (s, 3H, *Me*), 3.43 (s, 3H, Me). HR LSIMS calcd for $C_{16}H_{16}N_2O_6SNa$ (M+Na)$^+$ 387.0627, found 387.0627. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69; S, 8.80. Found: C, 52.84; H, 4.76; N, 7.47; S, 8.57.

4.2.1.2. (*RS*)-6-Chloro-9-[1-(2-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-9*H*-purine 3a. Elution by flash chromatography, 1/1 EtOAc/hexane or CH_2Cl_2; R_f (MeOH/CH_2Cl_2 0.5/10): 0.63; white solid; mp 123–125 °C; yield 2%. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.89 (s, 1H, H-8″), 8.81 (s, 1H, H-2″), 8.12 (dd, $J_{3'-4'}$=7.9 Hz, $J_{3'-5'}$=0.6 Hz, 1H, H-3′), 8.08 (d, J=7.2 Hz, 1H, H-6′), 8.01 (ddd, $J_{4'-3'}$=$J_{4'-5'}$=7.7 Hz, $J_{4'-6'}$=0.9 Hz, 1H, H-4′), 7.92 (t, $J_{5'-4'}$=$J_{5'-6'}$=7.7 Hz, 1H, H-5′), 7.55 (dd, J_{7-8}=6.8 Hz, J_{7-9}=2.0 Hz, 1H, H-6), 7.42 (m, 1H, H-7), 7.40–7.38 (m, 1H, H-8), 7.08 (dd, J_{9-8}=7.1 Hz, J_{9-7}= 1.7 Hz, 1H, H-9), 6.18 (dd, $J_{3\beta-2\alpha}$=10.0 Hz, $J_{3\beta-2\beta}$=1.5 Hz, 1H, H-3β), 4.94 (d, $J_{gem\ \text{benzylic H}}$=13.8 Hz, 1H, benzylic H), 4.86 (d, $J_{gem\ \text{benzylic H}}$=13.7 Hz, 1H, benzylic H), 4.61 (dd, $J_{gem\ 2\beta-2\alpha}$=15.0 Hz, $J_{2\beta-3\beta}$=1.6 Hz, 1H, H-2β), 4.33 (dd, $J_{gem\ 2\alpha-2\beta}$=15.1 Hz, $J_{2\alpha-3\beta}$=10.2 Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 152.0 (CH-2″), 151.3 (C-4″), 149.5 (C-6″), 147.3 (C-2′), 145.6 (CH-8″), 138.7 (C-10a), 137.5 (C-5a), 135.6 (CH-4′), 133.2 (CH-5′), 132.0 (C-1′), 130.9 (C-5″), 130.5 (CH-6′), 130.3 (CH-6), 129.6 (CH-8), 128.8 (CH-7), 127.7 (CH-9), 125.2 (CH-3′), 84.0 (CH-3), 70.1 (benzylic CH_2), 53.2 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-9″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{15}ClN_6O_5SNa$ (M+Na)$^+$ 509.0411, found 509.0412. Anal. Calcd for $C_{20}H_{15}ClN_6O_5S$: C, 49.34; H, 3.11; N, 17.26; S, 6.59. Found: C, 49.64; H, 3.06; N, 17.43; S, 6.67.

4.2.1.3. (*RS*)-6-Chloro-7-[1-(2-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-7*H*-purine 3b. Elution by flash chromatography, 3/1 EtOAc/hexane or 1.2/10 $(CH_3)_2CO/CH_2Cl_2$; R_f (EtOAc/hexane 3/1): 0.24; white solid; mp 220.0–221.0 °C; yield 32%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 9.00 (s, 1H, H-8″), 8.86 (s, 1H, H-2″), 8.12–8.08 (m, 2H, H-3′, H-6′), 8.00 (ddd, $J_{4'-3'}$=$J_{4'-5'}$=7.7 Hz, $J_{4'-6'}$=1.5 Hz, 1H, H-4′), 7.91 (ddd, $J_{5'-4'}$=$J_{5'-6'}$=7.7 Hz, $J_{5'-3'}$=1.4 Hz, 1H, H-5′), 7.53 (m, 1H, H-6), 7.44–7.38 (m, 2H, H-8, H-8), 7.19 (m, 1H, H-9), 6.34 (dd, $J_{3\beta-2\alpha}$=10.0 Hz, $J_{3\beta-2\beta}$=1.8 Hz, 1H, H-3β), 4.92 (d, $J_{gem\ \text{benzylic H}}$=13.8 Hz, 1H, benzylic H), 4.83 (dd, $J_{gem\ 2\beta-2\alpha}$=15.0 Hz, $J_{2\beta-3\beta}$=1.9 Hz, 1H, H-2β), 4.74 (d, $J_{gem\ \text{benzylic H}}$=13.8 Hz, 1H, benzylic H), 4.27 (dd, $J_{gem\ 2\alpha-2\beta}$= 15.0 Hz, $J_{2\alpha-3\beta}$=10.1 Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 161.4 (C-4″), 152.2 (CH-2″), 148.0 (CH-8″), 147.2 (C-2′), 142.3 (C-6″), 138.5 (C-10a), 137.2 (C-5a), 135.5 (CH-4′), 133.2 (CH-5′), 132.0 (C-1′), 130.3 and 130.1 (CH-6′, CH-6), 129.5 (CH-8), 128.8 (CH-7), 128.1 (CH-9), 125.1 (CH-3′), 121.4 (C-5″), 84.5 (CH-3), 69.6 (benzylic CH_2), 53.1 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-9″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{15}ClN_6O_5SNa$ (M+Na)$^+$ 509.0411, found 509.0411. Anal. Calcd for $C_{20}H_{15}ClN_6O_5S$: C, 49.34; H, 3.11; N, 17.26; S, 6.59. Found: C, 49.69; H, 3.27; N, 17.50; S, 6.39.

4.2.1.4. (*RS*)-6-Chloro-9-{2-[*N*-(2-hydroxymethylphenyl)-2-nitrobenzenesulfonamide]-1-methoxyethyl}-9*H*-purine 4a. Elution by flash chromatography, 3/1 EtOAc/hexane or 1.3/10 $(CH_3)_2CO/CH_2Cl_2$; R_f (MeOH/CH_2Cl_2 0.5/10): 0.53; white solid; mp 89.3–90.0 °C; yield 7% [DMSO-d_6, rt, isomer A (53%), isomer B (47%)]. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 8.99 (2s, 2H, H-8″, *H-8″*), 8.90 (s, 1H, H-2″ or *H-2″*), 8.86 (s, 1H, H-2″ or *H-2″*), 8.13–8.02 (m, 4H, H-4′, *H-4′*, 2H-3′ or 2H-5′), 7.93–7.84 (m, 2H, 2H-3′ or 2H-5′), 7.77 (d, $J_{6'-5'}$=7.2 Hz, 1H, H-6′ or *H-6′*), 7.69–7.61 (m, 3H, H-6′ or *H-6′*, H-6, *H-6*), 7.55–7.45 (m, 2H, H-5, *H-5*), 7.33 (ddd, J_{4-3}=J_{4-5}=7.6 Hz, J_{4-6}=1.3 Hz, 1H, *H-4*), 7.20 (ddd, J_{4-3}=J_{4-5}=7.6 Hz, J_{4-6}=1.2 Hz, 1H, H-4), 7.11 (d, J_{3-4}=7.7 Hz, 1H, *H-3*), 6.81 (d, J_{3-4}= 7.5 Hz, 1H, H-3), 5.98 (t, J_{NCH_2CH} = 6.2 Hz, 1H, H-9), 5.89 (t, J_{NCH_2CH} = 6.0 Hz, 1H, *aminalic H*), 5.25 (bb), 4.78–4.69 (m, 2H, H-8, *NCH_2*), 4.63–4.46 (m, 4H, H-7, *benzylic H*, H-8, *NCH_2*), 4.33 (d, $J_{gem\ \text{benzylic H}}$=14.0 Hz, 1H, benzylic H or *benzylic H*), 4.25 (d, $J_{gem\ \text{benzylic H}}$= 14.1 Hz, 1H, benzylic H or *benzylic H*), 3.33 (s, 6H, H-10, *Me*). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 151.8 (C-4″, *C-4″*), 151.7 (CH-2″, *CH-2″*), 149.3 (C-6″, *C-6″*), 147.4 (C-2′, *C-2′*), 145.9 and 145.8 (CH-8″, *CH-8″*), 142.4 (*C-1*), 141.9 (C-1), 135.3 (CH-4′, *CH-4′*), 134.5 (C-2), 134.2 (*C-2*), 132.1 and 132.0 (2CH-3′ or 2CH-5′), 131.2 and 131.1 (C-5″, *C-5″*), 130.7 (CH-6′, *CH-6′*), 129.6 and 129.2 (C-1′, *C-1′*), 129.4 (*CH-3*), 129.1 and 129.0 (CH-3, CH-5, *CH-5*), 128.6 (*CH-6*), 128.4 (CH-6), 127.5 (*CH-4*), 127.2 (CH-4), 124.1 (2CH-3′ or 2CH-5′), 85.1 (aminalic CH), 84.2 (*aminalic CH*), 58.3 (CH_2-7, *benzylic CH_2*), 56.2 (OMe, *OMe*), 53.8 and 53.2 (CH_2-8, *NCH_2*) (proton and carbon atom shifts, and the nature of the *N*-9″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{21}H_{19}ClN_6O_6SNa$ (M+Na)$^+$ 541.0673, found 541.0673. Anal. Calcd for $C_{21}H_{19}ClN_6O_6S$: C, 48.60; H, 3.69; N, 16.19; S, 6.18. Found: C, 48.75; H, 3.67; N, 16.00; S, 6.03.

4.2.1.5. (*RS*)-6-Chloro-7-{2-[*N*-(2-hydroxymethylphenyl)-2-nitrobenzenesulfonamide]-1-methoxyethyl}-7*H*-purine 4b. Elution by flash chromatography, 1/0 EtOAc/hexane or 1/3 $(CH_3)_2CO/CH_2Cl_2$; R_f (EtOAc/hexane 0.5/10): 0.48; white solid; mp 88.0–89.0 °C; yield 6% [$CDCl_3$, rt, isomer A (50%), *isomer B* (50%)]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.83 and 8.80 (2s, 2H), 8.52 and 8.47 (2s, 2H), 7.73–7.55 (m, 6H), 7.51–7.34 (m, 6H), 7.17 (ddd, J_1=J_2=7.7 Hz, J_3=1.7 Hz, 1H), 7.13 (ddd, J_1=J_2=7.7 Hz, J_3=1.6 Hz, 1H), 6.84 (pt, J=7.3 Hz, 2H), 6.25 (dd, J_{NCH_2CH} = 7.3 Hz, J_{NCH_2CH} = 4.9 Hz, 1H, aminalic H), 6.03 (dd, J_{NCH_2CH} = 8.4 Hz, J_{NCH_2CH} = 3.6 Hz, 1H, *aminalic H*), 4.76 and 4.61 ($2d_{system\ AB}$, $J_{gem\ benzylic\ H,\ part\ A}$= 12.5 Hz, $J_{gem\ benzylic\ H,\ part\ B}$=12.4 Hz, 2H, 2H benzylic or *2H benzylic*), 4.61 (dd, $J_{gem\ NCH_2}$ = 14.7 Hz, J_{NCH_2CH} = 8.3 Hz, 1H, *NCH*$_2$), 4.51 and 4.46 ($2d_{system\ AB}$, $J_{gem\ benzylic\ H,\ part\ A}$=12.1 Hz, 2H, H-7 or *benzylic H*), 4.46 (dd, J_{CHCH_2N} = 4.8 Hz, 1H, NCH_2), 4.28 (dd, $J_{gem\ NCH_2}$ = 15.0 Hz, J_{NCH_2CH} = 7.6 Hz, 1H, NCH_2), 4.01 (dd, $J_{gem\ NCH_2}$ = 14.6 Hz, J_{NCH_2CH} = 3.6 Hz, 1H, *NCH*$_2$), 3.44 (s, 3H, Me or *Me*), 3.37 (s, 3H, Me or *Me*). HR LSIMS calcd for $C_{21}H_{19}ClN_6O_6SNa$ (M+Na)$^+$ 541.0673, found 541.0674. Anal. Calcd for $C_{21}H_{19}N_6O_6SCl\cdot 0\cdot 26H_2O$: C, 48.17; H, 3.76; N, 16.05; S, 6.12. Found: C, 48.31; H, 3.42; N, 15.65; S, 5.74.

4.2.2. Reaction of 2[1] with 6-chloropurine: 3c, 3d, 4c, 5b. The general method was followed and the reaction was maintained at 50 °C for 67 h.

4.2.2.1. *N*-(2-Hydroxymethylphenyl)-*N*-(2-methoxyvinyl)-4-nitrobenzenesulfonamide 5b. Elution by flash chromatography, 1/1.5 EtOAc/hexane or 0.15/10 $(CH_3)_2CO/CH_2Cl_2$; R_f (EtOAc/hexane 2/1): 0.61; yellow liquid; yield 7%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.39 (d, $J_{3'-2'}$=$J_{5'-6'}$=8.0 Hz, 2H, H-3′,5′), 7.92 (d, $J_{2'-3'}$= $J_{6'-5'}$=8.0 Hz, 2H, H-2′,6′), 7.68–7.64 (m, 1H), 7.44–7.40 (m, 1H), 7.17–7.13 (m, 1H), 6.42–6.38 (m, 1H), 6.35 (d, J_{NCH_2CH} ~ 12 Hz, 1H, NCH_2 or aminalic H), 6.04 (d, J_{8-9} ~ 12 Hz, 1H, NCH_2 or aminalic H), 4.75 (s, 2H, benzylic H), 3.55 (s, 3H, Me). HR LSIMS calcd for $C_{16}H_{16}N_2O_6SNa$ (M+Na)$^+$ 387.0627, found 387.0627. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69; S, 8.80. Found: C, 52.88; H, 4.54; N, 7.71; S, 8.54.

4.2.2.2. (*RS*)-6-Chloro-9-[1-(4-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-9*H*-purine 3c. Elution by flash chromatography, 1/2 EtOAc/hexane or 2/10 $(CH_3)_2CO/CH_2Cl_2$; R_f (EtOAc/hexane 2/1): 0.51; light yellow solid; yield 2%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 8.95 (s, 1H, H-8″), 8.90 (s, 1H, H-2″), 8.52 (d, $J_{3'-2'}$=$J_{5'-6'}$=9.0 Hz, 2H, H-3′,5′), 8.27 (d, $J_{2'-3'}$=$J_{6'-5'}$= 9.0 Hz, 2H, H-2′,6′), 7.60–7.28 (m, 4H, H-6, H-7, H-8, H-9), 6.26 (dd, $J_{3\beta-2\alpha}$=10.2 Hz, $J_{3\beta-2\beta}$=1.8 Hz, 1H, H-3β), 4.96 (d, $J_{gem\ benzylic\ H}$=12.0 Hz, 1H, benzylic H), 4.83–4.73 (m, 2H, H-2β, benzylic H), 4.27 (dd, $J_{gem\ 2\beta-2\alpha}$= 15.0 Hz, $J_{2\alpha-3\beta}$=9.9 Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 152.0 (CH-2″), 151.2 (C-4″), 150.2 (C-4′), 149.4 (C-6″), 145.5 (CH-8″), 145.4 (C-1′), 139.0 (C-10a), 136.9 (C-6), 131.0 (C-5″), 130.1 (CH-6), 129.6, 128.5 and 127.2 (CH-7, CH-8, CH-9), 128.6 (CH-2′, CH-6′), 125.1 (CH-3′, CH-5′), 83.7 (CH-3), 69.9 (benzylic CH_2), 52.6 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-9″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{15}ClN_6O_5SNa$ (M+Na)$^+$ 509.0411, found 509.0412. Anal. Calcd for $C_{20}H_{15}ClN_6O_5S$: C, 49.34; H, 3.11; N, 17.26; S, 6.59. Found: C, 49.09; H, 3.17; N, 17.38; S, 6.69.

4.2.2.3. (*RS*)-6-Chloro-7-[1-(4-nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-7*H*-purine 3d. Elution by flash chromatography, 1.5/1 EtOAc/hexane; R_f (EtOAc/hexane 2/1): 0.35; white solid; mp 219.0–220.0 °C; yield 15%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 9.04 (s, 1H, H-8″), 8.95 (s, 1H, H-2″), 8.52 (d, $J_{3'-2'}$=$J_{5'-6'}$= 8.9 Hz, 2H, H-3′,5′), 8.26 (d, $J_{2'-3'}$=$J_{6'-5'}$=8.9 Hz, 2H, H-2′,6′), 7.58–7.45 (m, 3H, H-6, H-7, H-8), 7.38 (dd, J_1=7.4 Hz, J_2=1.4 Hz, 1H, H-9), 6.42 (dd, $J_{3\beta-2\alpha}$=10.0 Hz, $J_{3\beta-2\beta}$=1.7 Hz, 1H, H-3β), 5.00 (dd, $J_{gem\ 2\beta-2\alpha}$=14.9 Hz, $J_{2\beta-3\beta}$=1.9 Hz, 1H, H-2β), 4.93 (d, $J_{gem\ benzylic\ H}$=14.0 Hz, 1H, benzylic H), 4.61 (d, $J_{gem\ benzylic\ H}$=13.9 Hz, 1H, benzylic H), 4.23 (dd, $J_{gem\ 2\beta-2\alpha}$=14.9 Hz, $J_{2\alpha-3\beta}$=10.1 Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 161.4 (C-4″), 152.2 (CH-2″), 150.2 (C-4′), 148.0 (CH-8″), 145.4 (C-1′), 142.4 (C-6″), 138.7 (C-10a), 137.0 (C-6), 130.0 (CH-6), 129.6 (CH-8), 128.6 (CH-2′, CH-6′), 127.7 (CH-9), 125.1 (CH-3′, CH-5′), 121.5 (C-5″), 84.2 (CH-3), 69.3 (CH_2-5), 52.6 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-7″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{15}ClN_6O_5SNa$ (M+Na)$^+$ 509.0411, found 509.0410. Anal. Calcd for $C_{20}H_{15}ClN_6O_5S$: C, 49.34; H, 3.11; N, 17.26; S, 6.59. Found: C, 49.46; H, 3.12; N, 17.56, S, 6.40.

4.2.2.4. (*RS*)-6-Chloro-9-{2-[*N*-(2-hydroxymethylphenyl)-4-nitrobenzenesulfonamide]-1-methoxyethyl}-9*H*-purine 4c. Elution by flash chromatography, 1.5/1 EtOAc/hexane; R_f (EtOAc/hexane 2/1): 0.24; white solid; mp 135.4–136.4 °C; yield 22% [DMSO-d_6, rt, isomer A (57%), *isomer B* (43%)]. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 8.90 (s, 1H, H-8″), 8.85 (s, 1H, *H-8″*), 8.77 (s, 1H, H-2″), 8.72 (s, 1H, *H-2″*), 8.41 (d, $J_{3'-2'}$=$J_{5'-6'}$= 8.9 Hz, 2H, H-3′,5′), 8.37 (d, $J_{3'-2'}$=$J_{5'-6'}$=8.9 Hz, 2H, *H-3′,5′*), 7.91 (d, $J_{2'-3'}$=$J_{6'-5'}$=8.9 Hz, 2H, H-2′,6′), 7.84 (d, $J_{2'-3'}$=$J_{6'-5'}$=8.9 Hz, 2H, *H-2′,6′*), 7.59 (d, J_{6-5}=7.6 Hz, 1H, H-6), 7.54 (d, J_{6-5}=6.8 Hz, 1H, *H-6*), 7.42–7.34 (m, 2H, H-5, *H-5*), 7.15 (dt, J_1=7.7 Hz, J_2=1.3 Hz, 2H, H-4, *H-4*), 6.72 (d, J_{3-4}=7.3 Hz, 1H, *H-3*), 6.56 (d, J_{3-4}= 7.2 Hz, 1H, H-3), 5.79 (t, J_{NCH_2CH} = 6.2 Hz, 1H, aminalic H), 5.69 (t, J_{NCH_2CH} = 6.1 Hz, 1H, *aminalic H*), 5.15 (m), 4.58 (dd, $J_{gem\ NCH_2}$ = 14.3 Hz, J_{NCH_2CH} = 6.7 Hz, 1H, NCH_2 or *NCH*$_2$), 4.47–4.39 [m, 6H, 2H-7, 2 *benzylic H*, NCH_2 (NCH_2 and/or *NCH*$_2$)], 4.22 (dd, $J_{gem\ NCH_2}$ = 14.3 Hz, J_{NCH_2CH} = 5.5 Hz, 1H, NCH_2 or *NCH*$_2$), 3.16 (s, 3H, *Me*), 3.12 (s, 3H, Me). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 151.9 and 151.9–151.7 (C-4″, *C-4″*), 151.8 and 151.7 (CH-2″, *CH-2″*), 150.1 and 150.0 (C-4′, *C-4′*), 149.3 and 148.8 (C-6″, *C-6″*), 146.0 and 145.7 (CH-8″, *CH-8″*), 142.8, 142.8, 142.7 and 142.5 (C-1′, *C-1′*, C-1, *C-1*), 135.7 and 134.9 (C-2, *C-2*), 132.0 and 131.0 (C-5″, *C-5″*), 129.4, 129.1 and 128.8 (CH-2′, CH-6′, *CH-2′*, *CH-6′*, CH-5, *CH-5*), 128.2 (CH-6, *CH-6*), 128.0 and 127.8 (CH-3, *CH-3*), 127.4 (CH-4, *CH-4*), 124.5 and 124.5 (CH-3′, *CH-3′*, CH-5′, *CH-5′*), 84.8 and 83.9 (aminalic CH, *aminalic CH-9*), 58.6 (benzylic CH_2, *benzylic CH*$_2$), 56.1 (Me, *Me*), 53.3 (CH_2-8, *NCH*$_2$) (proton and carbon atom shifts, and the

nature of the *N*-9″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{21}H_{19}ClN_6O_6SNa$ $(M+Na)^+$ 541.0673, found 541.0673. Anal. Calcd for $C_{21}H_{19}ClN_6O_6S$: C, 48.60; H, 3.69; N, 16.19; S, 6.18. Found: C, 48.79; H, 3.57; N, 15.81; S, 6.15.

4.3. Substitutions on 7-alkyl 6-chloropurines: formation of 7-alkyl 6-oxopurines 11 and 12

Solutions A (27 mM of **3b** in DMSO-d_6 with 16 mM of H_2O/D_2O) and B (27 mM of **3d** in DMSO-d_6 with 16 mM of H_2O/D_2O) were prepared and kept at 4 °C. Periodic registration of ^1H NMR spectra was performed to control any changes that took place. In solution A, a mixture of compounds **11** (more than 50%) and **3b** could be observed after 3 days, and after 1 week from the preparation of the solution **11** was the only existing compound. In solution B, no traces of **12** could be observed after one week and it was necessary one month for the complete transformation of **3d** into **12**.

Solutions C containing 10 μM **3b** in DMSO-d_6 (1 mL, 16 mM D_2O/H_2O), solution D containing 10 μM **3b** in DMSO-d_6 (50 μL, 16 mM D_2O/H_2O) (0.95 mL), solution E containing 10 μM **3d** in DMSO-d_6 (1 mL, 16 mM D_2O) and solution F containing 10 μM **3d** in DMSO-d_6 (50 μL, 16 mM D_2O/H_2O) (0.95 mL) were prepared, maintained at rt and controlled in a qualitative manner by TLC. Compound **3b** disappeared in favour of **11** in solution D after 44 h but 5 days were necessary for its disappearance from solution C. However, **3d** was the only compound noticeable in solutions E and F after 6 days from the preparation.

4.3.1. (*RS*)-7-[1-(2-Nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1,7-dihydropurin-6-one 11. R_f ($MeOH/CH_2Cl_2$ 0.5/10): 0.39; white solid; mp 215.0–217.0 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.55 (s, 1H, H-8″), 8.09–8.05 (m, 2H, H-3′, H-6′), 8.04 (s, 1H, H-2″), 7.97 (ddd, $J_{4'-3'}=J_{4'-5'}=7.7$ Hz, $J_{4'-6'}=1.2$ Hz, 1H, H-4′), 7.88 (ddd, $J_{5'-4'}=J_{5'-6'}=7.7$ Hz, $J_{5'-3'}=1.2$ Hz, 1H, H-5′), 7.49 (dd, $J_{6-7}=7.1$ Hz, $J_{6-8}=1.9$ Hz, 1H, H-6), 7.41–7.33 (m, 2H, H-8, H-8), 7.04 (dd, $J_{9-8}=7.2$ Hz, $J_{9-7}=1.8$ Hz, 1H, H-9), 6.35 (dd, $J_{3\beta-2\alpha}=10.1$ Hz, $J_{3\beta-2\beta}=1.6$ Hz, 1H, H-3β), 4.85 (d, $J_{gem\ \text{benzylic H}}=13.8$ Hz, 1H, benzylic H), 4.64 (d, $J_{gem\ \text{benzylic H}}=13.7$ Hz, 1H, benzylic H), 4.53 (dd, $J_{gem\ 2\beta-2\alpha}=14.8$ Hz, $J_{2\beta-3\beta}=1.6$ Hz, 1H, H-2β), 4.24 (dd, $J_{gem\ 2\alpha-2\beta}=14.9$ Hz, $J_{2\alpha-3\beta}=10.2$ Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 156.7 (C-4″), 153.8 (C-6″), 147.2 (C-2′), 145.3 (CH-2″), 142.1 (CH-8″), 138.5 (C-10a), 137.6 (C-6), 135.4 (CH-4′), 133.1 (CH-5′), 132.1 (C-1′), 130.4 (CH-6′), 130.1 (CH-6), 129.4 (CH-8), 128.7 (CH-7), 127.8 (CH-9), 125.0 (CH-3′), 114.1 (C-5″), 85.0 (CH-3), 69.7 (CH_2-5), 53.5 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-7″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{16}N_6O_6NaS$ $(M+Na)^+$ 491.0750, found 491.0749. Anal. Calcd for $C_{20}H_{16}N_6O_6S$: C, 51.28; H, 3.44; N, 17.94; S, 6.85. Found: C, 51.42; H, 3.61; N, 17.90; S, 6,74.

4.3.2. (*RS*)-7-[1-(4-Nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-1,7-dihydropurin-6-one 12. R_f (EtOAc): 0.2; white solid; mp 171.8–172.6 °C. ^1H NMR (DMSO-d_6, 300 MHz): δ (ppm) 12.50 (s, 1H, NH-1″), 8.45 (s, 1H, H-8″), 8.41 (d, $J_{3'-2'}=J_{5'-6'}=8.8$ Hz, 2H, H-3′,5′), 8.15 (d, $J_{2'-3'}=J_{6'-5'}=8.8$ Hz, 2H, H-2′,6′), 8.02 (s, 1H, H-2″), 7.46–7.36 (m, 3H, H-6, H-8, H-9), 7.27 (dd, J_{9-8}=not det., $J_{9-7}=1.8$ Hz, 1H, H-9), 6.32 (d, $J_{3-2}=8.7$ Hz, 1H, H-3β), 4.76 (d, $J_{gem\ \text{benzylic H}}=13.9$ Hz, 1H, benzylic H), 4.68 (dd, $J_{gem\ 2\beta-2\alpha}$=not det., $J_{2\beta-3\beta}$=not det., 1H, H-2β), 4.29 (d, $J_{gem\ \text{benzylic H}}=13.9$ Hz, 1H, benzylic H), 4.10 (dd, $J_{gem\ 2\alpha-2\beta}=14.9$ Hz, $J_{2\alpha-3\beta}=10.3$ Hz, 1H, H-2α). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 157.0 (C-4″), 154.0 (C-6″), 150.1 (C-4′), 145.5 (C-1′), 145.1 (CH-2″), 142.0 (CH-8″), 138.5 (C-10a), 137.0 (C-5a), 130.0 (CH-6), 129.4 (CH-8), 128.6 (CH-2′, CH-6′), 128.5 (CH-7), 127.9 (CH-9), 125.0 (CH-3′, CH-5′), 114.0 (C-5″), 84.3 (CH-3), 69.4 (CH_2-5), 53.2 (CH_2-2) (proton and carbon atom shifts, and the nature of the *N*-7″ aminalic bond were confirmed by HMBC and HMQC studies in DMSO-d_6). HR LSIMS calcd for $C_{20}H_{16}N_6O_6SNa$ $(M+Na)^+$ 491.0750, found 491.0750. Anal. Calcd for $C_{20}H_{16}N_6O_6S$: C, 51.28; H, 3.44; N, 17.94; S, 6.85. Found: C, 51.35; H, 3.70; N, 17.89; S, 6.66.

4.4. Substitutions on 7-alkyl-6-chloropurines: formation of 7-alkyl 6-phenylthiopurines

4.4.1. (*RS*)-7-[1-(2-Nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-6-phenylthio-7*H*-purine 13. K_2CO_3 (1.6 equiv) and PhSH (0.8 equiv) were added at rt to a solution of **3b** (1.0 equiv) in DMF (5 mL/mmol). The mixture was stirred at rt for 40 min. The reaction was halted by the addition of EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. Purification of **15** was carried out by flash chromatography with gradient elution using EtOAc/hexane mixtures (0/1→2/1). Compound **15**: R_f (EtOAc): 0.34; white solid; mp 131.9–132.3 °C; yield 61%. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.77 (s, 1H, H-8″ or H-2″), 8.23 (s, 1H, H-2″ or H-8″), 7.92 (dd, $J_1=7.4$ Hz, J_2=not det., 1H), 7.79–7.75 (m, 2H), 7.70–7.59 (m, 3H), 7.49–7.43 (m, 4H), 7.39 (ddd, $J_1=J_2=7.4$ Hz, $J_3=1.1$ Hz, 1H), 7.28 (ddd, $J_1=J_2=7.6$ Hz, $J_3=1.8$ Hz, 1H), 7.00 (d, $J=7.7$ Hz, 1H), 6.59 (dd, $J_{3\beta-2\alpha}=10.0$ Hz, $J_{3\beta-2\beta}=2.0$ Hz, 1H, H-3β), 5.20 (d, $J_{gem\ \text{benzylic H}}=13.6$ Hz, 1H, benzylic H), 4.91 (dd, $J_{gem\ 2\beta-2\alpha}=14.6$ Hz, $J_{2\beta-3\beta}=2.0$ Hz, 1H, H-2β), 4.90 (d, $J_{gem\ \text{benzylic H}}=13.6$ Hz, 1H, benzylic H), 3.82 (dd, $J_{gem\ 2\alpha-2\beta}=14.7$ Hz, $J_{2\alpha-3\beta}=10.0$ Hz, 1H, H-2α). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 159.2 (C-4″), 153.3 (C-6″), 153.2 (CH-2″ or CH-8″), 148.0 (C-2′), 144.2 (CH-8″ or CH-2″), 138.6, 138.4, 133.6, 127.2, 122.2, 135.5 (2C, PhS), 134.7, 132.2, 132.2, 130.4, 129.8, 129.7, 129.5, 128.4 and 124.9 (CH-aromatics), 86.8 (CH-3), 71.2 (benzylic CH_2), 54.8 (CH_2-2). HR LSIMS calcd for $C_{26}H_{20}N_6O_5S_2Na$ $(M+Na)^+$ 583.0834, found 583.0833. Anal. Calcd for $C_{26}H_{20}N_6O_5S_2$: C, 55.70; H, 3.60; N, 14.99; S, 11.44. Found: C, 55.51; H, 3.81; N, 15.21; S, 11.59.

4.4.2. (*RS*)-7-[1-(4-Nitrobenzenesulfonyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]-6-phenylthio-7*H*-purine 14 and (*RS*)-6-phenylthio-7-(1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)-7*H*-purine 15. Compound **15** was prepared from **3d** following the procedure described for **13**, using 0.8 equiv of PhSH and 1.6 equiv of K_2CO_3 for each equivalent of **3d**. After 40 min the reaction was halted as explained for the preparation of **13**. The purification of the products

was carried out by flash chromatography [gradient elution with $(CH_3)_2CO/CH_2Cl_2$ mixtures (0/1→1/0)] and compounds **14** and **15** were obtained. Compound **14**: elution by flash chromatography, $(CH_3)_2CO/CH_2Cl_2$ 2/10; R_f (EtOAc): 0.57; white solid; mp 116.8–117.5 °C; yield 36%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.79 (s, 1H, H-8″ or H-2″), 8.34 (d, J=8.9 Hz, 2H, H-3′,5′), 8.19 (s, 1H, H-2″ or H-8″), 8.02 (d, J=8.9 Hz, 2H, H-2′,6′), 7.66–7.63 (m, 2H), 7.54–7.50 (m, 3H), 7.45–7.33 (m, 4H), 6.50 (dd, $J_{3\beta-2\alpha}$=10.0 Hz, $J_{3\beta-2\beta}$=2.0 Hz, 1H, H-3β), 4.92 (dd, $J_{gem\ 2\beta-2\alpha}$=14.5 Hz, $J_{2\beta-3\beta}$=2.0 Hz, 1H, H-2β), 4.78 (d, $J_{gem\ \text{benzylic H}}$=13.8 Hz, 1H, benzylic H), 4.63 (d, $J_{gem\ \text{benzylic H}}$=13.7 Hz, 1H, benzylic H), 3.73 (dd, $J_{gem\ 2\alpha-2\beta}$=14.6 Hz, $J_{2\alpha-3\beta}$=10.0 Hz, 1H, H-2α). HR LSIMS calcd for $C_{26}H_{20}N_6O_5S_2Na$ $(M+Na)^+$ 583.0834, found 583.0834. Anal. Calcd for $C_{26}H_{20}N_6O_5S_2$: C, 55.70; H, 3.60; N, 14.99; S, 11.44. Found: C, 55.79; H, 3.91; N, 15.01; S, 11.63.

Compound **15**: elution by flash chromatography, $(CH_3)_2CO/CH_2Cl_2$ 1/1; yield, 37%. R_f (EtOAc): 0.17; white solid; mp 90.0–91.3 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 8.76 (s, 1H, H-2″ or H-8″), 8.56 (s, 1H, H-2″ or H-8″), 7.65–7.59 (m, 2H, Ph–S), 7.50–7.44 (m, 3H, Ph–S), 7.25–7.20 (m, 2H), 6.97 (ddd, J_1=J_2=not det., J_3=not det., 1H), 6.89 (d, J=7.6 Hz, 1H), 6.45 (dd, $J_{3\beta-2\alpha}$=6.9 Hz, $J_{3\beta-2\beta}$=2.1 Hz, 1H, H-3β), 4.92 (d, $J_{gem\ \text{benzylic H}}$=14.2 Hz, 1H, benzylic H), 4.88 (d, $J_{gem\ \text{benzylic H}}$=14.1 Hz, 1H, benzylic H), 4.16 (s, 1H, NH-1), 3.95 (d, J=13.2 Hz, 1H, H-2β), 3.48 (dd, $J_{gem\ 2\alpha-2\beta}$=13.4 Hz, $J_{2\alpha-3\beta}$=6.9 Hz, 1H, H-2α). ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 159.2 (C-4″), 153.0 (CH-2″ or CH-8″), 152.7, 148.3 (C-6″, C-11), 145.6 (CH-8″ or CH-2″), 135.4 (2CH, PhS), 129.9, 129.6, 129.6, 129.4, 121.8 and 119.0 (CH-aromatics), 128.4, 127.0, 122.0, 87.1 (CH-3), 70.5 (CH_2-5), 53.5 (CH_2-2). HR LSIMS calcd for $C_{20}H_{17}N_5OSNa$ $(M+Na)^+$ 398.1052, found 398.1051. Anal. Calcd for $C_{20}H_{17}N_5OS$: C, 63.98; H, 4.54; N, 18.65; S, 8.54. Found: C, 63.65; H, 4.61; N, 18.91; S, 8.64.

4.4.3. (*RS*)-6-Phenylthio-7-(1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl)-7*H*-purine 15. The reaction from **3b** was performed as described for the preparation of **13**, using 2.0 equiv of PhSH and 3 equiv of K_2CO_3. After 40 min of stirring at rt the reaction was halted as described for the preparation of **13**. The only product **15** was purified by flash chromatography [gradient elution using EtOAc/hexane (0/1→1/0)]: yield 89%.

4.5. Crystallization and X-ray diffraction on 3b

Suitable crystals of **3b** were obtained after dissolving this compound in the minimum volume of dichloromethane and the addition of a slightly larger volume of chloroform. A vial with a screw top allowed the slow evaporation of the solvents at 4 °C, to the formation of colourless crystals. A crystal of **3b** was mounted on a glass fibre and used for data collection. Crystal data were collected at 100(2) K, using a Bruker SMART CCD 1000 diffractometer. Graphite monochromated Mo Kα radiation (λ=0.71073 Å) was used throughout. The data were processed with SAINT[28] and corrected for absorption using SADABS (transmissions factors: 0.9465–0.8537).[29] The structure was solved by direct methods using the programme SHELXS-97[30] and refined by full-matrix least-squares techniques against F^2 using SHELXL-97.[31] Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters. Criteria of a satisfactory complete analysis were the ratios of rms shift to standard deviation less than 0.001 and no significant features in final difference maps. Molecular graphics and geometrical calculations were obtained from PLATON[32] and SHELXTL.[33] Relevant crystal data: formula $C_{20}H_{15}ClN_6O_5S$, formula weight 486.89, T=100(2) K, crystal system monoclinic, space group $P2_1/n$, unit cell dimensions a=7.9549(6), b=14.6821(10), c=17.0430(12) Å and α=90°, β=90.6720(10)° and γ=90°, Z=4, D=1.625 Mg/m^3, μ(MoKα)=0.348 mm^{-1}, measured/unique reflections 12,114/4508 (R(int) 0.0233), refined parameters 298, final R_1 ($I>2\sigma(I)$)=0.0505 and wR_2=0.1229, GOF=1.125. CCDC reference number 625270. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccd.cam.ac.uk].

Acknowledgements

This study was supported by the Instituto de Salud Carlos III (Fondo de Investigación Sanitaria) through the project no. PI041206, and by the Junta de Andalucía through the Excellence Research Project no. 00636.

References and notes

1. Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J. A.; Marchal, J. A.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Tetrahedron* **2004**, *60*, 11547.
2. Díaz-Gavilán, M.; Gómez-Vidal, J. A.; Entrena, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *J. Org. Chem.* **2006**, *71*, 1043.
3. Vorbrüggen, H.; Ruh-Pohlenz, C. Synthesis of Nucleosides. *Organic Reactions (New York)*; Paquette, L. A., Ed.; John Wiley and Sons: New York, NY, 2000; Vol. 55, pp 1–630.
4. Hasan, A.; Srivstava, P. *J. Med. Chem.* **1992**, *35*, 1435.
5. Brik, A.; Wu, C. Y.; Best, M. D.; Wong, C. H. *Bioorg. Med. Chem.* **2005**, *13*, 4622.
6. Yamada, K.; Sakata, S.; Yoshimura, Y. *J. Org. Chem.* **1998**, *63*, 6891.
7. Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787.
8. Hocková, D.; Budesinsky, M.; Marek, R.; Marek, J.; Holy, A. *Eur. J. Org. Chem.* **1999**, 2675.
9. Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294. *N*-7 Alkylated regioisomers were obtained from silylated purines using $SnCl_4$ and MeCN at rt, while the *N*-9 alkylated products were obtained with the same purines, but using TMSOTf and refluxing 1,2-dichloroethane as solvent.
10. Okumura, K.; Oine, T.; Yamada, Y.; Tomie, M.; Adachi, T.; Natura, T.; Kawazu, M.; Mizoguchi, T.; Inoue, I. *J. Org. Chem.* **1971**, *36*, 1573.
11. Marek, R.; Brus, J.; Tousek, J.; Kovacs, L.; Hocková, D. *Magn. Reson. Chem.* **2002**, *40*, 353.
12. Holy, A.; Dvorakova, H.; Jindrich, J.; Masojidkova, M.; Budesinsky, M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 4073.
13. For the numbering of the compounds, the atoms of the benzoxazepine are tagged with numbers without primes, the atoms of

the R_1 group are numbered with primes ($'$), while the purine bases are numbered with double primes ($''$).

14. (a) Saniger, E.; Campos, J. M.; Entrena, A.; Marchal, J. A.; Suárez, I.; Aránega, A.; Choquecillo, D.; Niclós, J.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **2003**, *59*, 5457; (b) Saniger, E.; Campos, J. M.; Entrena, A.; Marchal, J. A.; Boulaiz, H.; Aránega, A.; Gallo, M. A.; Espinosa, A. *Tetrahedron* **2003**, *59*, 8017.
15. Studies about stability of each tautomer of 6-chloropurine in DMSO-d_6 have been developed at 303 and 213 K, and prevalence of the 9*H* tautomer has been found, see: Seckárová, P.; Marek, R.; Malinaková, K.; Kolehmainen, E.; Hockova, D.; Hocek, M.; Sklenár, V. *Tetrahedron Lett.* **2004**, *45*, 6259.
16. Boryski, J.; Manikowski, A. *Nucleosides Nucleotides* **1999**, *18*, 1057.
17. Isomer's identification has been made from the value of the coupling constant between the olefinic hydrogens in each structure.
18. For examples of E2 *syn* eliminations of hydrogen atoms α- to protonated purines, see: Rodgers, M. T.; Campbell, S.; Marzluff, E. M.; Beauchamp, J. L. *Int. J. Mass Spectrom. Ion Processes* **1995**, *148*, 1.
19. Girgis, N. S.; Cottam, H. B.; Larson, S. B.; Robins, R. K. *J. Heterocycl. Chem.* **1987**, *24*, 821.
20. Horhota, A. T.; Szostak, J. W.; McLaughlin, L. W. *Org. Lett.* **2006**, *8*, 5345.
21. Koppel, H. C.; O'Brien, D. E.; Robins, R. K. *J. Org. Chem.* **1959**, *24*, 259.
22. Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2004**, *47*, 273.
23. Keck, J. H., Jr.; Simpson, R. A.; Wong, J. L. *J. Org. Chem.* **1978**, *43*, 2587.
24. The 6-chloropurine activation as an ammonium salts using NEt_3 allows the nucleophile attack at the position 6, in DMF, see: Gurvich, V.; Kim, H. Y.; Hodge, R. P.; Harris, C. M.; Harris, T. M. *Abstracts of Papers*, 218th ACS National Meeting, New Orleans, 1999.
25. Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
26. Willker, W.; Leibfritz, D.; Kerssebaum, R.; Bermel, W. *Magn. Reson. Chem.* **1993**, *31*, 287.
27. Hurd, R. E.; John, B. K. *J. Magn. Reson.* **1991**, *91*, 648.
28. Bruker. *SMART and SAINT. Area Detector Control and Integration Software*; Bruker Analytical X-ray Instruments: Madison, WI, 1997.
29. Sheldrick, G. M. *SADABS. Program for Empirical Absorption Correction of Area Detector Data*; University of Göttingen: Göttingen, Germany, 1997.
30. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.
31. Sheldrick, G. M. *SHELXL-97. Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
32. Spek, A. L. *PLATON. A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, 2003.
33. Bruker. *SHELXTL: Integrated System for the Determination of Crystal Structures*; Bruker AXS: Madison, WI, 2000.