Thermal *N*-9' → *N*-7' Isomerization of (6'-Substituted)-9-(2,3-Dihydro-5*H*-1,4-Benzodioxepin-3-yl)-9*H*-Purines in Solution: Mechanistic Aspects

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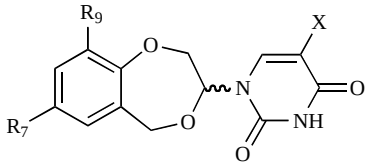
Abstract: The purine ring system is undoubtedly among the most ubiquitous of all the heterocyclic compounds. In recent years modified purine structures both of natural and synthetic origin have been a rich source of biologically active materials. The halogen at 6 position of the purine moiety of the (*RS*)-9 or 7-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-or 7*H*-purines shows an interesting reactivity which is presented and discussed. The anticarcinogenic potential of the target molecules is reported against the MCF-7 cancer cell line.

Keywords: Amination, antitumour compounds, benzodioxepins, purines, suzuki reaction, trifluoromethylation reaction.

INTRODUCTION

The purine ring system is undoubtedly among the most ubiquitous of all the heterocyclic compounds. This arises not only from the universal occurrence of adenine and guanine in DNA and RNA and of additional modified derivatives in the various tRNAs but also from the subsidiary uses of the ring system in a great number of biochemical systems. In recent years modified purine structures, both of natural and synthetic origin have been a rich source of a wide variety of biologically active materials. Such compounds generally include structural modifications in the carbohydrate moiety of ribose or deoxyribose derivatives as with arabinosides, simple changes in known purines including cytokinins, which are 6-*N*-alkylated adenines, and more deep seated changes in the purine skeleton as deaza and aza purines which involve carbon to nitrogen skeletal changes. Very recently Sabatino and Damha [1] have published the synthesis and properties of oligonucleotides containing a seven-membered (oxepane) sugar ring. During our ongoing research we have planned the synthesis of 1,4-benzodioxepin-3-yl *O*,*N*-acetals [2] with the purine moiety linked to the aminalic carbon through the *N*-9' or the *N*-7' atoms [3] to be tested subsequently against the human breast cancer cell line MCF-7.



1 $R_7 = R_9 = H$; X = F
2 R_7 = OMe; $R_9 = H$; X = F
3 $R_7 = H$; R_9 = OMe; X = F
4 $R_7 = R_9 = H$; X = H

Fig. (1).

After having reported several 5-fluorouracil benzene-fused seven-membered *O*,*N*-acetals **1-3** [4] and one uracil analogue **4** [5,6] (Fig. (**1**)), we decided to substitute the pyrimidine base for the purine one, with the objective of increasing both the lipophilicity and the structural diversity of the target molecules. In this case, two isomers were obtained: the *N*-9'-purines **5-11** [3], and the *N*-7'-purines **12-19** [3] (Fig. (**2**)). Should these compounds show antiproliferative activities, new avenues in anticancer research would be opened based on non-toxic purines.

RESULTS AND DISCUSSION

Synthesis

In order to obtain the (*RS*)-(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)adenine derivatives **8** (*N*-9') and **15** (*N*-7') (see Fig. (**2**)) the direct condensation reaction between **20** [4] and adenine was tried under our simple standard one-step/one-pot conditions [4,7]. However, an inseparable mixture of compounds was obtained and this inconvenience compelled us to change the synthetic strategy, i.e., starting from 6-chloropurine derivatives **5** and **12**, we decided to change the chlorine atom for the amino group. The condensation reaction between **20** and 6-chloropurine was accomplished using tin(IV) chloride as a 1.0 M solution in dichloromethane, trimethylchlorosilane (TCS) and 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in dry acetonitrile for 18 h at 45 ºC (Fig. (**3**)). The *N*-9' (**5**, 60%) and *N*-7' (**12**, 24%) regioisomers produced were separated by flash chromatography. Nucleophilic displacement of halogen atoms in halopurines, especially the readily available chloropurines, has provided the major route to a wide variety of substituted purines including nucleosides [8]. The purine 6-position is the most reactive towards nucleophilic substitution, and moderately elevated temperatures (25-80 ºC) are usually applied in order to introduce aliphatic or aromatic amines [9]. Several conditions were used, such as treating **5** and **12** with a saturated solution of ammonia in ethanol at 80 ºC during 4 and 27 h in a sealed tube. As the starting materials were recovered unaltered we decided to force the experimental conditions, changing the solvent (ethanol by DMF) thus allowing us to increase the heating temperature in a sealed tube (120 ºC). Under such conditions, **5** yielded the *N*-9' adenine derivative **8** and the *N*-7' adenine one **15**, which were separated by flash chroma-

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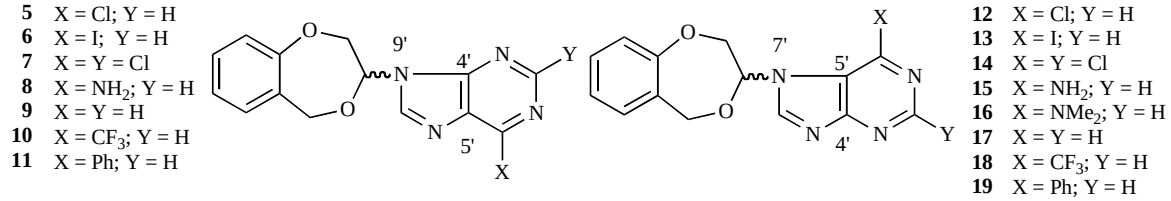
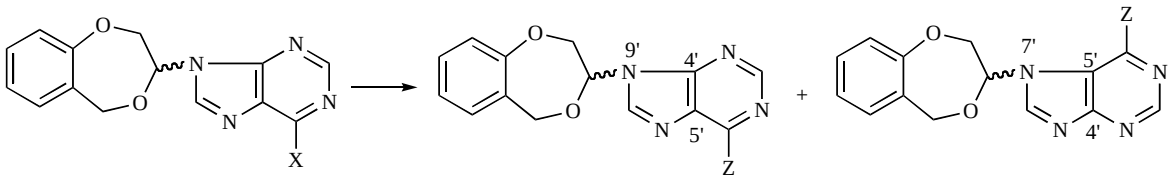


Fig. (2).

Table 1. Amination, copper(I) iodide/potassium fluoride-mediated trifluoromethylation and Suzuki cross-coupling reactions carried out on the *N*-9'-(6-halopurines) 5 and 6



Entry	Starting Material	Conditions	*N*9'-(6-Substituted)Purine, Yield (%)	*N*7'-(6-Substituted)Purine, Yield (%)
1	**5** (X = Cl)	DMF Saturated solution of NH_3, 120 ºC, sealed tube	**8** (Z = NH_2), 60	**15** (Z = NH_2), 22
2	**6** (X = I)	CF_3SiMe_3, KF and CuI (DMF and NMP), 60 ºC, sealed tube	**10** (Z = CF_3), 49	**18** (Z = CF_3), 20
3	**6** (X = I)	$PhB(OH)_2$, $PdCl_2$(dppf),[a] 85 ºC, Na_2CO_3 in dimethoxyethane	**11** (Z = Ph), 52	**19** (Z = Ph), 26

[a] [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

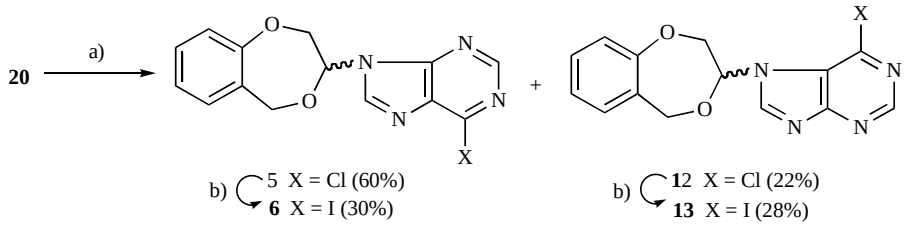


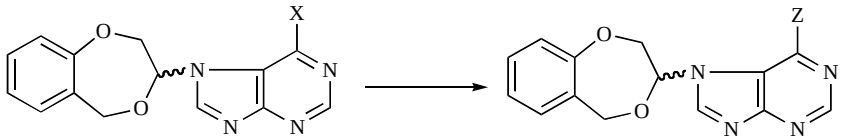
Fig. (3). *Reagents and conditions*: a) 6-chloropurine, HMDS, TCS, $SnCl_4/CH_2Cl_2$, MeCN, 18 h, 45 ºC; b) NaI/TFA/butanone at -50 to -40 ºC.

tography (Table **1**, entry 1). Reversibility of such a process is the more plausible interpretation for the course of this reaction. The *N*-9'-tetrahydropyranyl-2,6-dichloropurine fragment, which is a similar compound to **5**, loaded in the Merrifield resin, has been reported in combinatorial chemistry [10,11]. The ligand contained two differentially reactive chlorine substituents at C-6' and C-2' that could be sequentially reacted with a variety of amines. In a first relatively mild reaction, the chlorine atom at C-6' was replaced (5 equiv of amine, 80 ºC, 3h). The *N*-9'-tetrahydropyranyl-2,6-dichloropurine moiety and compounds **5** and **12** are very similar but the latter are more stable and consequently, their chlorine atoms at C-6' were displaced under harsher conditions.

When the *N*-7'-(6-chloropurine) **12** was treated under the conditions used with **5**, the *N*-7'-(dimethylamino)purine **16** was obtained, together with the *N*7-adenine **15** (Table **2**, entry 1). Trying to extend the scope of the unreported reversibility from the *N*-9'-(6-halopurine) we used two cross-coupling reactions. To produce these reactions we previously changed the *N*-9'-(6-chloropurine) **5** to the 6-iodo analogue **6** [(Finkelstein reaction, Fig. (**3**)], under conditions successfully used to perform the same process in nucleosides [12]. Such a process carried out on the *N*-7'-(6-chloropurine) **12** gave the *N*-7'-(6-iodopurine) **13** (Fig. (**3**)). Compounds **6** and **13** were also obtained by the direct condensation between **20** [4] and 6-iodopurine [13] but were produced with poorer yields (9% of **6**, and 15% of **13**).

The copper(I) iodide/potassium fluoride-mediated trifluoromethylation reaction on **6** was next tried under conditions previously used for a 9-(THP-protected) 6-iodopurine [13]. In this way 6-trifluoromethyl isomers **10** and **18** were isolated (Table **1**, entry 2), proving the reversibility of the process, in contrast to what was reported by Hocek and Holý [14]. The same reaction carried out on the *N*-7'-protected 6-iodopurine **13** produced only the *N*-7' isomer **18** (Table **2**,

Table 2. Amination, copper(I) iodide/potassium fluoride-mediated trifluoromethylation and Suzuki cross-coupling reactions carried out on the *N*-7'-(6-halopurines) 12 and 13



Entry	Starting Material	Conditions	*N*7-(6-Substituted) Purine, Yield (%)
1	**12** (X = Cl)	DMF Saturated solution of NH_3, 120 ºC, sealed tube	**16** (Z = NMe_2), 70 + **15** (Z = NH_2), 12
2	**13** (X = I)	CF_3SiMe_3, KF and CuI in a mixture of DMF and NMP, 60 ºC, sealed tube	**18** (Z = CF_3), 14
3	**13** (X = I)	$PhB(OH)_2$, $PdCl_2(dppf)$,[a] 85 ºC, Na_2CO_3 in dimethoxyethane	**19** (Z = Ph), 13

[a] [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

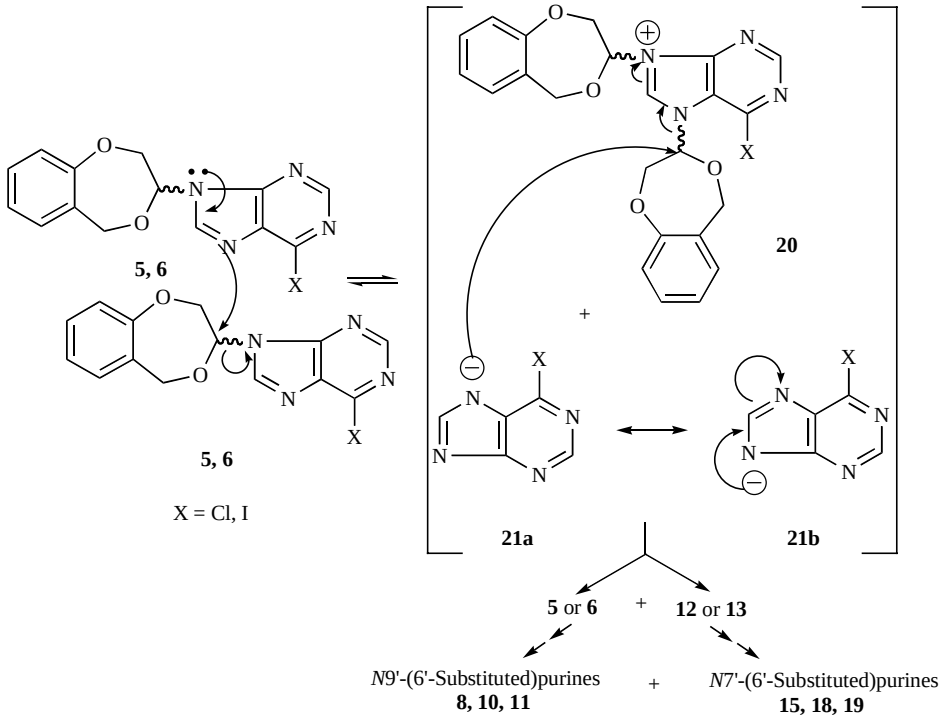


Fig. (4). Mechanism of the transformation of the 9-(6'-halopurine)purines **5, 6** into the *N*-9'-(6'-substituted)purines **8, 10,** and **11**, and the *N*-7'-(6'-substituted)purines **15, 18,** and **19**.

entry 2). Finally the Suzuki cross-coupling reaction was carried out on **6** by the conditions described by Mederski *et al.* [15], and the two 6-phenyl isomers **11** and **19** (Table **1**, entry 3) were produced. When the same reaction was carried out on **14**, compound **20** was the only product obtained (Table **2**, entry 3).

Mechanistic Aspects on the Synthesis of the *N*-9' and *N*-7' Alkylated Purines

Little attention has been paid to the fact that preformed purine *N*-7- or *N*-9-nucleosides can isomerize at elevated temperatures. It was observed that *N*-9-ribosylated 6-oxopurines or their corresponding acyclic derivatives, which are fully acylated, undergo thermal isomerization to *N*-7/*N*-9-mixtures [16,17]. The reaction takes place even in the absence of a catalyst when the starting material is melted for 5 – 10 min at a temperature exceeding 190 ºC. Golankiewicz *et al.* [18] have reported the isomerization of protected 2'-deoxyguanonosine derivatives melted and in solution. In relation to the mechanism of the *N*-9 → *N*-7 isomerization reactions of 6-oxopurine ribonucleosides [19] and acyclonucleosides [20], it has been postulated that a bis-riboside is the intermediate of such transformations. A similar intermediate such as a 7,9-diglycosyl-6-oxopurine quaternary salts was hypothesized to explain the regioselectivity and mechanism of transpurination reactions in the guanine nucleoside series [21]. We used this background and a tentative explanation is depicted in Fig. (**4**), through the intermediate (*RS*)-6-halo-7,9-bis(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)purine **20**.

The electronic pair of *N*-9' assisted the nucleophilic attack of the $N_{7'}=C_{8'}$ double bond of compounds **5** and **6** to the hemiaminalic carbon atom [2] (C-3) of the benzo-1,4-dioxepin-3-yl moiety of other molecules **5** and **6**, consequently producing the leaving of 6-halopurine in its anionic forms **21a** and **21b**. Nevertheless, it has to be pointed out that the resonance hybrid **21a** is favoured over **21b** due to the stabilization of its negative charge on *N*-7' by the –I effect caused by the halogen atom at position 6'. Anion derived from the 7*H*-purine **21a** is responsible for the formation of compounds **12** and **13**, the deficient electronic character *N*-9' atom of the intermediate **20** being the driving force of such a process. The whole transformation is reversible, the major products being the *N*-9'-purines **8**, **10,** and **11**, over their corresponding regioisomers **15**, **18** and **19**. Compounds **8**, **10** and **11** are more stable than their regioisomers **15**, **18** and **19**. The most stable conformation of **8** is thermodynamically favoured over the most stable one of its *N*-7'-isomer **15**, the difference in the heats of formation being ≈ 5 kcal/mol. Conformational analysis of **8** and **15** was performed as previously reported [6]. Therefore, it can be concluded that the isomerization *N*-9' → *N*-7' is termodinamically controlled (the *N*-9'/*N*-7' ratios are always > 1: **8**/**15** = 60/22 = 2.7; **10**/**18** = 49/20 = 2.4; **11**/**19** = 52/26 = 2, Table **1**). Once the isomerization *N*-9' → *N*-7' had taken place, the subsequent irreversible process occurred (S_NAr by the amino group, and cross-coupling reactions) to produce the target compounds **15**, **18** and **19**. In order to cast some light on the mechanism, we heated compound **8** at 130 ºC for 27 h in a sealed tube that contained a saturated solution of NH_3 gas in DMF and no transformation was observed. This experimental feature may be accounted for if we assume that the *N*-9'-(6-halo)purine → *N*-7'-(6-halo)purine isomerizations (**5** → **12**, and **6** → **13**) took place *before* the substitution process (Fig. (**4**)).

When we tried to systematize the transformation shown in Table **2**, entry 1 there was one distinctive fact: the chlorine atom at position 6' of the purine base was substituted by the NMe_2 group when, in the case of **5** (*N*-9'), the only nucleophile was ammonia. The irreversible interchange reaction between the chlorine atom of **12** and the two nucleophilic species (NH_3 and $HNMe_2$) produced **16** and **15** (Table **2**, entry 1). It has been reported that the synthesis of 4-(dimethylamino)quinoline is accomplished by the treatment of 4-chloroquinoline with DMF and KOH at reflux for 20 h [23]. Moreover, a convenient dimethylamination of various heterocyclic, including 6-chloropurine, and aromatic compounds having the activated chlorine atom has been published [23]. By means of this procedure the dimethylamino compound **16** is obtained, together with the amino one **15**.

It can be hypothesized that a reversible process took place when the *N*-7'-(6-halopurines) **12** or **13** were the starting reactants through the intermediate **22** (Fig. (**5**)). In this case, the target molecules **15**, **16**, **18** and **19** could be formed directly from the starting materials **12** or **13**, or from the resonance hybrid **21a**. It is worth pointing out that the nucleophilic attack of **21a** over C-3 of the intermediate **22** [similar to the attack of **21a** to **20**, depicted in Fig. (**4**)] would give rise to two molecules of **12** or **13**. Moreover, the *N*-9'-(6-halopurines) **5** or **6**, or the substitution products at their 6'-positions were not detected, in accordance with the experimental results. On comparing both intermediates (**20** and **22**), it seems that **22** is less stable than **20**, owing to the –I effect of the 6'-halogen. Accordingly, the yields of compounds **15**, **18** and **19** obtained from the *N*-9'-(6'-halopurines) **5** and **6** were higher than those of the same compounds prepared from the *N*-7'-(6'-halopurines) **12** and **13** (Compare entries 1, 2 and 3 of Tables **1** and **2**). Entries 2 and 3 of Table **2** show the yields of the 6'-trifluoromethyl-*N*'-7-alkylated purine (**18**, 14%) and the 6'-phenyl-*N*'-7-alkylated purine (**19**, 13%) derivatives.

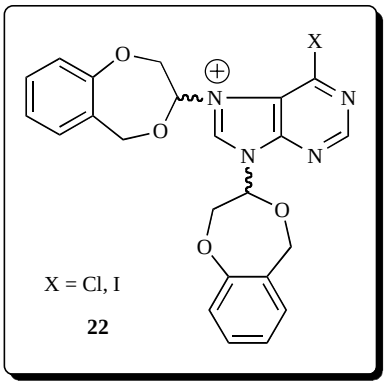


Fig. (5). Intermediate **22** is hypothesized when the 7-(6-halopurine)purines **12, 13** are the starting materials for their transformations into the *N*-7'-(6'-substituted)purines **15, 18,** and **19**.

Spectroscopic Analysis of the *N*-9' and the *N*-7' Alkylated Purines

^1H-^{13}C Heteronuclear Multiple Bond Coherence (HMBC) experiments enabled the complete regiochemical assignment of **5** and **12**. The discrimination between *N*-9'-substituted derivatives on one hand, and *N*-7'-substituted derivatives on the other, relies on the correlation between H-3 of the seven-membered moiety and C-4' and C-5', respectively. Very important is the correlation between H-3 (δ 6.32 ppm) and the quaternary carbon at δ 151.58 ppm of **5**, which has the following two consequences: a) this signal can be assigned to C-4' and b) this correlation proves unequivocally that the linkage between the seven-membered moiety and the purine base takes place through *N*-9' in compound **5**. Moreover, a cross-peak was found in the HMBC spectrum among H-3 (δ 6.55 ppm) and C-5' (δ 143.26 ppm) of **12**; this experimental fact is irrefutable evidence that the 2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl fragment and the 6-chloropurine system are linked through *N*-7' in **12**.

Assignments of *N*-9' versus *N*-7' isomers can be readily made from the ^{13}C NMR signal of the C-4' peaks ($CDCl_3$); for the *N*-9' isomers: δ 151.58 ppm (**5**), δ 152.28 ppm (**7**), δ 150.00 ppm (**8**), and δ 153.07 ppm (**9**); for the *N*-7' isomers: δ 162.07 ppm (**12**), δ 163.78 ppm (**14**), δ 162.84 ppm (**15**), δ 160.85 ppm (**16**), δ 161.00 ppm (**17**), and δ 161.40 ppm (**19**). These values agree with previous findings on acyclic adenine derivatives [24].

The most pronounced differences in *N*-9' (**5**) and *N*-7' (**12**) regioisomers were found for the proton signals H-2' and H-8' of the purine skeleton. Thus, the protons H-2' and H-8' in the *N*-7' isomer (**12**) were shifted downfield (δ 8.90 and

Table 3. Antiproliferative activities against the MCF-7 cell line for the uracil (5-FU and 1-4), *N*-9' (5-11) and *N*-7' (12-19) purine compounds

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
5-FU	4.32 ± 0.02	**7**	4.40 ± 0.88	**14**	1.28 ± 0.61
1	7.00 ± 0.61[b]	**8**	18.4 ± 3.16	**15**	27.1 ± 4.93
2	4.50 ± 0.33[b]	**9**	44.9 ± 9.83	**16**	22.2 ± 3.80
3	22.0 ± 0.93[b]	**10**	3.21 ± 0.40	**17**	40.4 ± 7.85
4	5.00 ± 0.05[c]	**11**	16.4 ± 0.26	**18**	24.9 ± 1.83
5	4.63 ± 0.01	**12**	2.74 ± 0.31	**19**	22.8 ± 0.19
6	6.75 ± 0.23	**13**	4.01 ± 0.33		

[a] Data taken from ref. [5], except for compounds **1**-**3** and **4**.
[b] Data taken from ref. [4].
[c] Data taken from ref. [6].

8.70 ppm, respectively) relative to the corresponding ones (δ 8.78 and 8.44 ppm) in the *N*-9'-substituted molecule (**5**). This principle applies for the remaining of the *N*-9' and *N*-7' purine isomers, except in two cases: a) the CF_3-6-substituted purine compounds (**10** and **18**) in which the ^1H chemical shifts of both H-2' and H-8' atoms are identical, and b) the adenine-containing compounds (**8** and **15**) in which H-2' are almost identical (δ 8.35 for **8**, and δ 8.36 ppm for **15**). Timár *et al*. have proposed empirical rules for differentiating *N*-9/*N*-7-substituted guanines based on their ^{13}C NMR chemical-shift differences [25]. Moreover, the determination of *N*-9/*N*-7–isomer ratio of alkyl(guaninyl)acetates by electrospray ionization tandem mass spectrometry has been recently published [26].

Antiproliferative Activity Against the MCF-7 Human Breast Cancer Cell Line

Table **3** shows the antiproliferative activities against the MCF-7 human breast cancer cell line for the target compounds, including 5-FU. As a rule the following could be stated: a) compound **4** shows a similar antiproliferative activity that the 5-FU-containing derivatives **1** and **2** and a better one than **3**; b) in general, the *N*-7' purine derivatives present a better activity than the their *N*-9' regioisomers, except in the case of the CF_3-6-substituted compounds (**10** and **18**); c) The adenine-containing derivatives (**8** and **15**) and the *N*,*N*-dimethyladenine structure (**16**) do not show any interesting antiproliferative activities, in contrast to the naturally base-containing (uracil) derivative **4**; d) The presence of at least one halogen atom on the purine skeleton (or in a 6'-methyl group such as **10**) is necessary to improve the antiproliferative activity; e) the most active compound is the *N*-7'-2,6-dichlorosubstituted purine (**14**), which is 3.4-fold more potent than 5-FU; its *N*-9'isomer is equipotent to 5-FU; f) to the best of our knowledge, the hemiaminals **12**, **13** and **14** represent a new kind of compounds with a novel structure and a significant anticancer activity against the MCF-7 cell line.

CONCLUSION

From a chemical point of view the following aspects have to be pointed out: b) the course of the formation of the target molecules **8**, **10**, and **11** is the first example of S_NAr and cross-coupling reactions of 6-halopurine through a reversible process, when starting from *N*-9'-6-halopurine isomers. When the starting materials are the *N*-7'-6-halopurine derivatives (**12** and **13**) the process is also reversible, but only the *N*-7' products (**15**, **18** and **19**) are produced. In both cases, (*RS*)-6-halo-7,9-bis(2,3-dihydro-5*H*-benzo-1,4-dioxepin-3-yl)purines (**20** and **22**) have been hypothesized as intermediates; c) in the amination that occurs from the *N*-7'-6-chloropurine **12**, together with ammonia, a second nucleophile arises (dimethylamine) as a consequence of the decomposition of DMF under the high temperature and basic conditions in the sealed tube; d) in relation to the ^{13}C NMR data, the most pronounced differences affect the C-4' and C-5' atoms of both isomers. The signal *circa* δ 162 ppm, corresponding to C-4' of the purine base, is unequivocal proof of an *N*-7' isomer against the one *circa* δ 151 ppm, corresponding to the same carbon atom of the other regioisomer (*N*-9').

Biologically speaking it is important to highlight that, a) the most active compound is the *N*-7'-2,6-dichloro-substituted purine **14**, which is 3.4-fold more potent than 5-fluorouracil (5-FU); its *N*-9'isomer **7** is equipotent to 5-FU; and b) to the best of our knowledge, the (6'-substituted)-9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-9*H*-purines represent a new kind of compounds with a novel structure and a significant anticancer activity against the MCF-7 cell line. These results provide promising information for further development of potent antiproliferative agents. At present, studies are being carried out to determine the mechanism of action at the molecular level of the most active compounds.

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REFERENCES

[1] Sabatino, D.; Damha, M.J. *Nucleosides Nucleotides Nucleic Acids*, **2007**, *26*, 1185.
[2] Functional groups possessing an sp^3 hybridized carbon bonded to oxygen and to nitrogen are known as *O*,*N*-acetals or hemiaminals.

[3] For the numbering of the compounds, the atoms of the benzodioxepin ring are tagged with numbers without primes, while those of the pyrimidine and purine bases are numbered with primes (').
[4] Saniger, E.; Campos, J.; Entrena, A.; Marchal, J. A.; Súarez, I.; Aránega, A.; Choquesillo, D.; Niclós, J.; Gallo, M.A.; Espinosa, A. *Tetrahedron*, **2003**, *59*, 5457.
[5] Núñez, M.C.; Pavani, M.G.; Díaz-Gavilán, M.; Rodríguez-Serrano, F.; Gómez-Vidal, J.A.; Marchal, J.A.; Aránega, A.; Gallo, M.A.; Espinosa, A.; Campos, J.M. *Tetrahedron*, **2006**, *62*, 11724.
[6] Marchal, J.A.; Núñez, M.C.; Suárez, I.; Díaz-Gavilán, M.; Gómez-Vidal, J.A.; Boulaiz, H.; Rodríguez-Serrano, F.; Aránega, A.; Gallo, M.A.; Espinosa, A.; Campos, J.M. *Breast Cancer Res. Treat.*, **2007**, *105*, 237.
[7] Saniger, E.; Campos, J.; Entrena, A.; Marchal, J.A.; Boulaiz, H.; Aránega, A.; Gallo, M.A.; Espinosa, A. *Tetrahedron*, **2003**, *59*, 8017.
[8] Hall, R.H. *The Modified Nucleosides in Nucleic Acids;* Columbia University Press: New York, **1971**.
[9] Rodenko, B.; Wanner, M. J.; Koomen, G.-J. *J. Chem. Soc. Perkin Trans., 1*, **2002**, 1247.
[10] Nugiel, D.A.; Cornelius, L.A.M.; Corbett, J.W. *J. Org. Chem.*, **1997**, *62*, 201.
[11] Chang, J.; Dong, C.; Guo, X.; Hu, W.; Cheng, S.; Wang, Q.; Chen, R. *Bioorg. Med. Chem.*, **2005**, *13*, 4760.
[12] Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.*, **2004**, *6*, 2917.
[13] Elion, G. B.; Hitchings, G.H. *J. Am. Chem. Soc.*, **1956**, *78*, 3508.
[14] Hocek, M.; Holý, A. *Collect. Czech. Chem C.*, **1999**, *64*, 229.
[15] Mederski, W.W.K.R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron*, **1999**, *55*, 12757.
[16] Boryski, J.; Golankiewicz, B. *Nucleic Acids Res. Symp. Ser.*, **1987**, *18*, 45.
[17] Boryski, J.; Golankiewicz, B. *Nucleosides Nucleotides*, **1989**, *8*, 529.
[18] Golankiewicz, B.; Ostrowski, T.; Leonard, P.; Seela, F. *Helv. Chim. Acta*, **2002**, *85*, 388.
[19] Dudycz, L.W.; Wright, G. E. *Nucleosides Nucleotides*, **1984**, *3*, 33.
[20] Boryski, J.; Manikowski, A. *Nucleosides Nucleotides*, **1999**, *18*, 1057.
[21] Boryski, J. *J. Chem. Soc. Perkin Trans.*, **1997**, *2*, 649.
[22] McCurdy, A.; Jiménez, L.; Stauffer, D.A.; Dougherty, D.A. *J. Am. Chem. Soc.*, **1992**, *114*, 10314.
[23] Agarwal, A.; Chauhan, P.M.S. *Synth. Commun.*, **2004**, *34*, 2925.
[24] Gómez, J.A.; Campos, J.; Marchal, J.A.; Trujillo, M.A.; Melguizo, C.; Prados, J.; Gallo, M.A.; Aránega, A.; Espinosa, A. *Tetrahedron*, **1997**, *53*, 7319.
[25] Timár, Z.; Kovács, L.; Kovács, G.; Schmél, Z. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 19.
[26] Ferenc, G.; Kele, Z., Kovács, L. *Rapid Commun. Mass Spectrom.*, **2005**, *19*, 236.

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