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Synthesis and Anticancer Activity of (*R*,*S*)-9-(2,3-Dihydro-1,4-Benzoxathiin-3-ylmethyl)-9*H*-Purines

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*A series of eleven 2- and 6-substituted (*R,S*)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine derivatives was obtained by applying a standard Mitsunobu protocol that led to a six-membered ring contraction from (*R,S*)-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol via an episulfonium intermediate. The signal ~δ= 151 ppm, which corresponds to the C4′ carbon atom, is unequivocal proof of the N9′ regioisomer. The potential of the target molecules as anticancer agents is reflected in their activity against the MCF-7 cancer cell line. The most active compounds have IC_{50} values of (6.18 ± 1.70) and (8.97 ± 0.83) μM. The results indicate that the anticancer activity for the most active compounds is correlated with their capacity to induce apoptosis.*

Introduction

The 2,3-dihydro-1,4-benzodioxin ring system is present in a large number of therapeutic agents that possess important biological activities.[1] Some of them are antagonists of α-adrenergic receptors, giving them antihypertensive properties.[2,3] Others have affinities toward serotonin receptors, which are involved in nervous breakdown and schizophrenia.[4] Twelve years ago, 2,3-dihydro-1,4-benzodioxins were developed as inhibitors of 5-lipoxygenase, an enzyme involved in the oxygenation of arachidonic acid to leukotrienes; they are also useful for the treatment of inflammatory diseases such as asthma and arthritis.[5] The occurrence of the 2,3-dihydro-1,4-benzodioxin structure in various natural products has been also reported.[6] Paradoxically, despite the considerable development of biologically active compounds with the 2,3-dihydro-1,4-benzodioxin moiety, the 2,3-dihydro-1,4-benzoxathiine skeleton has still remained inaccessible.

The development of new anticancer drugs is among the top priorities in fundamental medicinal chemistry research. Because it is difficult to discover novel agents that selectively kill tumor cells or inhibit their proliferation without general toxicity, the use of traditional cancer chemotherapy is still very limited. A series of pyrimidine-linked benzene-fused seven-membered *O,N*-acetals were designed and synthesized (**1**–**4**, Figure 1).[7] Later, the pyrimidine base was substituted with a purine group, with the objective of increasing both the lipophilicity and structural diversity of the target molecules (**5**, Figure 1).[8]

The importance of 5-fluorouracil (5-FU) as the first-choice drug in the treatment of gastrointestinal tract carcinomas is well known despite its side effects. With the aim of diminishing the toxicity and obtaining biologically active derivatives of 5-FU suitable for oral administration, considerable effort has

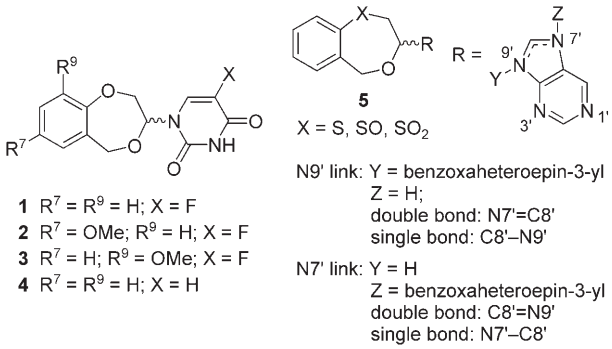

Figure 1. Several benzene-fused seven-membered ring pyrimidine and purine *O,N*-acetals previously reported our research group.

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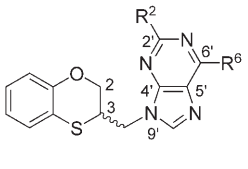
been made in the preparation of 5-FU prodrug derivatives, and a review of the various prodrugs of 5-FU has appeared.[9] Some 5-FU prodrugs are active against certain malignant cell lines through the inhibition of thymidylate synthase by the formation of 5-fluorodeoxyuridine monophosphate or by the incorporation of 5-fluorouridine triphosphate into RNA. In studies on masked 5-FU derivatives, it has been found that the bond strength between the N1 atom of the 5-FU ring and the substituent attached to N1 is an important factor influencing the antitumor activity and toxicity of these compounds. The results indicated that the weaker the bond, the greater the antitumor activity and toxicity of the masked compounds.[10] In the case of *N*-alkyl-5-FU derivatives, the strong $N1_{5\text{-FU}}$–$C_{exocyclic}$ bond conversely prevented these derivatives from being easily hydrolyzed in vivo, and indeed these compounds showed no antitumor activity against L1210 leukemia.[10] When oxygen was introduced at the position α to the alkyl group,[11] the N–C bond became labile under hydrolytic conditions, and the resulting derivatives showed antitumor activity.

We previously reported the selective activity of these new compounds toward the regulatory molecules of the G_1/G_0 phase of the cell cycle, and also their ability to modulate the activity of p53 and bcl-2 for the induction of apoptosis.[12] Therefore, such compounds may be considered as drugs in their own right, with antitumor activity independent of that of 5-FU. If the previously described compounds are not prodrugs, it is not necessary to maintain the *O*,*N*-acetal characteristics with the corresponding weakness of the *O*,*N*-acetal bond. Therefore, from this point forward, we are involved in the design of molecules in which both structural entities (the benzene-fused heterocyclic ring and the purine base) are linked by a heteroatom-C-C-base-N-atom bond. We describe herein the design, synthesis, and biological evaluation of a series of 2- and 6-substituted (*R*,*S*)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine derivatives **6**–**16** (Figure 2).



6 R^2 = H, R^6 = Cl
7 R^2 = H; R^6 = Br
8 R^2 = H; R^6 = SMe
9 R^2 = H; R^6 = OPh
10 R^2 = H; R^6 = SPh
11 R^2 = H; R^6 = NHPh
12 R^2 = H; R^6 = $OCH_2CH{=}CH_2$
13 R^2 = H; R^6 = OCH_2Ph
14 R^2 = H; R^6 = SCH_2Ph
15 R^2 = H; R^6 = $OCH_2C_6H_{11}$
16 R^2 = Cl; R^6 = Cl

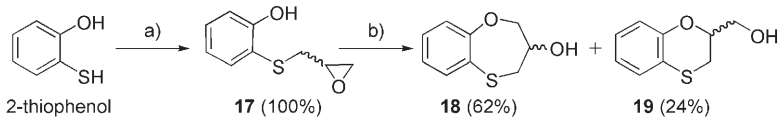
Figure 2. Target molecules synthesized.

Results and Discussion

Reaction between 3-[(2-hydroxyphenyl)thio]-1,2-epoxypropane (17) and sodium hydroxide

1,5-Benzoxathiepine derivatives were obtained in good yields by the reaction of epichlorohydrins with 2-hydroxybenzenethiols in an aqueous alkaline hydroxide medium.[13] A comparison of the results obtained for catechols[14] that produce the 1,4-benzodioxin rings with those given by 2-hydroxybenzenethiols suggests that the larger atomic radius of the sulfur atom causes the attack to occur at the secondary carbon atom of the epoxide moiety rather than the tertiary one, thus producing the seven-membered ring (compound **18**) as the major product.

Compound **18** was prepared as shown in Scheme 1: Cabiddu et al.[13] described the formation of **18** as a consequence of nucleophilic attack by the phenoxide ion at the secondary epoxide carbon of **17**; nevertheless, when these same experimental conditions were applied, we also observed formation of the six-membered ring in **19**, caused by the attack of the phenolic oxygen atom at the more hindered position of the epoxide ring.



2-thiophenol **17** (100%) **18** (62%) **19** (24%)

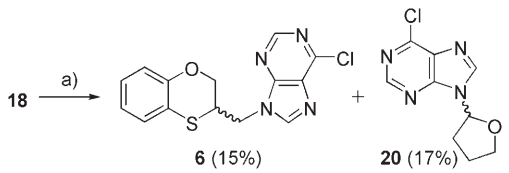
Scheme 1. Reagents and conditions: a) see Ref. [13]; b) NaOH, H_2O, 100 °C.

The structure of **19** was confirmed by a previously reported constitutive synthesis,[15] that is, preparation of ethyl-1,4-benzoxathiane-2-carboxylate from 2-hydroxybenzenethiol and ethyl-2,3-dibromopropionate in acetone with anhydrous potassium carbonate, and its subsequent reduction with sodium bis(2-methoxyethoxy)aluminum hydride in benzene.

Mitsunobu reaction between 18 and 6-chloropurine

The conventional Mitsunobu conditions employing diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in anhydrous tetrahydrofuran (THF) were applied in the reaction between **18** and 6-chloropurine (Scheme 2).

The structure of **6** was determined by ^1H and ^{13}C NMR, HMQC, HMBC, and X-ray diffraction (the crystallization was car-



6 (15%) **20** (17%)

Scheme 2. Reagents and conditions: a) 6-chloropurine, Ph_3P, DIAD, anhydrous THF, 45 °C.

ried out in a $CHCl_3$/acetone mixture). In the HMBC experiment to three bonds, the interaction between the hydrogen atom of the aliphatic CH and the quaternary carbon atom of the benzene ring was observed. Nevertheless, no interaction from the methylene groups with such a carbon atom was found, as would be the case if the seven-membered ring were formed (Figure 3). Importantly, the correlation between the methylene

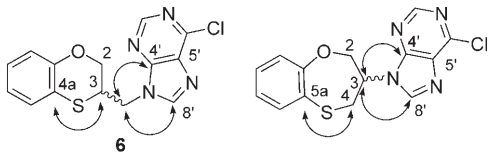


Figure 3. Representation of the HMBC interactions (with double-tipped arrows) that were or should be observed in the six- and seven-membered rings and purine group atoms.

group that links the six-membered and the purine rings ($\delta =$ 4.54 ppm, dd, $J_{gem} = 14.3$ Hz, $J_2 =$ 8.0 Hz, 1H) and the quaternary carbon at $\delta = 151.82$ ppm of **6**, has the following two consequences: a) this signal can be assigned to C4′[15] and b) this correlation proves unequivocally that the linkage between the six-membered moiety and the purine base takes place through N9′ in compound **6**. The chemical shift of C4′ in **6** agrees with previous findings on related N9′ purine *O*,*N*-acetals.[7,16]

Alkylation of purine nucleobases and analogues is rarely regiospecific, and mixtures of N9′ and N7′ isomers are usually obtained. The N9′ compound is normally the major product, but formation of significant amounts of the N7′ isomer[16] is often observed.

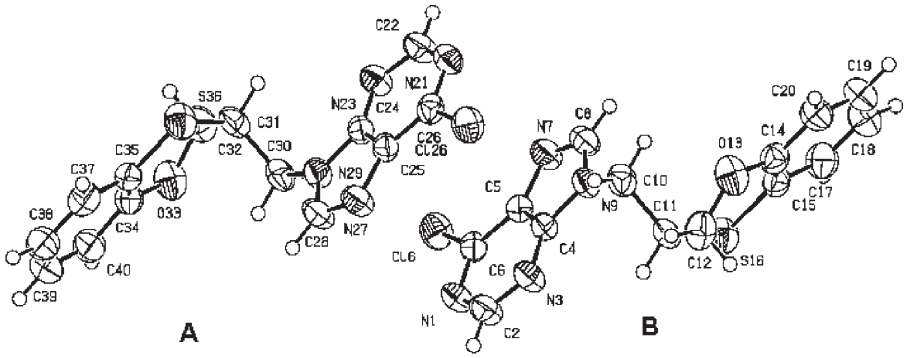


Figure 4. A view of the asymmetric unit of **6** containing both enantiomers.

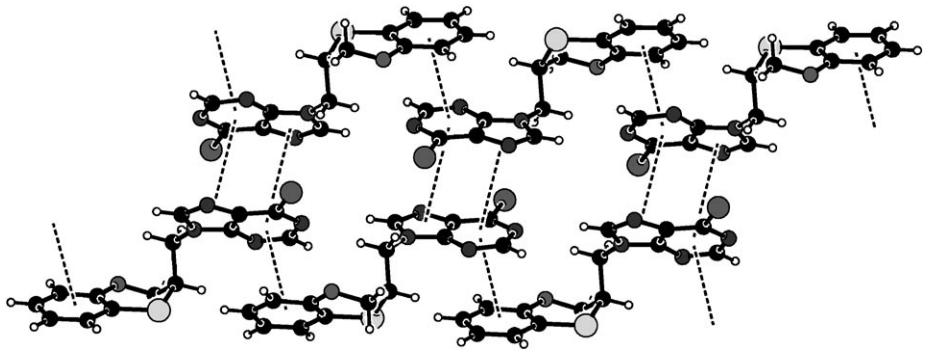


Figure 5. Contribution of π–π stacking interactions in the construction of a ribbon structure in the crystal of **6**.

with the planes of the involved rings nearly parallel, slipping angles of 10–16°, and distances between centroids and between ring planes close to 3.5 Å.

Interestingly, pairs of both enantiomer chains build a ribbon parallel to the *ac* plane by means of a double π–π stacking interaction between the rings of purine moieties from two enantiomeric molecules (Figure 5). This interaction involves the five-membered ring of each purine with the six-membered cycle of another. However, the strength of these stacking interactions is less than that mentioned above for the formation of the enantiomer chains. Stacked purine moieties fall nearly parallel at ~3.5 Å but with slipping angles close to 25° and centroid–centroid distances close to 3.8 Å. These ribbons build up the crystal by additional hydrophobic interactions.

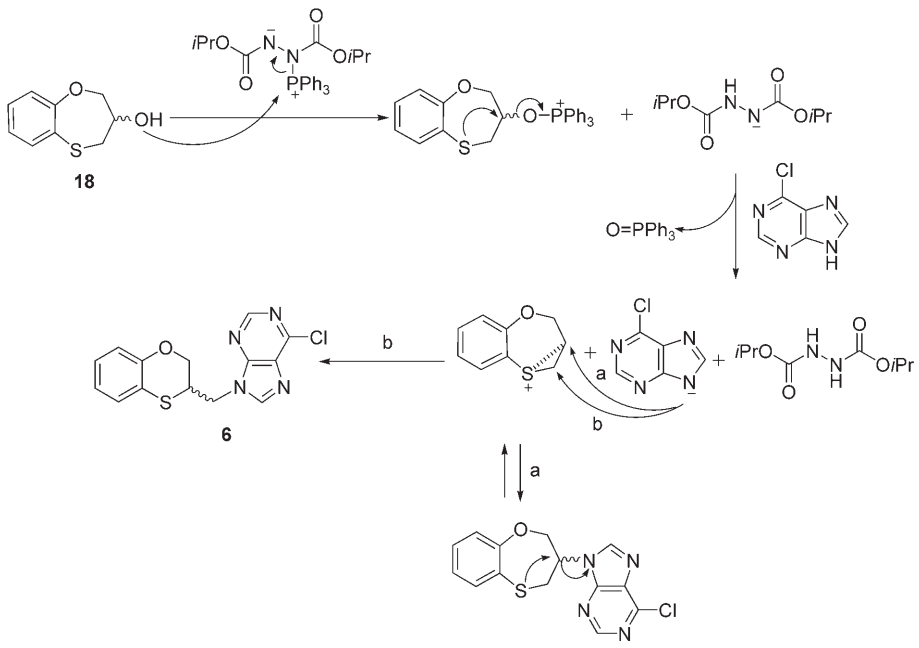
X-ray structure of 6

The asymmetric unit contains two independent molecules (**A** and **B**) which correspond to the *R* and *S* enantiomers. The lowest numeration corresponds to the **B** molecule (Figure 4). In the crystal, enantiomers have a closely similar conformation, in which both contain the 6-chloropurine fragment in the axial position. Such enantiomers build infinite chains of $\mathbf{A}_n$ or $\mathbf{B}_n$ running along the *a* axis. There is a π–π stacking interaction that involves the benzene ring of one molecule and the six-membered ring of the 6-chloropurine moiety of the next molecule in each chain. The stacking parameters of this interaction reveal an appreciable strength in both chains of enantiomers,

Mechanism of formation of 6 and 20

A plausible process is shown in Scheme 3: the formation of **6** could be explained by the steric hindrance caused by the triphenylphosphine linked to the secondary OH group of **18** that affects attack by bulky nucleophiles such as 6-chloropurine during the course of the Mitsunobu reaction. Hence, the reaction would deviate because the sulfur atom competes as an alternative nucleophile. This S-3[1] neighboring participation im-

[1] *In descriptions of nucleophilic participation, the term G-*n *is often used, for which G is the participating group and* n *is the size of the ring that is formed in the transition state.*



Scheme 3. Possible mechanism for the formation of **6** under Mitsunobu conditions.

plies the formation of an episulfonium ion intermediate. Nevertheless, the formation of the expected seven-membered ring from this three-membered ring would be possible. Not the slightest trace was detected, and therefore its instability can be presumed because of the strong nucleophilic character of the sulfur atom and good leaving ability of 6-chloropurine (Scheme 3).

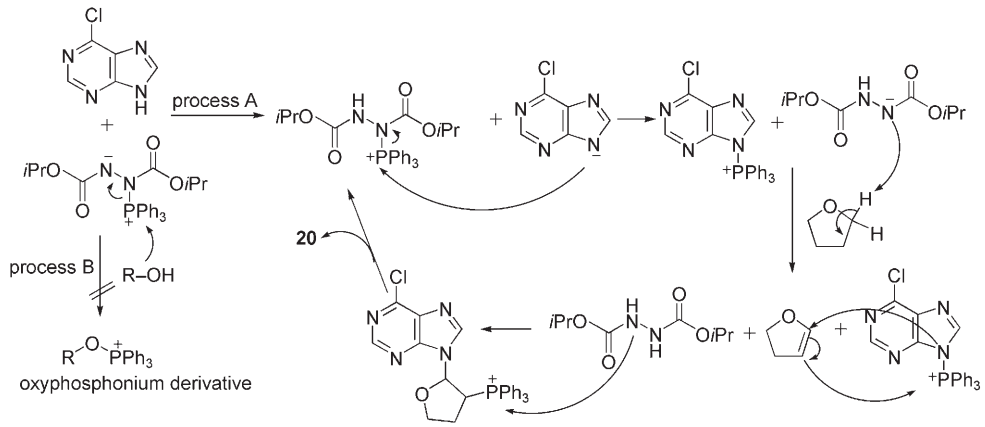
The formation of episulfonium rings by intramolecular attack of a nucleophilic sulfur atom at electrophilic positions in the same molecule has been extensively reported and is the cause of the instability of compounds and deviation of reactions towards unexpected products.[17] Several ring-contraction reactions of 5-thiopyranose to 4-thiofuranose have been reported.[18]

Compound **20** was previously synthesized by reaction of 2,3-dihydrofuran with 6-chloropurine in the presence of a catalytic amount of acid.[19] Compound **20** was isolated in the reaction between **18** and 6-chloropurine with a yield similar to that of **6**. The formation of **20** under the Mitsunobu conditions has never been reported before. To determine if the intervention of **18** or any intermediate derived from it is necessary for the formation of **20**, the reaction was repeated under the same conditions as shown in Scheme 4, but without adding the secondary alcohol **18** to the medium. Compound **20** was obtained again, and this time in better yield (50%).

Formation of **20** seemed to be a consequence of the reaction of 6-chloropurine with the THF solvent, probably through 2,3-dihydrofuran. This could be formed in cases in which the alcohol is not present or is slightly reactive, owing to the accumulation of a certain quantity of the azo derivative–triphenylphosphine complex in the reaction medium. In the case of a slightly reactive alcohol, the formation of the oxyphosphonium intermediate is slow, and probable recruitment of a proton from the purine group by the negatively charged atom of the complex (process A, Scheme 4) takes place at greater velocity. The resulting species would progress by the removal of an acidic proton of THF, as shown in Scheme 4.

Microwave-assisted Mitsunobu reaction

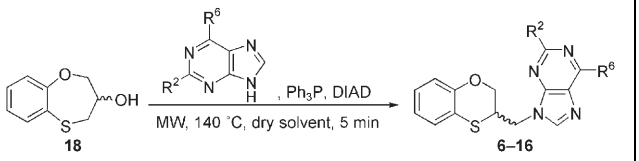
Modern drug discovery steadily relies on high-speed organic synthesis. Microwave-assisted organic synthesis[20,21] is becoming instrumental for the rapid synthesis of compounds with new and improved biological activities.[22] Compound **20** was not formed when the reaction between **18** and 6-chloropurine



Scheme 4. Process proposed for the formation of **20**: the abnormal process A is favored in the case of less-reactive alcohols; the normal process B is rendered difficult in the case of less-reactive alcohols.

(under the Mitsunobu conditions) was carried out under microwave conditions, and the yield of **6** increased (conditions were fixed at 140 °C for 5 min at a pressure of 100 kPa). At this point there are only four reports of a microwave-assisted Mitsunobu reaction.[23] When the reaction between **18** and 6-chloropurine was carried out under both microwave and conventional heating, the yield of **6** increased in the microwave [from 15% under classical conditions to 80% in dry THF, or 85% in dry MeCN under microwave heating (see Table 1, entries 1 and 2)].

Table 1. Microwave-assisted synthesis[a] of (*R,S*)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purines **6**–**16**.



18 6–16

Compd	R^2	R^6	Solvent	Yield [%][b]
6	H	Cl	THF	80
6	H	Cl	MeCN	85
7	H	Br	MeCN	62
8	H	SMe	THF	37
9	H	OPh	THF	41
10	H	SPh	THF	36
11	H	NHPh	THF	23
12	H	$OCH_2CH{=}CH_2$	THF	34
13	H	OCH_2Ph	THF	60
14	H	SCH_2Ph	THF	52
15	H	$OCH_2C_6H_{11}$	THF	31
16	Cl	Cl	THF	81

[a] Single-mode microwave on a 0.27-mmol scale. [b] Isolated yield of pure compounds.

Therefore, the increased yield could be due to the lack of formation of **20**. The higher temperature and pressure of this nonclassical heating method, or the involvement of the so-called specific or nonthermal microwave effects[21a] could increase the reactivity of the alcohol and therefore favor the normal course of the reaction towards the oxyphosphonium derivative, which would explain the decreased formation of **20**.

Because of all the advantages of microwave heating, the remaining target molecules were obtained under the same conditions, and the structures and yields are shown in Table 1. 6-Cyclohexylmethoxypurine,[24] 6-allyloxypurine,[24] 6-benzyloxypurine,[25] 6-phenoxypurine,[26] 6-phenylthiopurine,[26] 6-benzylthiopurine,[26] and 6-anilinopurine[26] were synthesized according to published procedures.

Spectroscopic characteristics of the N9′-alkylated purines

Assignments of N9′ versus N7′ isomers can be readily made from the ^{13}C NMR signal of the C4′ peaks ($CDCl_3$):[8] the signal $\sim\delta = 151$ ppm is characteristic of the C4′ atom of the N9′ regioisomers, whilst the signal $\sim\delta = 160$ ppm is characteristic of the C4′ atom of the N7′ regioisomers. In our case, the signals for C4′ appear at the following chemical shifts for compounds **6**–**16**: $\delta = 151.82$ (**6**), 150.70 (**7**), 148.34 (**8**), 152.54 (**9**), 148.95 (**10**), 149.77 (**11**), 151.90 (**12**), 152.73 (**13**), 148.53 (**14**), 152.16 (**15**) and 152.29 ppm (**16**). The nature of the substituent at position 6 of the purine ring causes a slight down- or upfield shift of about 2 ppm (148 ppm for the thio-substituted derivatives, 149 ppm for the amino-substituted one, and 152 ppm for the oxy-substituted analogues).

Antiproliferative activity, cell-cycle distribution, and apoptosis induction in the human breast cancer cell line MCF-7

Table 2 shows the antiproliferative activities against the MCF-7 human breast cancer cell line for the target compounds, including 5-FU as reference drug. In general it seems that bulky substituents at position 6′ are detrimental to anticancer activity. The presence of a halogen atom at position 6′ (compounds **6** and **7**) or two chlorine atoms at both 2′ and 6′ positions (compound **16**) have led to the most active compounds. Compound **7** is nearly equipotent to 5-FU.

Table 2. Antiproliferative activities against the MCF-7 cell line for 5-FU and the six-membered ring alkylated purine derivatives.

Compound	IC_{50} [μM]
5-FU	4.32 ± 0.02
6	10.6 ± 0.66
7	6.18 ± 1.70
8	20.5 ± 1.81
9	20.5 ± 1.11
10	10.5 ± 1.06
11	11.2 ± 2.73
12	17.5 ± 0.25
13	23.2 ± 1.26
14	16.7 ± 3.03
15	17.4 ± 1.60
16	8.97 ± 0.83

The three most potent compounds **7**, **16**, and **6**, were subjected to cell cycle and apoptosis studies on the MCF-7 human breast cancer cell line (Table 3). The following two consequences can be stated:

a) The six-membered-ring-containing compounds **6**, **7**, and **16**, in contrast to 5-FU, provoke a G_0/G_1-phase cell-cycle arrest upon treatment of MCF-7 cells with the compounds at their respective IC_{50} concentrations over the course of 48 h, mainly at the expense of the S-phase populations. The fact that the novel derivatives at similar doses exhibit different sequences of cell-cycle perturbations in comparison with 5-FU indicates that these compounds act through different pathways.[27] Moreover, in the case of **7**, there is an increase in the G_2/M phase of the cancerous cells.

b) The apoptotic indexes of the target compounds are very significant, especially for **16** (58.29% for **6**, 63.05% for **7**, and 76.22% for **16**). To our knowledge, compound **16** is the most potent inducer of apoptosis against the MCF-7 human breast cancer cell line so far reported.

Table 3. Cell-cycle distribution and apoptosis induction in the MCF-7 human breast cancer cell line after treatment for 48 h for the three most active compounds as antiproliferative agents.

Compd	Cell cycle[a]			Apoptosis[b]
	G_0/G_1	S	G_2/M	
Control	58.62 ± 0.74	33.82 ± 0.72	7.55 ± 1.34	0.22 ± 0.16
5-FU[c]	58.07 ± 0.11	39.38 ± 0.98	2.10 ± 0.12	52.81 ± 1.05
6	69.71 ± 1.50	23.73 ± 1.65	6.56 ± 0.17	58.29 ± 0.75
7	62.85 ± 0.87	26.71 ± 1.25	10.43 ± 0.38	63.05 ± 0.26
16	70.30 ± 0.32	23.67 ± 2.40	6.06 ± 2.72	76.22 ± 2.02

[a] Determined by flow cytometry.[27] [b] Apoptosis was determined using an annexin V-based assay.[27] The data indicate the percentage of cells undergoing apoptosis in each sample. [c] Data were taken from Ref. [12]. All experiments were conducted in duplicate and gave similar results. The data are means ± SEM of three independent determinations.

Conclusions

A series of 2- and 6-substituted (*R*,*S*)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine derivatives has been obtained from a Mitsunobu reaction that led to a six-membered ring contraction from a secondary alcohol in a seven-membered cycle under microwave heating. In addition, the (*R*,*S*)-3,4-dihydro-2*H*-1,5-benzoxathiepine derivative, which would be formed by nucleophilic attack at the 3-position of the seven-membered moiety, was not found in the reaction mixture. This also shows that the nucleophilic ring opening of the episulfonium cation takes place regiospecifically, controlled by the thermodynamic stability of the products. The signal at $\sim\delta = 151$ ppm, which corresponds to the C4′ carbon atom, is unequivocal proof of the N9′ regioisomers. HMBC NMR studies on **6** confirmed the regiospecificity of this methodology. The molecular structure of **6** was confirmed by single-crystal X-ray diffraction. The anticancer potential of the target molecules is reported against the MCF-7 cancer cell line. The most active compounds are **7** and **16**, with IC_{50} values of (6.18 ± 1.70) and (8.97 ± 0.83) μM, respectively. These results indicate that the anticancer activities of **16**, **7**, and **6** are correlated with their ability to induce apoptosis. The mechanism through which these molecules elicit their effects is currently being elucidated.

Experimental Section

Chemistry

Melting points were taken in open capillaries on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Bruker ARX 400 instrument or at 300 MHz (^{1}H) and 75 MHz (^{13}C) on a Bruker AMX 300 instrument, or 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Varian NMR System TM 400 or at 300 MHz (^{1}H) and 75 MHz (^{13}C) on a Varian Inova TM instrument at ambient temperature. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Signals are designated as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; ddd, double doublet of doublets; dt, doublet of triplets; t, triplet; m, multiplet. High-resolution liquid secondary ion mass spectrometry (HR LSIMS) was carried out on a VG AutoSpec Q high-resolution mass spectrometer (Fisons Instruments). The HMBC spectra 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 (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. All products had satisfactory (within ±0.4%) C, H, and N analyses. Small-scale microwave-assisted synthesis was carried out in an Initiator 2.0 single-mode microwave instrument producing controlled irradiation at 2.450 GHz (Biotage AB, Uppsala, Sweden). Reaction time refers to the hold time at 140 °C, not to total irradiation time. The temperature was measured with an IR sensor on the outside of the reaction vessel. 6-Cyclohexylmethoxypurine,[24] 6-allyloxypurine,[24] 6-benzyloxypurine,[25] 6-phenoxypurine,[26] 6-phenylthiopurine,[26] 6-benzylthiopurine,[26] and 6-anilinopurine[26] were synthesized according to published procedures. 6-Chloropurine, 6-bromopurine, 6-methylthiopurine, and 2,6-dichloropurine were purchased from Aldrich. Anhydrous solvents were purchased from VWR International Eurolab.

Starting materials

Conversion of (*R*,*S*)-3-[(2-hydroxyphenyl)thio]-1,2-epoxypropane (**17**) into (*R*,*S*)-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**18**) and (*R*,*S*)-2,3-dihydro-1,4-benzoxathiin-2-methanol (**19**) was performed according to reported procedures,[13] except with a reaction time of 6 h instead of 8 h. Purification was carried out by flash chromatography with a gradient elution (EtOAc/hexanes 1:6→1:4).

18: White solid (62%); mp = 91.2–92.2 °C (Ref. [15] mp = 78 °C). Its ^{1}H NMR analysis has not yet been described, and its ^{13}C NMR analysis was described in the fully proton-coupled mode:[15] ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta = 7.32$ (dd, $J_1 = 8.7$ Hz, $J_2 = 1.7$ Hz, 1H), 7.16 (apparent dt, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, 1H), 6.99–6.94 (m, 2H), 4.38 (d, $J = 6.6$ Hz, 1H, OH), 4.33 (dd, $J_{gem} = 12.2$ Hz, $J_2 = 3.3$ Hz, 1H, H-2), 4.22–4.13 (m, 1H, H-3), 3.89 (dd, $J_{gem} = 12.2$ Hz, $J_2 = 6.3$ Hz, 1H, H-2), 3.09 (dd, $J_{gem} = 14.1$ Hz, $J_2 = 3.9$ Hz, 1H, H-4), 2.86 ppm (dd, $J_{gem} = 14.1$ Hz, $J_2 = 7.9$ Hz, 1H, H-4); ^{13}C NMR ([D$_6$]acetone, 75 MHz): $\delta = 160.96$ (C10a), 132.48, 129.16, 124.27, 122.72 (CH-aromatics), 128.64 (C5a), 76.73 (CH_2), 70.85 (CH-3), 38.13 ppm (CH_2); HR LSIMS calcd for $C_9H_{10}O_2NaS$ $[M+Na]^+$ 205.0299, found 205.0300.

19: Colorless oil. Its 60 MHz ^{1}H NMR spectrum was previously reported in $CDCl_3$.[15] ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta = 7.03$ (dd, $J_1 = 7.8$ Hz, $J_2 = 1.7$ Hz, 1H), 6.97 (apparent dt, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, 1H), 6.85–6.76 (m, 2H), 4.23–4.14 (m, H-2), 4.16 (t, $J = 6.1$ Hz, 1H, OH), 3.87–3.79 (m, 1H, CH_2OH), 3.76–3.68 (m, 1H, CH_2OH), 3.16 (dd, $J_{gem} = 13.2$ Hz, $J_2 = 2.3$ Hz, 1H, H-3), 3.04 ppm (dd, $J_{gem} = 13.2$ Hz, $J_2 = 8.6$ Hz, 1H, H-3); ^{13}C NMR ([D$_6$]acetone, 75 MHz): $\delta = 152.68$ (C8a), 127.98, 126.34, 122.09, 119.19 (CH-aromatics), 118.60 (C4a), 76.36 (CH-2), 64.50 (CH_2OH), 27.26 ppm (CH_2-3).

Final products

Conventional heating. Reaction between **18** and 6-chloropurine by using the conventional Mitsunobu protocol: Synthesis of (*R*,*S*)-6-chloro-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (**6**) and (*R*,*S*)-6-chloro-9-(2-tetrahydrofuryl)-9*H*-purine (**20**). DIPAD (120 μL, 0.61 mmol) was added dropwise to a solution of **18** (91 mg, 0.55 mmol), 6-chlororopurine (85 mg, 0.55 mmol), and triphenylphosphine (160 mg, 0.61 mmol) in dry THF (3 mL) stirred under argon atmosphere at −20 °C. The reaction mixture was allowed to reach 0 °C before heating at 45 °C for 27 h. The solvent

was evaporated, and the crude product was purified by flash column chromatography on silica gel using as eluent hexanes/EtOAc (15:1→1:1.5) to afford **6** and **20**.

6: White solid (15%); mp = 168–170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.75 (s, 1H, H-2′), 8.14 (s, 1H, H-8′), 7.08–7.03 (m, 2H, H-7, H-8), 6.95–6.88 (m, 2H, H-5, H-6), 4.67 (dd, J_{gem} = 14.3 Hz, J_2 = 7.3 Hz, 1H, CH_2N), 4.54 (dd, J_{gem} = 14.3 Hz, J_2 = 8.0 Hz, 1H, CH_2N), 4.35 (dd, J_{gem} = 12.1 Hz, J_2 = 3.0 Hz, 1H, H-2), 4.29 (dd, J_{gem} = 12.0 Hz, J_2 = 2.0 Hz, 1H, H-2), 3.87 ppm (apparent dd, J_1 = 7.6 Hz, J_2 = 2.5 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.14 (CH-2′), 151.82 (C4′), 151.43 (C6′), 151.09 (C8a), 145.93 (CH-8′), 131.89 (C5′), 127.82 (C8), 126.34 (C7), 122.75 (C6), 118.80 (C5), 115.34 (C4a), 65.73 (CH_2-2), 46.22 (CH_2N), 37.59 ppm (CH-3); HR LSIMS calcd for $C_{14}H_{12}N_4OSCl$ $[M+H]^+$ 319.0420, found 319.0420; Anal. for $C_{14}H_{11}ClN_4OS$: calcd C 52.75, H 3.48, N 17.58, S 10.06, found C 52.44, H 3.45, N 17.71, S 9.99.

20: White solid (17%); mp = 93–95 °C (Ref. [19] mp = 93–95 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.73 (s, 1H, H-2′), 8.23 (s, 1H, H-8′), 6.33 (dd, J_1 = 6.2 Hz, J_2 = 3.2 Hz, 1H, H-2), 4.29 (apparent dt, J_1 = 8.5 Hz, J_2 = 6.5 Hz, 1H, H-5), 4.08 (m, 1H, H-5), 2.65–2.46 (m, 2H, H-3), 2.20–2.10 ppm (m, 2H, H-4); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.92 (CH-2′), 151.10, 150.98 (C4′, C6′), 143.43 (CH-8′), 132.46 (C5′), 86.68 (CH-2), 70.04 (CH_2-5), 32.56 (CH_2-3), 24.30 ppm (CH_2-4); HR LSIMS calcd for $C_9H_{10}N_4OCl$ $[M+H]^+$ 225.0543, found 225.0543.

General procedure for the microwave-assisted synthesis of compounds 6–16

A microwave vial (2–5 mL) equipped with a magnetic stirrer bead was charged with **18** (50 mg, 0.27 mmol), triphenylphosphine (79 mg, 0.30 mmol), and the corresponding purine derivative (0.27 mmol) in dry THF (3.5 mL) for **6** and **8**–**16** or dry acetonitrile (3.5 mL) for **6** and **7**, cooled in an ice bath, and DIPAD (50 μL, 0.30 mmol) was slowly added. The vial was sealed and microwave irradiated at a set temperature of 140 °C for 5 min. After completion of the irradiation time, the reaction mixture was cooled to room temperature through rapid pressurized air supply gas-jet cooling. The solvent was evaporated, and the crude product was loaded onto a silica column and purified by flash column chromatography using as eluent hexanes/EtOAc (7:1→1:1) to afford **6**–**16**. For isolated yields, see Table 2. The reaction was very clean and only one spot (in TLC) was observed (apart from the starting material that did not react).

(*R*,*S*)-6-Bromo-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (7). Off-white solid; mp = 134–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (s, 1H), 8.09 (s, 1H), 7.03–6.95 (m, 2H), 6.80–6.91 (m, 2H), 4.61 (dd, J_{gem} = 14.5 Hz, J_2 = 7.5 Hz, 1H), 4.49 (dd, J_{gem} = 14.5 Hz, J_2 = 8.0 Hz, 1H), 4.29 (dd, J = 12.0 Hz, J_2 = 3.0 Hz, 1H), 4.24 (dd, J_{gem} = 12.0 Hz, J_2 = 2.0 Hz, 1H), 3.84–3.78 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.22, 151.22, 150.70, 145.99, 143.66, 134.62, 127.98, 126.50, 122.91, 118.96, 115.47, 65.87, 46.41, 37.74 ppm; HR LSIMS calcd for $C_{14}H_{12}N_4OSBr$ $[M+H]^+$ 362.9915, found 362.9915; Anal. for $C_{14}H_{11}ClN_4OS$: calcd C 46.29, H 3.05, N 15.42, S 8.83, found C 46.45, H 3.16, N 15.61, S 8.97.

(*R*,*S*)-6-Methylthio-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (8). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.72 (s, 1H), 7.96 (s, 1H), 7.07–7.01 (m, 2H), 6.94–6.88 (m, 2H), 4.59 (dd, J_{gem} = 14.5 Hz, J_2 = 8.0 Hz, 1H), 4.49 (dd, J_{gem} = 14.5 Hz, J_2 = 8.0 Hz, 1H), 4.29 (dd, J_{gem} = 12.0 Hz, J_2 = 2.9 Hz, 1H), 4.24 (dd, J_{gem} = 12.0 Hz, J_2 = 1.8 Hz, 1H), 3.87 (apparent dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1H), 2.73 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.35, 152.21, 151.34, 148.38, 143.51, 131.78, 127.99, 126.37, 122.82, 118.94, 115.85, 65.86, 46.02, 37.81, 22.12 ppm; HR LSIMS calcd for $C_{15}H_{15}N_4O_1S_2$ $[M+H]^+$ 331.0687, found 331.0691; Anal. for $C_{15}H_{14}N_4OS_2$: calcd C 54.52, H 4.27, N 16.96, S 19.41, found C 54.65, H 4.27, N 17.01, S 19.32.

(*R*,*S*)-6-Phenoxy-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (9). White solid; mp = 83–85 °C melts, 120 °C liquefies; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (s, 1H), 8.10 (s, 1H), 7.53–7.48 (m, 2H), 7.36–7.30 (m, 3H), 7.16–7.06 (m, 2H), 7.00–6.95 (m, 2H), 4.68 (dd, J_{gem} = 14.2 Hz, J_2 = 8.0 Hz, 1H), 4.55 (dd, J_{gem} = 14.3 Hz, J_2 = 7.4 Hz, 1H), 4.43–4.33 (m, 2H), 4.00–3.91 ppm (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 160.50, 153.08, 152.47, 152.35, 151.80, 151.21, 143.88, 129.70 (×2), 127.83, 126.23, 125.92, 122.66, 121.92 (×2), 118.77, 115.67, 65.76, 46.04, 37.69 ppm; HR LSIMS calcd for $C_{20}H_{17}N_4O_2S$ $[M+H]^+$ 377.1072, found 377.1077; Anal. for $C_{20}H_{16}N_4O_2S$: calcd C 63.81, H 4.28, N 14.88, S 8.52, found C 64.89, H 4.39, N 14.77, S 8.25.

(*R*,*S*)-6-Phenylthio-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (10). White solid; mp = 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (s, 1H), 8.03 (s, 1H), 7.69–7.66 (m, 2H), 7.50–7.47 (m, 3H), 7.10–7.03 (m, 2H), 6.96–6.89 (m, 2H), 4.62 (dd, J_{gem} = 14.2 Hz, J_2 = 7.4 Hz, 1H), 4.51 (dd, J_{gem} = 14.2 Hz, J_2 = 7.6 Hz, 1H), 4.35–4.26 (m, 2H), 3.92–3.84 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.25, 152.44, 151.22, 148.95, 143.87, 135.72 (×2), 131.05, 129.69, 129.39 (×2), 127.84, 127.26, 126.24, 122.67, 118.79, 115.68, 65.76, 45.91, 37.67 ppm; HR LSIMS calcd for $C_{20}H_{17}N_4O_1S_2$ $[M+H]^+$ 393.0845, found 393.0841; Anal. for $C_{20}H_{16}N_4OS_2$: calcd C 61.20, H 4.11, N 14.27, S 16.34, found C 61.33, H 4.35, N 14.51, S 16.04.

(*R*,*S*)-6-Anilino-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (11). White solid; mp = 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (s, 1H), 7.97–7.90 (bs, 2H), 7.87 (d, J = 7.9 Hz, 2H), 7.47 (m, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.16–7.10 (m, 2H), 7.03–6.96 (m, 2H), 4.66 (dd, J_{gem} = 14.2 Hz, J_2 = 7.6 Hz, 1H), 4.56 (dd, J_{gem} = 14.2 Hz, J_2 = 7.6 Hz, 1H), 4.43–433 (m, 2H), 4.03–3.96 ppm (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 153.00, 152.44, 151.39, 149.77, 141.55, 138.61, 129.34 (×2), 128.01, 126.35, 124.19, 122.80, 120.92 (×2), 120.50, 118.94, 115.97, 65.91, 46.07, 37.87 ppm; HR LSIMS calcd for $C_{20}H_{18}N_5OS$ $[M+H]^+$ 376.1232, found 376.1225; Anal. for $C_{20}H_{17}N_5OS$: calcd C 63.98, H 4.56, N 18.65, S 8.54, found C 64.06, H 4.55, N 18.83, S 8.67.

(*R*,*S*)-6-Allyloxy-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (12). White solid; mp = 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (s, 1H), 8.00 (s, 1H), 7.09–7.04 (m, 2H), 6.94–6.89 (m, 2H), 6.17 (ddd, J = 17.1 Hz, J = 10.6 Hz, J = 5.3 Hz, 1H), 5.47 (d, J = 17.1 Hz, 1H), 5.30 (d, J = 10.6 Hz, 1H), 5.13 (d, J = 5.3 Hz, 2H), 4.62 (dd, J_{gem} = 14.1 Hz, J_2 = 7.5 Hz, 1H), 4.51 (dd, J_{gem} = 14.1 Hz, J_2 = 7.7 Hz, 1H), 4.34–4.25 (m, 2H), 3.91–3.86 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.51, 152.15, 151.90, 151.08, 142.86, 132.20, 127.72, 126.10, 122.54, 121.31, 118.66, 118.69, 115.59, 67.82, 65.59, 45.90, 37.56 ppm; HR LSIMS calcd for $C_{17}H_{16}N_4O_2SNa$ $[M+Na]^+$ 363.0897, found 363.0894; Anal. for $C_{17}H_{16}N_4O_2S$: calcd C 59.98, H 4.74, N 16.46, S 9.42, found C 60.14, H 4.55, N 16.68, S 9.34.

(*R*,*S*)-6-Benzyloxy-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (13). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 7.94 (s, 1H), 7.55 (d, J = 7.0 Hz, 2H), 7.38–7.30 (m, 3H), 7.07–7.03 (m, 2H), 6.94–6.90 (m, 2H), 5.69 (s, 2H), 4.61 (dd, J_{gem} = 14.1 Hz, J_2 = 7.4 Hz, 1H), 4.50 (dd, J_{gem} = 14.1 Hz, J_2 = 7.8 Hz, 1H), 4.30 (dd, J_{gem} = 12.5 Hz, J_2 = 3.5 Hz, 1H), 4.26 (dd, J_{gem} = 12.5 Hz, J_2 = 2.0 Hz, 1H), 3.91–3.84 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.91, 152.73, 152.39, 151.37, 143.17, 136.33, 128.71 (×2),

128.64 (×2), 128.43, 127.98, 126.33, 122.78, 121.98, 118.92, 115.96, 68.77, 65.83, 46.05, 37.81 ppm; HR LSIMS calcd for $C_{21}H_{18}N_4O_2SNa$ $[M+Na]^+$ 413.1048, found 413.1041; Anal. for $C_{21}H_{18}N_4O_2S$: calcd C 64.60, H 4.65, N 14.35, S 8.21, found C 64.87, H 4.37, N 14.35, S 8.43.

(*R*,*S*)-6-Benzylthio-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (14). White solid; mp = 58–62 °C melts, 125 °C liquefies; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1H), 7.96 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.32–7.22 (m, 3H), 7.07–7.02 (m, 2H), 6.94–6.89 (m, 2H), 4.68 (s, 2H), 4.63 (dd, J_{gem} = 14.2 Hz, J_2 = 7.6 Hz, 1H), 4.51 (dd, J_{gem} = 14.2 Hz, J_2 = 7.6 Hz, 1H), 4.32–4.25 (m, 2H), 3.89–3.85 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.10, 151.94, 151.16, 148.53, 143.44, 137.43, 131.34, 129.24 (x2), 128.59 (x2), 127.81, 127.39, 126.18, 122.63, 118.76, 115.67, 65.66, 45.81, 37.60, 32.94 ppm; HR LSIMS calcd for $C_{21}H_{18}N_4OS_2Na$ $[M+Na]^+$ 429.0820, found 429.0818; Anal. for $C_{21}H_{18}N_4OS_2$: calcd C 62.04, H 4.46, N 13.78, S 15.78, found C 61.87, H 4.23, N 13.71, S 16.00.

(*R*,*S*)-6-Cyclohexylmethyloxy-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (15). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 7.92 (s, 1H), 7.10–7.01 (m, 2H), 6.96–6.87 (m, 2H), 4.59 (dd, J_{gem} = 14.4 Hz, J_2 = 7.8 Hz, 1H), 4.49 (dd, J_{gem} = 14.4 Hz, J_2 = 7.6 Hz, 1H), 4.40 (d, J = 6.3 Hz, 2H), 4.30 (dd, 1H, J_{gem} = 11.7 Hz, J_2 = 3.1 Hz), 4.27–4.34 (m, 1H), 3.95–3.83 (m, 1H), 2.02–1.62 (m, 6H), 1.35–1.02 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.52, 152.45, 152.16, 151.33, 142.92, 127.95, 126.30, 122.75, 121.83, 118.89, 115.92, 72.72, 65.80, 46.03, 37.78, 37.48, 29.96 (×2), 26.63, 25.92 ppm (×2); HR LSIMS calcd for $C_{21}H_{25}N_4O_2S$ $[M+H]^+$ 397.1698, found 397.1696; Anal. for $C_{21}H_{24}N_4O_2S$: calcd C 63.61, H 6.10, N 14.13, S 8.09, found C 63.84, H 6.37, N 14.01, S 7.87.

(*R*,*S*)-2,6-Dichloro-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9*H*-purine (16). White solid; mp = 159–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1H), 7.13–7.06 (m, 2H), 6.99–6.92 (m, 2H), 4.68 (dd, J_{gem} = 14.5 Hz, J_2 = 7.0 Hz, 1H), 4.55 (dd, J_{gem} = 14.5 Hz, J_2 = 8.0 Hz, 1H), 4.41 (dd, J_{gem} = 12.0 Hz, J_2 = 3.0 Hz, 1H), 4.33 (dd, J_{gem} = 12.0 Hz, J_2 = 2.0 Hz, 1H), 3.90–3.85 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.35 (× 2), 152.29, 151.16, 146.83, 131.18, 128.01, 126.59, 122.97, 118.98, 115.27, 65.87, 46.38, 37.63 ppm; HR LSIMS calcd for $C_{14}H_{11}N_4OSCl_2$ $[M+H]^+$ 353.0030, found 353.0038; Anal. for $C_{14}H_{10}Cl_2N_4OS$: calcd C 47.60, H 2.85, N 15.86, S 9.08, found C 47.63, H 2.65, N 15.89, S 8.87.

X-ray diffraction

X-ray diffraction on 6A colorless crystal was mounted on a glass fiber and used for data collection. Data were collected using a Bruker SMART CCD 1000 diffractometer. Graphite monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) was used throughout. The data were processed with SAINT[28] and corrected for absorption using SADABS.[29] The structure was solved by direct methods,[30] which revealed the position of all non-hydrogen atoms. These atoms were refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters.[31] Hydrogen atoms were included in geometrically idealized positions employing appropriate riding models, with isotropic displacement parameters constrained to 1.2 times those of their carrier atoms. Molecular graphics and geometric calculations were obtained from PLATON.[32] Relevant crystal data: formula $C_{14}H_{11}ClN_4OS$, M_w = 318.78 Da, T = 298(2) K, crystal system orthorhombic, space group $Pna2_1$, unit cell dimensions a = 15.5862(9), b = 6.5701(4), and c = 27.4106(16) Å, Z = 8, D = 1.509 mg m^{-3}, $\mu(Mo_{K\alpha})$ = 0.424 mm^{-1}, measured/unique reflections 16684/6103 [R_{int} = 0.0275], refined parameters 358, final R_1 ($I > 2\sigma(I)$) = 0.0439 and wR_2 = 0.1035, GOF = 0.997. CCDC 641277 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Biological activity

The biological assay methods were the same as those previously described.[27]

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