6-Substituted Purines as Inhibitors of 15-Lipoxygenase; a Structure-Activity Study

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15-Lipoxygenase (15-LO) has been implicated in oxidation of low-density lipoproteins (LDL), a process believed to be important for the development of atherosclerosis, as well as other pathogenic conditions. Potent and selective inhibitors of 15-LO may have a drug potential. In this study, purines with a variety of substituents have been examined as inhibitors of 15-lipoxygenase (15-LO) from soybeans. Several 6-substitued purines where the purine ring and a phenyl ring in the substituent were separated by a "spacer" were synthesized and their ability to inhibit the enzyme was explored. Separation of the purine and the phenyl rings with none, one or two sp^3-carbons resulted in essentially inactive compounds, *trans*-styrylpurines and phenylethynylpurines, on the other hand, they exhibited activity close to the well-known 15-LO inhibitor quercetin. High activity was also found when the "spacer" was a *trans*-cyclopropyl ring. The shape of the spacer was important; a corresponding *cis*-cyclopropylpurine exhibited much less affinity for the enzyme. Only minor differences in inhibitory activity against 15-LO were found regardless of whether an *N*-substituent was situated on *N*-9 or *N*-7, even when the *N*-substituent was relatively large. Also, a variety of substituents in the purine 2- and 8-position were well tolerated.

Keywords: 6-Substituted purines; Pd-catalyzed couplings; 15-Lipoxygenase; Enzyme inhibition

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Introduction

Cytokinins (CK) are naturally occurring plant growth hormones. In our study of biological activities of cytokinins and synthetic analogs [1−4], we identified certain 6-alkenyl- and 6-alkynylpurines as potent inhibitors of 15-lipoxygenase (15-LO) from soybeans [3]. The active compounds did not exhibit significant scavenging of the radical diphenylpicrylhydrazyl (DPPH) and we proposed that the purine derivatives were so-called non-antioxidant inhibitors; they exert their activity by a direct interaction with the enzyme.

15-LO has been implicated in oxidation of low-density lipoproteins (LDL), a process believed to be important for the development of atherosclerosis [5, 6], as well as for instance in prostate cancer [7, 8], and spontaneous abortions [9]. Even though the clinical importance of these effects in humans is currently not known, development of potent and selective inhibitors of 15-LO appears to be an important task.

In the present study, we have examined the inhibitory activity of purines with a variety of substituents in order to gain further insight in structure activity relationships regarding purines as 15-LO inhibitors.

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Results and discussion

Our initial study indicated that a double or triple bond in the purine 6-position was essential for activity. Both 6-styryl and 6-phenylalkynylpurines were potent 15-LO inhibitors [3]. Here, we now further investigate the importance of the "spacer" between the purine and the aryl group (Scheme 1, Table 1). The 6-substituted purines **2**−**8** are readily available from palladium catalyzed cross couplings on the corresponding 6-halopurines **1**. The syntheses of the novel compounds **3**, **5**, and **6** are shown in Scheme 1. 1-Bromo-2-phenylcyclopropane, required for the generation of the organozinc reagent used in the synthesis of the *cis*-cyclopropane **6**, was prepared from 1,1-dibromo-2-phenylcyclopropane by literature methods, but unfortunately with much lower *cis*-selectivity than reported [10]. Hence, pure *cis*-cyclopropyl purine **6** was only available in low yields. The other compounds in Table 1 were available by literature procedures. For some of the compounds in Table 1, inhibitory activity against 15-LO has been reported before [3], but we observed large differences in enzyme inhibition from our standard quercetin, indicating that we had previously been working with a batch of the 15-LO enzyme with lower ac-

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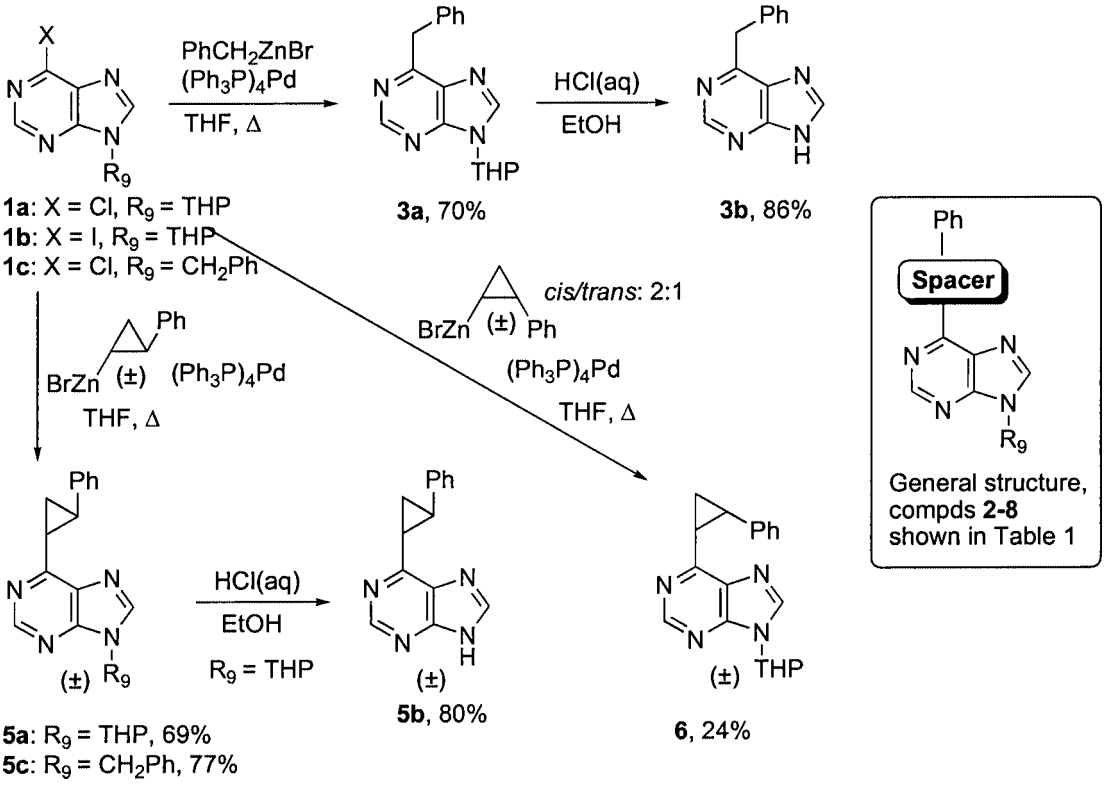


Scheme 1. General synthesis route for the 6-substituted purine derivatives.

Table 1. 15-LO inhibitory activity of 6-substituted purines with different "spacers" between the aromatic rings. A general structure for compounds discussed in this table is shown in Scheme 1.

Compound No.	"Spacer"	R_9	% Inhibition of 15-LO from soy beans at 42 μM conc.[†]	IC_{50} [μM][‡]
2	–	-THP[§]	n.d.	>167
3a	-CH_2-	-THP	27 ± 4	97 ± 5
3b	-CH_2-	-H	20 ± 3	146 ± 7
4a	-CH_2CH_2-	-THP	n.d.	>167
4b	-CH_2CH_2-	-H	n.d.	>167
5a	*trans c*-propyl	-THP	26 ± 4	86 ± 5
5b	*trans c*-propyl	-H	36 ± 5	58 ± 6
5c	*trans c*-propyl	-CH_2Ph	35 ± 3	51 ± 2
6	*cis c*-propyl	-THP	15 ± 3	130 ± 7
7a	(*E*) −CH=CH-	-THP	42 ± 3	51 ± 3
7b	(*E*) −CH=CH-	-H	49 ± 2	46 ± 2
7c	(*E*) −CH=CH-	-CH_2Ph	58 ± 1	45 ± 4
8a	-C≡C-	-THP	50 ± 2	42 ± 2
8b	-C≡C-	-H	49 ± 2	46 ± 2
8c	-C≡C-	-CH_2Ph	54 ± 2	<42

[†] Data are shown ± SD.
[‡] IC_{50} for quercetin was 40 μM.
[§] THP: tetrahydropyran-2-yl.

tivity. Hence, we are now reporting activity against an enzyme batch where the inhibitory activity of quercetin was 30−40 μM.

The results in Table 1 demonstrate that the identity of the "spacer" is very important for the inhibitory activity whereas the substituent in the purine 9-position seems to be of lesser importance (see below). Separation of the purine and the phenyl rings with none, one or two sp^3-carbons resulted in essentially inactive compounds **2**−**4**. The *trans*-alkenes **7** and the alkynes **8** on the other hand, exhibited activity close to the well-known 15-LO inhibitor quercetin. It has been reported previously that the electron deficient 6-alkenyl- or alkynylpurines may be attacked by nucleophiles at the b-carbon in the double or triple bond [11]. Hence, it is possible that inhibition of 15-LO is mediated by an attack from nucleophilic parts of the enzyme at the alkenes and alkynes. On the other hand, the *trans*-cyclopropanes **5** are expected to be less prone to nucleophilic attack. Still, compounds **5b** and **5c** are almost as active as the corresponding *trans*-alkenes.

The shape of the "spacer" appears to be important since the *cis*-cyclopropane **6** is a much weaker inhibitor than the *trans*-isomer **5a**. We have previously found that 6-alkynylpurines, but generally not 6-alkenylpurines, are highly cyto-

toxic [4]. Because the noxious alkynes do not have a drug potential as 15-LO inhibitors, and the cyclopropanes are more difficult to synthesize than the alkenes, we focused our further attention on purines with the *trans*-alkenyl "spacer".

The results above indicate that the inhibitory activity is not very sensitive regarding the identity of the substituent in the purine 9-position. Our further results from examining the importance of the position and structure of the *N*-substituent on inhibitory activity against 15-LO are summarized in Table 2, and the general structure of the compounds discussed are shown in Figure 1. The compounds were prepared by Stille coupling on the corresponding 6-chloropurines.

For the *trans*-6-styrylpurines studied (Table 2), only minor differences in inhibitory activity against 15-LO were found regardless of whether the *N*-substituent was situated on *N*-9 (comps. **7**) or *N*-7 (comps. **9**) even when the *N*-substituent was relatively large. Also, a variety of *N*-substituents were tolerated in the purine 9-position and no significant differences in activity could be found for any of the compounds **7** examined.

Finally, we explored effects associated with substituents in the purine 2- and 8-positions. The syntheses of novel compounds are shown in Schemes 2 and 3, and the inhibitory activity against 15-LO in Table 3.

The alkyl and aryl substituents in the purine 2-position were introduced by Pd-catalyzed cross couplings on the 2-chloro-6-styrylpurine **7i** to give compounds **7j**, **7o,** and **7p**, and the 2-methoxypurine **7k** was formed when compound **7i** was reacted with sodium methoxide.

6,8-Dichloropurine **1d** was the starting point for the synthesis of 8-substituted 6-styrylpurines. Halogen can easily be introduced in the 8-position of most purine derivatives by lithiation followed by trapping with an electrophilic halogen reagent [12]. However, this protocol is not compatible with a benzyl substituent on *N*-9 [13]. We have previously shown that the 6,8-dichloropurine **1d** can be formed by reacting 6-chloropurine **1c** with *N*-chlorosuccinimide (NCS) in refluxing DCE partly in the dark for several days. We have now found that the dichloropurine **1d** is more efficiently formed, on a relatively small scale, when 6-chloropurine **1c** and NCS are reacted in chlorobenzene at 125 °C. Regioselective Stille coupling on 6,8-dichloropurine **1d** [13] gave the 6-styrylpurine **7q** and a methyl group could be introduced in the 8-position by Negishi coupling to give compound **7r**. Even though there are several reports on 8-methoxypurines formed by the reaction of 8-halopurines with sodium methoxide in dry methanol [14], we were only able

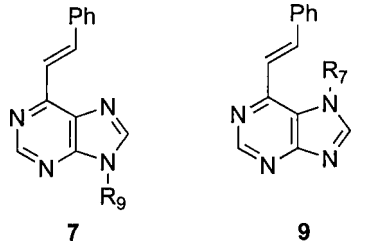
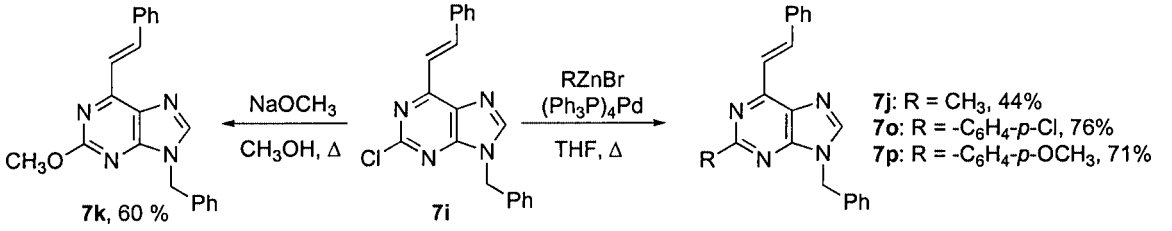


Figure 1. General structure of compounds discussed.

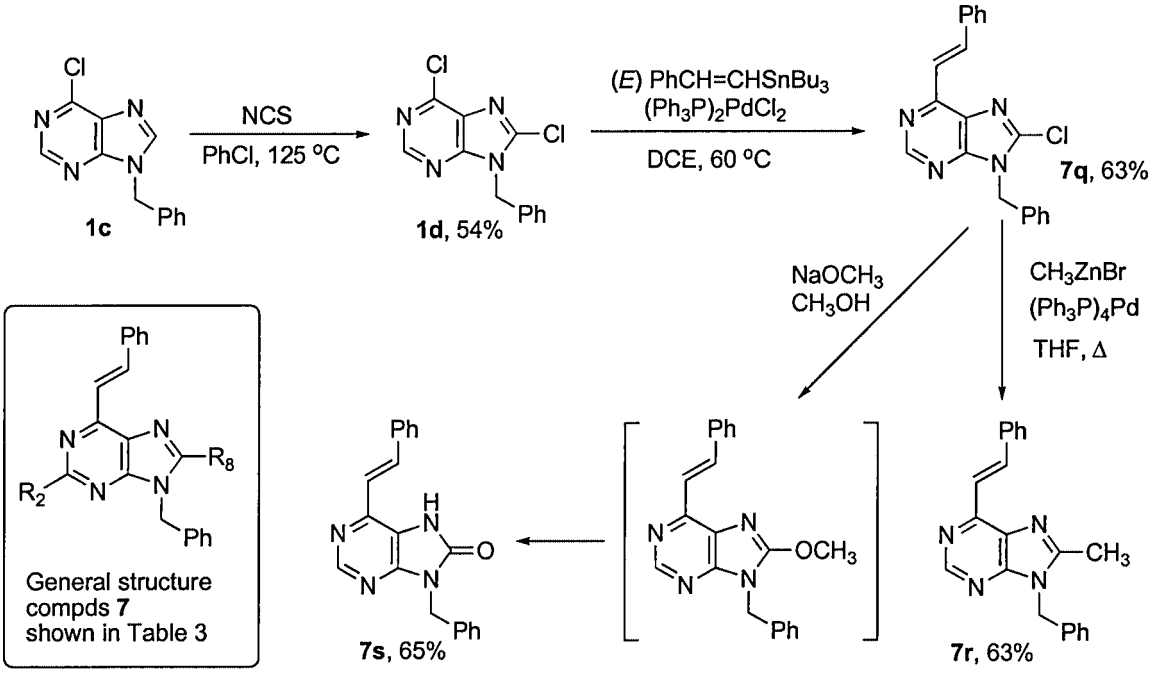
Table 2. 15-LO inhibitory activity of 7- and 9-alkylated 6-*E*-styrylpurines and 6-*E*-styrylpurines carrying different substituents on *N*-9. A general structure for compounds discussed in this table is shown in Figure 1.

Compound No.	R_9	R_7	% Inhibition of 15-LO from soy beans at 83 μM conc.†	IC_{50} [μM]‡
7b	H§	–	68 ± 4	59 ± 5
7c	-CH_2Ph	–	90 ± 3	54 ± 4
9a	–	-CH_2Ph	75 ± 2	49 ± 3
7d	-CH_3	–	74 ± 1	51 ± 3
9b	–	-CH_3	68 ± 2	57 ± 4
7e	-$CH(CH_3)_2$	–	78 ± 4	47 ± 7
7f	-CH_2SCH_3	–	75 ± 4	44 ± 4
7g	-Ph	–	79 ± 4	48 ± 5
7h	-Riboside	–	74 ± 6	47 ± 4
7a	-THP	–	68 ± 2	59 ± 3

† Data are shown ± SD.
‡ IC_{50} for quercetin was 34 ± 4 μM.
§ Arbitrary drawn as the 9*H*-tautomer.



Scheme 2. Synthesis route for 2-substituted derivatives.



Scheme 3. Synthesis route for 8-substituted derivatives.

Table 3. 15-LO inhibitory activity of 2- and 8-substituted 6-*E*-styryl-9-benzylpurines. A general structure for compounds discussed in this table is shown in Scheme 3.

Compound No.	R_2	R_8	% Inhibition of 15-LO from soy beans at 83 μM conc.[†]	IC_{50} [μM][‡]
7c	-H	-H	90 ± 3	54 ± 4
7i	-Cl	-H	75 ± 3	37 ± 3
7j	$-CH_3$	-H	83 ± 2	49 ± 1
7k	$-OCH_3$	-H	94 ± 1	36 ± 3
7l	$-COCH_3$	-H	89 ± 5	35 ± 4
7m	$-NH_2$	-H	67 ± 2	58 ± 3
7n	-Ph	-H	94 ± 1	30 ± 3
7o	$-C_6H_4$-*p*-Cl	-H	96 ± 1	30 ± 2
7p	$-C_6H_4$-*p*-OCH_3	-H	93 ± 1	36 ± 4
7q	-H	-Cl	92 ± 1	34 ± 2
7r	-H	$-CH_3$	89 ± 2	42 ± 4
7s	-H	-OH	73 ± 3	50 ± 5

[†] Data are shown ± SD.
[‡] IC_{50} for quercetin was 34 ± 4 μM.

to isolate the 8-hydroxypurine **7s** after subjecting the 8-chloropurine **7q** to these sets of reaction conditions. NMR indicates that compound **7s** exists mainly as the 8-oxopurine tautomer drawn in Scheme 3. 8-Methoxypurines have been hydrolyzed to 8-hydroxy compounds [14a] but under much stronger acidic conditions than employed in our work-up procedure.

Except for the introduction of hydrogen-bond donor substituents (**7m** and **7s**), inhibitory activity was generally improved when the purine 2- or 8-position was substituted. A variety of substituents with different electronic properties, steric requirements and variations in lipophilicity could be introduced in the purine 2-position to give compounds significantly more active than the parent styrylpurine **7c**. Among the substituents examined in the 8-position, chlorine enhanced activity, and compound **7q** was among the most active 15-LO inhibitors in this study.

Acknowledgments

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Experimental

Chemistry

15-Lipoxygenase (Type 1) was purchased from Sigma (St. Louis, MO, USA). Silica gel for flash chromatography was available from Merck (Darmstadt, Germany) (Merck No. 9385) or Fluka (Buchs, Switzerland) (Fluka No. 60752). DMF was distilled from BaO, DCE and methanol from CaH_2, and THF from Na/benzophenone. Other reagents were used as received. All reactions were performed under N_2 or Ar atmosphere. The ^1H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument (Bruker, Rheinstetten,

Germany). The ^{13}C NMR spectra were recorded at 125, 75, or 50 MHz using the instruments mentioned above. Unless otherwise stated, the spectra are recorded at 20 °C. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane (TMS). MS spectra under electron impact conditions were recorded with a VG Prospec instrument (Micromass UK, Manchester, UK) at 70 eV ionizing voltage, and are presented as *m/z* (% rel. int.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Melting points are uncorrected. All measurements of 15-lipoxygenase activities were carried out in a Shimadzu UV-160A spectrophotometer (Shimadzu, Kyoto, Japan) at 20–22 °C. Compounds available by literature methods: **1a** and **1b** [15], **1c**, **7c** and **8c** [16], **2** and **7n** [17], **4a** and **4b** [3], **7a**, **7b**, **8a** and **8b** [1], **7h** [4], **7k** [18], **7l**, **7m** and **9a** [19].

*6,8-Dichloro-9-phenylmethyl-9H-purine **1d***

6-Chloro-9-phenylmethyl-9*H*-purine **1c** (407 mg, 1.66 mmol) and NCS (2.219 g, 16.60 mmol) were equally distributed in two heavy walled test tubes under Ar atmosphere. Chlorobenzene (1.0 mL per tube) was added, and heated to 125 °C for 27 h. The tubes were cooled to ambient temperature and their contents carefully added to saturated aq. $NaHSO_3$ (20 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and evaporated, and the crude product was purified by flash chromatography on silica gel eluting with 10% and 20% EtOAc in hexane; yield 249 mg (54%) colorless oil. Spectroscopic data were in good agreement with those reported before [13].

*6-Phenylmethyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purine **3a***

To a mixture of benzylzinc bromide (10 mmol) in THF (20 mL) was added a solution of 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1a** (1.193 g, 5.00 mmol), $(dba)_3Pd_2$ (129 mg, 0.125 mmol) and triphenylphosphine (262 mg, 1.00 mmol) in dry THF (7 mL). The mixture was heated at 60 °C for 19 h, cooled to ambient temperature and diluted with EtOAc (30 mL). Saturated aq. NH_4Cl (40 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 40 mL). The combined EtOAc extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the crude product was purified by flash chromatography on silica gel eluting with hexane-EtOAc (95:5) followed by hexane-EtOAc-CH_2Cl_2 (90:5:5), (80:15:5), (70:20:10), EtOAc-hexane (1:1), and, finally, EtOAc-hexane (7:3); yield 848 mg (58%), pale yellow waxy material. ^1H NMR (200 MHz, $CDCl_3$): δ 8.87 (s, 1H, H-2), 8.26 (s, 1H, H-8), 7.44 (m, 2H, Ph), 7.22 (m, 3H, Ph), 5.76 (m, 1H, THP), 4.52 (s, 2H, NCH_2), 4.17 (m, 1H, THP), 3.77 (m, 1H, THP), 2.09 (m, 3H, THP), 1.71 (m, 3H, THP); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.3, 152.4, 150.0, 142.3, 137.3, 128.9, 128.2, 126.3, 81.8, 68.5, 39.1, 31.3, 24.5, 22.4, C-5 is "hidden" under one of the CH in Ph sign; MS (EI) *m/z* (rel.%): 294 (39, M^+), 293 (5), 266 (5), 265 (5), 237 (6), 212 (5), 211 (45), 210 (90), 209 (100); HRMS: Found 294.1486, calcd. for $C_{17}H_{18}N_4O$ 294.1481; Anal: Found: C, 69.15; H, 6.06; N, 18.41. $C_{17}H_{18}N_4O$ requires C, 69.37; H, 6.16; N, 19.03%.

*6-Phenylmethyl-1H-purine **3b***

A mixture of 6-(phenylmethyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **3a** (575 mg, 1.95 mmol) in EtOH (20 mL) and HCl (15 mL, 1 M) was stirred at ambient temperature for 2 h, neutralized with solid Na_2CO_3, and evaporated under reduced pressure together with a small amount of silica gel. The residue was added on top of a flash chromatography column and the product was eluted with 50–100% EtOAc–hexane; yield 360 mg (86%), colorless crystalline solid, mp. 162–165 °C (Reference [20], 165–166 °C). ^1H NMR (200 MHz, CD_3OD): δ 8.79 (s, 1H, H-2), 8.48 (s, 1H, H-8), 7.33 (m, 2H, Ph), 7.17 (m, 3H, Ph), 4.45 (s, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.6, 153.3, 146.4, 138.8, 130.5, 130.1, 129.6, 129.5, 127.7, 40.1; MS (EI) *m/z* (rel.%): 211 (9, M^++1), 210 (60, M^+), 209 (100), 183 (6), 182 (5), 155 (8), 128 (3), 105 (7), 91 (7), 77 (3); HRMS: Found 210.0914, calcd. for $C_{12}H_{10}N_4$ 210.0905.

*6-(trans-2-Phenylcycloprop-1-yl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purine **5a***

trans-1-Bromo-2-phenylcyclopropane [21] (47 mg, 2.4 mmol) was dissolved in dry THF (1.5 mL) and cooled to −89 °C. *n*-BuLi (1.5 mL, 2.4 mmol, 1.6 M in hexane) was added and the reaction mixture was stirred for 50 min before a solution of $ZnBr_2$ in THF (2.4 mL, 2.4 mmol, 1.0 M) was added. After an additional 50 min, the mixture was allowed to reach ambient temperature. In another flask, 6-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-purine **1b** (660 mg, 2.0 mmol), $(dba)_3Pd_2CHCl_3$ (52 mg, 0.050 mmol) and triphenylphosphine (105 mg, 0.40 mmol) was dissolved in dry THF (3 mL) and stirred until a transparent yellow solution was obtained. The purine solution was transferred to the flask containing the zinc reagent, and the resulting mixture was refluxed for 3 h and poured into sat. aq. NH_4Cl (35 mL). The mixture was extracted with chloroform (3 × 30 mL) and the combined organic phases were dried ($CaCl_2$) and evaporated, and the crude product was purified by flash chromatography on silica gel eluting with 0–65% EtOAc in hexane; yield 440 mg (69%) colorless crystalline solid, mp. 118–120 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.86 (s, 1H, H-2), 8.25 (s, 1H, H-8), 7.27 (m, 5H, Ph), 5.81 (m, 1H, THP), 4.22 (m, 1H, THP), 3.83 (m, 1H, THP), 3.11 (m, 1H, cyclopropyl), 2.95 (m, 1H, cyclopropyl), 2.15 (m, 3H), 1.75 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.3, 152.5, 149.38, 149.36, 141.25, 141.22, 141.20, 132.3, 128.3, 126.1, 126.08, 126.05, 81.9, 81.8, 68.78, 68.77, 31.80, 31.76, 29.54, 29.48, 24.8, 24.7, 22.7, 20.3, 20.2 (Double set of signals were seen for several carbons in the diastereomeric mixt.); MS (EI) *m/z* (rel.%): 320 (M^+, 2), 237 (19), 236 (100), 235 (55), 221 (6), 208 (6), 159 (13), 134 (30), 115 (10), 91 (7); HRMS: Found 320.1630, calcd. for $C_{19}H_{20}N_4O$ 320.1637; Anal: Found: C, 70.94; H, 6.51; N, 17.10. $C_{19}H_{20}N_4O$ requires C, 71.23; H, 6.29; N, 17.49%.

*6-(trans-2-Phenylcycloprop-1-yl)-1H-purine **5b***

6-(*trans*-2-phenylcycloprop-1-yl)-9-(tetrahydro-2*H*-pyran-2-yl)-purine **5a** (282 mg, 0.88 mmol) was deprotected employing the same conditions as for the synthesis of **3b** above. The crude product was purified by flash chromatography on silica gel eluting with 0–5% EtOH in EtOAc; yield 170 mg (80%) colorless crystalline solid, mp. 226–228 °C. ^1H NMR (500 MHz, CD_3OD, 50 °C): δ 8.74 (s, 1H, H-2), 8.40 (br s, 1H, H-8), 7.27 (m, 2H, Ph), 7.21 (m, 2H, Ph), 7.17 (m, 1H, Ph), 2.93 (br s, 1H, cyclopropyl), 2.82 (m, 1H, cyclopropyl), 2.04 (m, 1H, cyclopropyl), 1.73 (m, 1H, cyclopropyl); ^{13}C NMR (125 MHz, CD_3OD, 50 °C): δ 153.6, 145.2 (br), 142.4, 129.5, 127.3, 127.2, 30.4, 25.6, 19.9 (the compound exist as a tautomeric mixture and all ^{13}C resonances from the purine could not be determined); MS (EI) *m/z* (rel.%): 236 (M^+,100), 235 (89), 234 (6), 221 (14), 208 (10), 159 (25), 158 (5), 134 (48), 115 (21); HRMS: Found 236.1051, calcd. for $C_{14}H_{12}N_4$ 236.1062.

*6-(trans-2-Phenylcycloprop-1-yl)-9-phenylmethyl-9H-purine **5c***

6-Chloro-9-phenylmethyl-9*H*-purine **1c** (371 mg, 1.51 mmol) was reacted with *trans*-2-phenylcyclopropylzinc bromide (6.3 mL, 0.48 M, 3.50 mmol) employing the procedure described for the synthesis of compound **5a** above. The crude product was purified by flash chromatography on silica gel eluting with 10–30% acetone in hexane; yield 378 mg (77%) colorless crystalline solid, mp. 129–132 °C. **1**H NMR (300MHz, $CDCl_3$): δ 8.83 (s, 1H, H-2), 7.94 (s, 1H, H-8), 7.24 (m, 10H, Ph), 5.40 (s, 2H, NCH_2), 3.06 (m, 1H), 2.91 (m,

1H), 2.08 (m, 1H), 1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 152.8, 150.3, 143.3, 141.2, 135.3, 132.2, 129.1, 128.5, 128.4, 127.4, 126.1, 126.1, 47.2, 29.6, 24.7, 20.3; MS (EI) *m/z* (rel.%): 326 (M^+, 100), 236 (9), 235 (67), 224 (11), 208 (2), 181 (2), 115 (1), 91 (48); Anal: Found: C, 76.93; H, 5.60; N, 16.90. $C_{21}H_{18}N_4$ requires C, 77.28; H, 5.56; N, 17.17%.

6-(cis-2-Phenylcycloprop-1-yl)-9-(tetrahydro-2H-pyran-2-yl)-9H-purine ***6***

2-Bromo-1-phenylcyclopropane (*cis*/*trans*: 1.85/1, 300 mg, 1.53 mmol) [10] was dissolved in dry THF (2 mL) and cooled −89 °C. *n*-BuLi (960 μL, 1.53 mmol) was added and the mixture was stirred for 1 h before a solution of $ZnBr_2$ (1.50 mL, 1.50 mmol, 1.0 M in THF) was added. After stirring for 1 h, the zinc reagent was reacted with 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-purine **1a** (239mg, 1.0 mmol) following the procedure described for the synthesis of **5a** above. The crude product was purified by flash chromatography on silica gel eluting with 10%, 15%, 20%, 25%, and 30% acetone in hexane; yield 80 mg, (16%) 6-(*trans*-2-phenylcycloprop-1-yl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **5a** and 116 mg (24%) of the title compound **6**, colorless crystalline solid, mp. 138−142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (s, 1/2H, H-2), 8.54 (s, 1/2H, H-2), 8.18 (s, 1/2H, H-8), 8.17 (s, 1/2H, H-8), 7.13 (m, 2H, Ph), 7.03 (m, 2H, Ph), 6.97 (m, 1H, Ph), 5.68 (m, 1H, THP-2), 4.14 (m, 1H), 3.74 (m, 1H), 3.26 (m, 1H), 2.91 (m, 1H), 2.44 (m, 1H), 2.03 (m, 3H, THP), 1.67 (m, 3H, THP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 159.5, 151.5, 149.2, 149.1, 141.0, 140.9, 136.8, 136.7, 133.93, 133.88, 129.5, 129.4, 127.5, 127.4, 125.94, 125.88, 81.8, 81.7, 68.8, 68.7, 31.8, 31.6, 28.7, 28.6, 24.8, 22.80, 22.75, 21.7, 21.4, 11.2, 11.1 (Double set of signals were seen for several carbons in the diastereomeric mixt.); MS (EI) *m/z* (rel.%): 320 (M^+, 3), 237 (19), 236 (100), 235 (42), 221 (6), 159 (8), 134 (20), 91(2), 85 (5), 77 (2), 65 (1), 41 (6), 29 (6); HRMS: Found 320.1638, calcd. for $C_{19}H_{20}N_4O$ 320.1637; Anal: Found: C, 70.77; H, 6.50; N, 17.23. $C_{19}H_{20}N_4O$ requires C, 71.23; H, 6.29; N, 17.49.

9-Methyl-6-[(E)-2-phenylethen-1-yl]-9H-purine ***7d***

6-Chloro-9-methyl-9*H*-purine [22] (135 mg, 0.799 mmol), (*E*)-tri(*n*-butyl)styryltin [23] (398 mg, 1.04 mmol) and $Pd(PPh_3)_2Cl_2$ (28 mg, 0.004 mmol) was dissolved in dry DCE (6 mL) and refluxed for 22 h. Solvents were removed *in vacuo,* saturated KF in MeOH (10 mL) was added and the residue was stirred for 20 h before evaporation *in vacuo* together with a small amount of silica gel. The residue was added on top of a flash chromatography column and the product eluted with EtOAc-hexane (3:1) followed by 5% MeOH in EtOAc; yield 134 mg (71%) colorless crystalline solid, mp. ca. 150 °C (dec). ^{1}H NMR (300 MHz, CD_3OD): δ 8.82 (s, 1H, H-2), 8.42 (s, 1H, H-8), 8.32 (d, 1H, *J* 16.2 Hz, vinyl), 7.69 (m, 2H, Ph), 7.66 (d, 1H, *J* 16.2 Hz, vinyl), 7.41 (m, 3H, Ph), 3.90 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.4 152.2, 144.4, 139.5, 135.9, 131.7, 129.2, 128.7, 128.6, 127.6, 122.2, 29.5; MS (EI) *m/z* (rel.%): 236 (M^+, 35), 235 (100), 222 (1), 221 (70), 194 (2), 140 (5), 91(1), 77 (4); HRMS: Found 236.1033, calcd. for $C_{14}H_{12}N_4$ 236.1062; Anal: Found: C, 70.95; H, 5.19. $C_{14}H_{12}N_4$ requires C, 71.17; H, 5.12.

9-(1-Methylethyl)-6-[(E)-2-phenylethen-1-yl]-9H-purine ***7e***

The compound was prepared by Stille coupling on 6-chloro-9-(1-methylethyl)-9*H*-purine [24] (202 mg, 1.03 mmol), as described above for the synthesis of compound **7d**. The crude product was purified by flash chromatography on silica gel eluting with 10−20% acetone in hexane; yield 222 mg (82%) pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.90 (s, 1H, H-2), 8.39 (d, 1H, *J* 16.2 Hz, =CH), 8.12 (s, 1H, H-8), 7.71 (d, 1H, *J* 16.2 Hz, =CH), 7.70 (m, 2H, Ph), 7.37 (m, 3H, Ph), 4.92 (m, 1H, *J* 6.97 Hz, CH *i*-Pr), 1.63 (d, 6H, *J* 6.87 Hz, CH_3 *i*-Pr); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 152.1, 151.5, 141.7, 139.52, 139.49, 136.1, 131.4, 129.3, 128.7, 127.8, 122.4, 47.2, 22.5; MS (EI) *m/z* (rel.%): 264 (M^+, 58), 263 (100), 222 (19), 221 (70), 194 (6), 140 (8), 91(1), 77 (3); HRMS: Found 264.1357, calcd. for $C_{16}H_{16}N_4$ 264.1375.

9-[(Methylthio)methyl]-6-[(E)-2-phenylethen-1-yl]-9H-purine ***7f***

The compound was prepared by Stille coupling on 6-chloro-9-[(methylthio)methyl]-9*H*-purine [25] (328 mg, 1.53 mmol) as described for the synthesis of compound **7d** above. The crude product was purified by flash chromatography on silica gel eluting with 10−20% acetone in hexane; yield 352 mg (82%) colorless crystalline solid, mp. 79−81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H, H-2), 8.31 (d, 1H, *J* 16.2 Hz, =CH), 8.15 (s, 1H, H-8), 7.60 (m, 3H, Ph and =CH), 7.27 (m, 3H, Ph), 5.17 (s, 2H, CH_2), 2.04 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 152.5, 151.8, 143.5, 139.9, 135.8, 130.7, 129.3, 128.7, 127.7, 122.1, 46.0, 15.0; MS (EI) *m/z* (rel.%): 282 (M^+, 63), 281 (100), 278 (7), 253 (7), 236 (32), 235 (26), 222 (14), 221 (69), 208 (5), 179 (4); HRMS (ESI): Found 283.1015, calcd. for $C_{15}H_{14}N_4C[H^+]$ 283.1011.

9-Phenyl-6-[(E)-2-phenylethen-1-yl]-9H-purine ***7g***

The compound was prepared by Stille coupling on 6-chloro-9-phenyl-9*H*-purine [26] (101 mg, 0.44 mmol), as described for the synthesis of compound **7d** above. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:3) followed by (1:1); yield 116 mg, (89%) colorless crystalline solid, mp. 155−158 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.96 (s, 1H, H-2), 8.42 (d, 1H, *J* 16.2 Hz, =CH) 8.33 (s, 1H, H-8), 7.78 (d, 1H, *J* 16.2 Hz, =CH), 7.73 (m, 3H, Ph), 7.55 (m, 2H, Ph), 7.39 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.3, 153.1, 151.6, 142.9, 140.0, 136.0, 134.4, 131.5, 129.9, 129.5, 128.8, 128.4, 127.9, 123.5, 122.1; MS (EI) *m/z* (rel.%): 298 (M^+, 41), 297 (100), 270 (3), 194 (2), 167 (2), 149 (2), 140 (3); HRMS (ESI): Found 299.1280, calcd. for $C_{19}H_{14}N_4[H^+]$ 299.1291.

2-Methyl-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7j***

MeMgBr in THF (190 μL, 3 M, 0.577 mmol) dissolved in dry THF (1.5 mL) was cooled to -78 °C before $ZnBr_2$ (580 μL, 1.0 M, 0.58 mmol) was added. The solution was stirred at -78 °C for 1 h. In a separate flask, 2-chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7i** (100 mg, 0.288 mmol), $(dba)_3Pd_2$ (6.6 mg, 0.0072 mmol) and PPh_3 (15 mg, 0.058 mmol) was dissolved in dry THF (3 mL) and stirred until a clear yellow solution was formed. The purine solution was transferred to the zinc reagent and refluxed for 22 h before evaporation. The crude product was purified by flash chromatography on silica gel eluting with 10−50% EtOAc in hexane; yield 42 mg (44%) yellow crystalline solid, mp. 109−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (d, 1H, *J* 16.4 Hz, =CH), 7.95 (s, 1H, H-8), 7.71 (m, 2H, Ph), 7.65 (d, 1H, *J* 16.4 Hz, =CH), 7.35 (m, 8H, Ph), 5.43 (s, 2H, CH_2), 2.05 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 153.6, 152.6, 143.4, 139.9, 136.3, 135.4, 129.2, 129.1, 128.8, 128.7, 128.5, 127.84, 127.83, 123.1, 46.9, 26.2; MS (EI) *m/z* (rel.%): 326 (M^+, 100), 325 (25), 236 (15), 235 (93), 140 (8), 115 (6), 91 (29). HRMS: Found 326.1530, calcd. for $C_{21}H_{18}N_4$ 326.1531.

2-Methoxy-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7k***

NaOMe (1.5 mL, 1.0 M in MeOH) was added to 2-chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7i** (175 mg, 0.505 mmol) and the solution was heated at 50 °C for 24 h. The reaction mixture was cooled to ambient temperature and aqueous $NaHCO_3$

was added before volatiles were evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 20, 30, and 50% EtOAc in hexane; yield 102 mg, (60%) pale yellow crystalline solid, mp. 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, 1H, *J* 16.0 Hz, =CH), 7.86 (s, 1H, H-8), 7.68 (m, 2H, Ph), 7.65 (d, 1H, *J* 16.0 Hz, =CH), 7.36 (m, 8H, Ph), 5.34 (s, 2H, NCH_2), 4.10 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 155.0, 154.1, 142.6, 139.6, 136.0, 135.4, 129.4, 129.0, 128.8, 128.5, 127.94, 127.91, 127.3, 121.9, 55.1, 47.0; MS (EI) *m/z* (rel.%): 342 (M^+, 100), 341 (50), 327 (4), 252 (6), 251 (37), 236 (4), 219 (9), 209 (5), 140 (6); HRMS: Found 342.1468, calcd. for $C_{21}H_{18}N_4O$ 342.1481.

2-(4-Chlorophenyl)-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7o***

p-Chloro-iodobenzene (238 mg, 1.00 mmol) was converted to the corresponding zinc reagent and reacted with 2-chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7i** (176 mg, 0.507 mmol) essentially as described for the preparation of compound **5a** above. The crude product was purified by flash chromatography on silica gel eluting with hexane-EtOAc (9:1) followed by (3:1); yield 163 mg (76%) pale yellow crystalline solid, mp. 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (m, 2H, Ph), 8.51 (d, 1H, *J* 16.2 Hz, =CH), 8.03 (s, 1H, H-8), 7.77 (m, 3H, Ph and =CH), 7.48 (m, 2H, Ph), 7.38 (m, 8H, Ph), 5.48 (s, 2H, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 153.5, 152.8, 144.1, 139.8, 136.8, 136.2, 136.1, 135.4, 129.7, 129.6, 129.4, 129.1, 128.8, 128.6, 128.5, 128.0, 127.9, 122.7, 47.1; MS (EI) *m/z* (rel.%): 424 (M^+, 37/100), 333 (19), 331 (53), 140 (9), 115 (7), 91 (48); HRMS: Found 422.1280, calcd. for $C_{26}H_{19}ClN_4$ 422.1298; Anal: Found: C, 73.97; H, 4.67. $C_{26}H_{19}ClN_4$ requires C, 73.84; H, 4.53%.

2-(4-Methoxyphenyl)-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7p***

p-Methoxy-iodobenzene (135 mg, 0.577 mmol) was converted to the corresponding zinc reagent and reacted with 2-chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7i** (100 mg, 0.288 mmol), essentially as described for the preparation of compound **5a** above. The crude product was purified by flash chromatography on silica gel eluting with hexane-EtOAc (9:1) followed by (3:1); yield 85 mg (71%) pale yellow crystalline solid, mp. 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (m, 2H, Ph), 8.51 (d, 1H, *J* 16.2 Hz, =CH), 7.99 (s, 1H, H-8), 7.75 (m, 3H, Ph and =CH), 7.37 (m, 8H, Ph), 7.05 (m, 2H, Ph), 5.49 (s, 2H, NCH_2), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 158.9, 153.4, 152.9, 143.6, 139.3, 136.4, 135.6, 131.2, 129.9, 129.3, 129.2, 129.1, 128.8, 128.4, 128.1, 128.0, 127.9, 123.1, 113.8, 55.4, 47.1; MS (EI) *m/z* (rel.%): 418 (M^+, 100), 417 (13), 348 (1), 328 (9), 327 (40), 140 (5), 115 (6), 91(27), 77 (1); HRMS: Found 418.1801, calcd. for $C_{27}H_{22}N_4O$ 418.1794.

8-Chloro-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7q***

6,8-Dichloro-9-phenylmethyl-9*H*-purine **1d** (350 mg, 1.25 mmol), $Pd(PPh_3)_2Cl_2$ (44 mg, 0.0063 mmol) and (*E*)-tri(*n*-butyl)styryltin [23] (625 mg, 1.63 mmol) was dissolved in dry DCE (5 mL), and heated at 60 °C for 42 h. Volatiles were evaporated *in vacuo*, the crude product was dissolved in MeCN (70 mL), and was washed with hexane (5 × 10 mL). The MeCN phase was evaporated and the crude product was purified by flash chromatography on silica gel eluting with 10–25% EtOAc in hexane; yield 190 mg, (44%) colorless crystalline solid, mp. 135–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (s, 1H, H-2), 8.33 (d, 1H, *J* 16.0 Hz, =CH), 7.69 (m, 2H, Ph), 7.63 (d, 1H, *J* 16.0 Hz, =CH), 7.36 (m, 8H, Ph), 5.47 (s, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.8, 152.7, 152.6, 143.0, 140.0, 135.9, 134.6, 130.0, 129.6, 129.0, 128.8, 128.5, 128.0, 127.9, 121.6, 46.8; MS (EI) *m/z* (rel.%): 348/346 (M^+, 18/54), 347/345 (43/100), 257 (8), 255 (22), 140 (6), 91 (76); HRMS: Found 346.0962, calcd. for $C_{20}H_{15}ClN_4$ 346.0985; Anal: Found: C, 69.59; H, 4.41. $C_{20}H_{15}ClN_4$ requires C, 69.26; H, 4.36%.

8-Methyl-6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-9H-purine ***7r***

The compound was synthesized from 8-chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7q** as described for the preparation of compound **7j** above. The crude product was purified by flash chromatography on silica gel eluting with 20, 30, and 50% EtOAc in hexane; yield 48 mg (63%) pale yellow crystalline solid, mp. 179–180 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.94 (s, 1H, H-2), 8.40 (d, 1H, *J* 16.1 Hz, =CH), 7.77 (d, 1H, *J* 16.1 Hz, =CH), 7.76 (m, 2H, Ph), 7.41 (m, 8H, Ph), 5.49 (s, 2H, NCH_2), 2.63 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.9, 153.5, 151.9, 139.0, 136.2, 135.3, 130.3, 129.2, 129.0, 128.8, 128.2, 127.9, 127.0, 122.1, 45.8, 14.7, C-5 is "hidden" under one of the CH in Ph sign; MS (EI) *m/z* (rel.%): 326 (M^+, 50), 325 (100), 236 (3), 235 (20), 234 (2), 233 (2), 194 (3), 140 (6), 91 (44); HRMS: Found 326.1515, calcd. for $C_{21}H_{18}N_4$ 326.1531.

6-[(E)-2-phenylethen-1-yl]-9-phenylmethyl-8H-purin-8-one ***7s***

8-Chloro-6-[(*E*)-2-phenylethen-1-yl]-9-phenylmethyl-9*H*-purine **7q** (103 mg, 0.297 mmol) was dissolved in dry MeOH (0.5 mL) and NaOMe (0.45 mL, 2.0 M in MeOH) was added. The mixture was heated at 75 °C for 19 h, poured into water (40 mL), and was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) before solvents were removed *in vacuo*. The crude product was purified by flash chromatography on silica eluting with 15–25% EtOAc in hexane; yield 62 mg (65%) colorless crystalline solid, mp. >300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.7 (s, 1H, NH), 8.72 (s, 1H, H-2), 7.91 (d, 1H, *J* 16.1 Hz, =CH), 7.68 (m, 2H, Ph), 7.52 (m, 2H, Ph), 7.38 (m, 3H, Ph), 7.29 (m, 3H, Ph), 7.22 (d, 1H, *J* 16.1 Hz, =CH), 5.20 (s, 2H, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 151.6, 150.4, 141.0, 137.3, 135.8, 135.6, 129.5, 128.9, 128.8, 128.5, 128.3, 127.6, 120.7, 117.8, 143.8; MS (EI) *m/z* (rel.%): 328 (M^+, 47), 327 (100), 261 (0,04). 237 (1), 91 (73); HRMS: Found 328.1328, calcd. for $C_{20}H_{16}N_4O$ 328.1324.

7-Methyl-6-[(E)-2-phenylethen-1-yl]-7H-purine ***9b***

The compound was prepared by Stille coupling on 6-chloro-7-methyl-7*H*-purine [22] (259 mg, 1.536 mmol) as described for the synthesis of compound **7d** above. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (3:1) followed by 10% MeOH in EtOAc; yield 144 mg (40%) pale yellow crystalline solid, mp. 208–209 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.96 (s, 1H, H-2), 8.13 (d, 1H, *J* 15.3 Hz, =CH), 8.09 (s, 1H, H-8), 7.57 (m, 2H, Ph), 7.47 (d, 1H, *J* 15.3 Hz, =CH), 7.35 (m, 3H, Ph), 4.14 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.0, 152.8, 149.0, 147.6, 138.8, 135.4, 129.6, 128.9, 127.6, 122.6, 119.4, 35.2; MS (EI) *m/z* (rel.%): 236 (M^+, 49), 235 (100), 208 (4), 159 (11), 140 (8), 128 (5), 115 (6), 91 (1); HRMS (ESI): Found 237.1124, calcd. for $C_{14}H_{12}N_4[H^+]$ 237.1134.

Inhibition of 15-lipoxygenase

Lipoxygenase activity was measured in borate buffer solutions (0.2 M, pH 9.00) as previously described [27, 28] by the increase in absorbance at 234 nm from 30 to 90 s after addition of the enzyme, using linoleic acid (134 μM) as substrate. The final enzyme concentration was 167 U/mL. Test substances were added as DMSO solutions (final DMSO conc. 1.6%); DMSO alone was added in uninhibited control experiments. Six or more parallel controls and three

or more parallel tests for each test-substance solution were measured. To ensure constant enzyme activity throughout the experiment, the enzyme solution was kept on ice, and controls were measured at regular intervals. Calculation of enzyme activity was carried out as previously described [28] and IC_{50} values were determined by linear interpolation between the measuring points closest to the 50% activity. Values are expressed as means ±SD. Student's *t*-test was employed for determination of statistical significance.

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