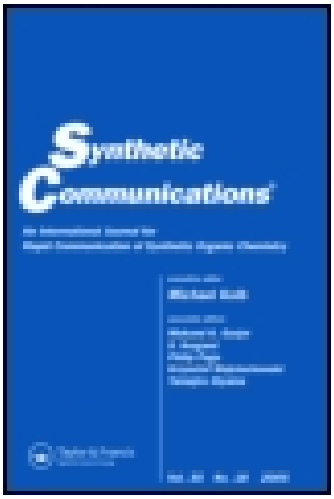

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Thywill Gamadeku [a] & Lise-Lotte Gundersen [a]

[a] Department of Chemistry , University of Oslo , Oslo, Norway

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SYNTHESIS OF 8-BROMO-*N*-BENZYLPURINES VIA 8-LITHIATED PURINES: SCOPE AND LIMITATIONS

Thywill Gamadeku and Lise-Lotte Gundersen
Department of Chemistry, University of Oslo, Oslo, Norway

9-Benzylpurines have been lithiated in the 8-position and subsequently brominated when trapped with $BrCCl_2CCl_2Br$. The 8-bromopurines were isolated in excellent yields when the benzyl group carried an alkoxy or alkyl group in the* ortho *or* para *position. Without these substituents, the conversion was generally less, and formation of 8,8′-purinyl dimers was observed. There was also evidence of debenzylation in some instances. Bromination of 7-benzylpurines employing the same set of reaction conditions has also been achieved.

Keywords: Bromination; debenzylation; dimerization; lithiation; purine

Purines and purine nucleosides have been subjected to direct lithiation in the 8-position when treated with BuLi, or preferably lithium diisopropylamide (LDA), and the metallated purines have been trapped with a variety of electrophiles including halogen sources, simple alkyl halides, and aldehydes.[1] We established a convenient procedure for halogenation of 9-tetrahydropyrane (THP)-purines and purine nucleosides, where the 8-lithiated species were trapped with appropriate halogen donors (CCl_3CCl_3, $BrCCl_2CCl_2Br$, BrCN, or ICN),[2] but we were not able to synthesize 8-halogenated 6-chloro-9-benzylpurines employing this protocol.[3] However, later we managed to lithiate 6-chloro-9-(4-methoxybenzyl)purine and trap this intermediate with MeI and CCl_3CCl_3, and both the 8-methyl- and 8-chloropurines were isolated in excellent yields.[4]

9-Benzylated purines are of great interest because of their potent biological activities. For instance, they may be selective adenosine A_{2A} receptor antagonists,[5] selective inhibitors of *Mycobacterium tuberculosis*,[4,6] inhibitors of 15-lipoxygenase (non-antioxidant inhibitors)[7] or they may have potential as antiviral[8] or anticancer[9] compounds. The continuous need for efficient syntheses of various 9-benzylated purines with potential biological activities led us to explore the scope and limitations of C-8 functionalization of such compounds via 8-lithiated intermediates.

The model reaction chosen in this study was treatment of the purines **1** with LDA followed by bromination with $BrCCl_2CCl_2Br$ (Scheme 1; Table 1). The purines were treated with LDA for 1 h, and the lithiated purine allowed to react with

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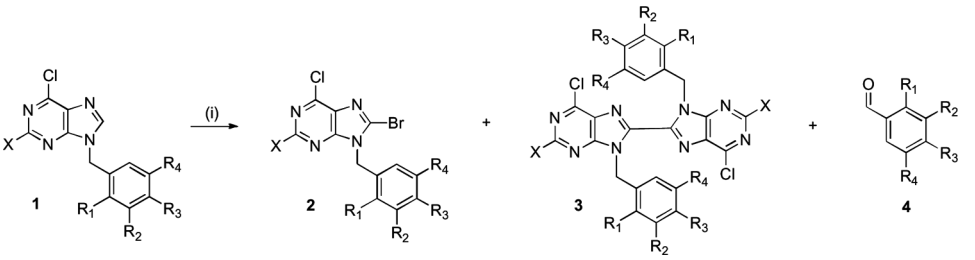
Address correspondence to Lise-Lotte Gundersen, Department of Chemistry, University of Oslo, Oslo, Norway. E-mail: l.l.gundersen@kjemi.uio.no



Scheme 1. (i) (1) LDA; (2) $BrCCl_2CCl_2Br$, THF, −78 °C.

$BrCCl_2CCl_2Br$ for approximately 2–3 h to compare reactivity with the previously studied purine nucleosides and THP-protected purines.[2] 9-Benzyl-6-chloropurine (**1a**) was quite unreactive, but a careful analysis of the ^1H NMR spectrum of the crude product showed that some desired product **2a** was formed, and the compound

Table 1. Lithiation–bromination of 9-benzylpurines **1**

Entry	X	R_1	R_2	R_3	R_4	Reaction time (h)[a]	Ratio **1**:**2**:**3**[b]	Yield (%) **2**	Yield (%) **3**	Yield (%) **4**
1	H	H	H	H	H	2.25	73:13:14	2, **2a**	11, **3a**	–[c]
2	H	H	H	Me	H	1.25	0:100:0	76, **2b**	–	–[c]
3	Cl	H	H	Me	H	2.00	3:96:1[d]	75, **2c**	–[e]	–[c]
4	H	H	H	OMe	H	3.00	0:100:0	83, **2d**	–	–[c]
5	Cl	H	H	OMe	H	2.50	0:100:0	80, **2e**	–	–[c]
6	NO_2	H	H	OMe	H	2.75	75:18:7[f]	6, **2f**	–[g]	+[h]
7	H	H	H	OBn	H	1.50	0:100:0	84, **2g**	–	+[h]
8	H	H	OMe	OMe	OMe	2.00	0:100:0	78, **2h**	–	8, **4h**
9	H	H	OMe	H	H	2.75	15:56:29	25, **2i**	26, **3i**	+[h]
10	Cl	H	OMe	H	H	2.30	16:75:9	51, **2j**	8, **3j**	+[h]
11	Cl	OMe	H	H	H	1.75	6:94:0	80, **2k**	–	–[c]
12	H	H	H	CF_3	H	3.00	76:19:5	8, **2l**	7, **3l**	–[c]
13	H	H	H	F	H	2.25	24:69:7	19, **2m**	5, **3m**	–[c]
14	H	F	H	H	H	2.50	62:18:20[e]	17, **2n**	–[i]	+[h]
15	Cl	H	H	Cl	H	2.00	25:75:0	34, **2o**	–	+[g]
16	H	H	Cl	Cl	H	2.00	29:71:0	19, **2p**	–	–[c]
17	H	H	Cl	H	H	2.50	74:13:13	15, **2q**	6, **3q**	–

[a]After adding $BrCCl_2CCl_2Br$.

[b]Molecular ratio taken from the ^1H NMR spectra of the crude products.

[c]No aldehyde present in the crude product according to ^1H NMR.

[d]Based on the presence of a signal at 6.10 ppm in the crude ^1H NMR spectrum, which may be assigned to the CH_2 in the dimer.

[e]Not isolated.

[f]Molecular ratio **1**:**2**:**5**.

[g]Dimer **5** (Fig. 1) isolated in 4%.

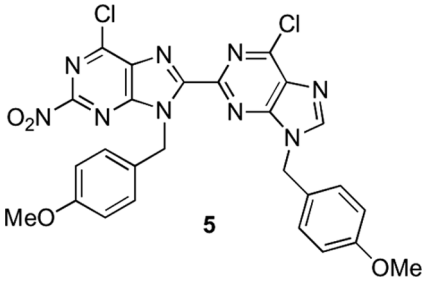
[h]A signal was present in the ^1H NMR spectrum of the crude product, which corresponded well with the reported ppm value for the CHO proton in the aldehyde **4**.

[i]Based on the presence of a signal at 6.27 ppm in the crude ^1H NMR spectrum, which may be assigned to the CH_2 in the dimer.

was isolated in very poor yield (Table 1, entry 1). A second product was also formed and isolated. This turned out to be the symmetrical dimer **3a**. Purine nucleoside 8,8′-dimers have been formed as a result of oxidative DNA damage,[10] but synthetic routes leading to such dimers are limited to Cu-mediated homodimerization of 8-iodopurines.[11] Also, dimerization of 8-unsubstituted purines in the presence of CuI and air has been observed.[12] However, introduction of carbon substituents in the purine 8-position by reacting phenyllithium[13] or allylic cuprates[14] with a C-8 unsubstituted purine have been achieved, probably by an addition–oxidation mechanism. Hence, the dimers **3** may have been formed by addition of lithiated purine to unreacted compound **1**. Alternatively, the dimers may have been formed by an attack from the lithiated purine on the 8-brominated products **2**, but the difference in reactivity between 6- and 8-halopurines toward nucleophiles are generally not very profound,[15] and exchange of the chloride was not observed for any of the 6-chloropurines **1** examined in this study.

As suspected, the substitution pattern in the benzylic substituent turned out to be important for the outcome of lithiation–bromination of compounds **1**. Compounds carrying a methyl or an alkoxy group in the *para* position (Table 1, entries 2–5 and 7–8) gave the desired 8-bromopurines **2** in excellent yields and with no or minimal dimer formation. The same was true for the 2-methoxybenzylpurine **2k** (Table 1, entry 11). A chlorine in the purine 2-position did not affect the outcome of the reaction (Table 1, entries 3 and 5), but in the case of the 2-nitropurine **1f** (Table 1, entry 6), the yield of the desired product **2f** was poor and substitution in the purine 2-position had taken place, giving the unsymmetrical dimer **5** (Fig. 1). There are also other examples of facile nucleophilic displacement of a nitro group at the purine C-2.[4,16]

In the reaction of the trimethoxybenzylpurine **1h**, 3,4,5-trimethoxybenzaldehyde (**4h**)[17] was isolated in 8% yield in addition to the desired product **2h**. Indoles has been debenzylated by initial deprotonation in the benzylic α-position, and the reaction was sometimes followed by benzaldehyde formation.[18] We were only able to isolate an aldehyde in the reaction of **1h**, but debenzylation may be partly responsible for reduced yields of the desired product **2** in several cases. In some instances, the ^{1}H NMR spectrum of the crude product indicated the presence of an aldehyde (Table 1, entries 6–10, 14, and 15), but formation of aldehydes may be difficult to detect because of volatility and/or because they are easily oxidized to acids.



5

Figure 1. Structure of the dimer **5**, formed in the synthesis of compound **2f**.

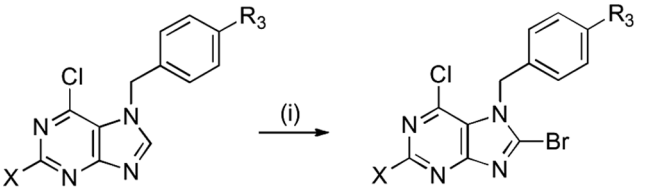
The purines not carrying an electron-donor substituent (methyl, alkoxy) in the benzylic *ortho* or *para* position reacted more sluggishly in the lithiation–bromination reaction (Table 1, entries 9, 10, and 12–17). The conversions of the starting materials **1** were lower and, except for the 4-chlorobenzylpurines **2p** and **2q** (Table 1, entries 16 and 17), some dimer formation took place in all these reactions. The isolated yields of the desired compounds **2** were poor, even in the cases where the ^{1}H NMR spectrum of the crude product indicated that more than 50% of the starting material was converted. This can be explained by loss of material during tedious chromatographic separation of product **2**, dimer **3**, and unconverted starting material **1** but may also (in part) be due to undetected debenzylation reactions giving polar products that were not isolated.

The reason why alkyl or alkoxy substituents in the benzylic *ortho* or *para* position is favorable in the reaction studied is not totally clear. These substituents may reduce the acidity of the benzylic CH_2 and hence prevent extensive aldehyde formation. However, it is more difficult to explain why other substitution patterns lead to dimer formation and/or poor conversion of the starting material.

Compound **2m** has been synthesized and isolated in a somewhat better yield (55%), employing almost the same set of reaction conditions.[19] It may be that the outcome of the reactions is also very sensitive to concentration, exact reaction temperature, rate of addition, and other factors. Also 6-bromo-9-benzylpurine has been lithiated and trapped with a brominating agent, BrCN, and the product was isolated in 34% yield.[20] Again, it is difficult to know at the present stage if the difference in reactivity between the 6-bromopurine and the 6-chloropurine **1a** studied herein is due to slight variations in reaction conditions and/or the identity of the substituent in the purine 6-position.

Finally, we examined lithiation–bromination of the 7-benzylated purines **6a** and **6b** (Scheme 2). In the reaction of **6a**, the conversion was ca. 40% according to the crude product ^{1}H NMR spectrum, and both conversion and isolated yield of the product **7a** were better than for the 9-benzylated isomer **1a**. In the reaction of compound **6b**, no unreacted starting material could be detected in the crude product ^{1}H NMR spectrum, but the isolated yield of product **7b** was only moderate. This may have been a result of debenzylation; there were indications of aldehyde formation in the crude product NMR spectra of both compounds **7a** and **7b**. Dimer formation was not observed in the reactions of the 7-benzylated purines **6**.

In summary, 9-benzylpurines can be lithiated in the 8-position and subsequently brominated when trapped with $BrCCl_2CCl_2Br$. The 8-bromopurines



6a: X=H, R_3=H
6b: X=Cl, R_3=OCH_3

7a: X=H, R_3=H, 23%
7b: X=Cl, R_3=OCH_3, 41%

Scheme 2. (i) (1) LDA; (2) $BrCCl_2CCl_2Br$, THF, −78 °C.

were isolated in excellent yields when the benzyl group carried an alkoxy or alkyl group in the *ortho* or *para* position. With other substitution patterns in the benzyl group, the conversion was generally less, and formation of 8,8′-purinyl dimers was observed. There was also evidence of debenzylation in some instances. Bromination of 7-benzylpurines employing the same set of reaction conditions has also been achieved. Here, no dimer formation was observed, and the outcome of the reaction appeared to be less dependant on the presence of electron-donating groups in the benzylic *ortho*/*para* positions. In this study, lithiation with LDA followed by reaction with $BrCCl_2CCl_2Br$ was chosen as a model reaction. We believe that the outcome of the reactions are mainly dependent on the ease of lithiation and/or stability of the 8-lithiated species and that the compounds reacting well under these set of reaction conditions also may be halogenated when the lithiated species is trapped with other sources of electrophilic halogens.

EXPERIMENTAL

^{1}H 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. Decoupled ^{13}C NMR spectra were recorded at 125, 75, or 50 MHz using the instruments mentioned. Mass spectra under electron-impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as m/z (% rel. int.). Melting points were determined with a Büchi melting-point B-545 apparatus and are uncorrected. Tetrahydrofuran (THF) was purified by a solvent purification system, MB SPS-800 from MBraun, or by distillation from Na/benzophenone. Diisopropylamine was distilled from CaH_2 and stored over molecular sieves (4 Å). Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). Starting materials were created using literature methods: **1a**,[19] **1b–e**,[6c] **1f**,[16b] **1g–q**,[6c] **6a**,[21] and **6b**.[6c] All other reagents were commercially available and used as received.

General Procedure

A solution of the purine **1** or **6** (0.50 mmol) in THF (2.0 mL) was added dropwise over 10 min to a stirred solution of LDA (ca. 0.5 M in THF, prepared in situ from butyllithium and diisopropylamine, 1.4 mL) under N_2 at −78 °C. After stirring for 1 h, a solution of $BrCCl_2CCl_2Br$ (326 mg, 1.00 mmol) in THF (1.0 ml) was added dropwise over 10 min. The resulting mixture was stirred at −78 °C, for the time given in Table 1, before sat. aq. NH_4Cl (15 mL) was added. The mixture was warmed to ambient temperature and extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was purified by flash chromatography on silica gel.

8-Bromo-6-chloro-9-(phenylmethyl)-9*H*-purine (2a)

Hexane, followed by EtOAc–hexane (1:5) and EtOAc–hexane (1:2), was used for flash chromatography; yield 4 mg (2%), off-white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 2H, CH_2), 7.29–7.36 (m, 5H, Ph), 8.74 (s, 1H, H-2); MS EI m/z

(rel. %) 324/322 (M^+, 9/7), 287 (6), 280 (5), 278 (8), 245 (6), 243 (18), 91 (100); HRMS (EI) calcd. for $C_{12}H_8BrClN_4$ 321.9616, found 321.9621.

6,6′-Dichloro-9,9′-di(phenylmethyl)-9*H*,9′*H*-[8,8′]-bipurinyl (3a)

Isolated in the synthesis of **2a**; yield 14 mg (11%), off-white solid, mp 228–230 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (s, 4H, CH_2), 7.13–7.17 (m, 6H, Ph), 7.28–7.30 (m, 4H, Ph), 8.88 (s, 2H, H-2); MS EI *m/z* (rel. %) 488/486 (M^+, 30/44), 397 (66), 396 (22), 395 (100), 91 (93); HRMS (EI) calcd. for $C_{24}H_{16}Cl_2N_8$ 486.0875; found 486.0880.

8-Bromo-6-chloro-9-[(4-methylphenyl)methyl]-9*H*-purine (2b)

Hexane, followed by EtOAc–hexane (1:8) and EtOAc–hexane (1:4), was used for flash chromatography; yield 127 mg (76%), yellow solid, mp 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 7.11 (d, $J = 7.9$ Hz, Hz, 2H, Ar), 7.22 (d, $J = 7.9$ Hz, 2H, Ar), 8.72 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 48.1, 127.9, 129.6, 131.1, 131.8, 134.2, 138.6, 149.4, 152.1, 152.9; MS EI *m/z* (rel. %) 340/338/336 (M^+, 3/11/8), 259 (5), 257 (16), 106 (9), 105 (100); HRMS (EI) calcd. for $C_{13}H_{10}BrClN_4$ 335.9777; found 335.9775.

8-Bromo-2,6-dichloro-9-[(4-methylphenyl)methyl]-9*H*-purine (2c)

Hexane, followed by EtOAc–hexane (1:6) and EtOAc–hexane (1:3), was used for flash chromatography; yield 129 mg (75%), yellow solid, mp 178–179 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 7.16 (d, $J = 8.0$ Hz, Hz, 2H, Ar), 7.25 (d, $J = 8.0$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 48.3, 128.0, 129.7, 130.6, 130.8, 134.7, 138.8, 150.1, 153.2, 153.9; MS EI *m/z* (rel. %) 374/372/370 (M^+, 5/11/7), 293 (3), 291 (5), 185 (2), 105 (100); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_4$ 369.9388; found 369.9393.

8-Bromo-6-chloro-9-[(4-methoxyphenyl)methyl]-9*H*-purine (2d)

The reaction was performed on a 0.99-mmol scale, and EtOAc–hexane (1:2) was used for flash chromatography; yield 293 mg (83%), off-white wax. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 6.83 (d, $J = 8.4$ Hz, 2H, Ar), 7.33 (d, $J = 8.4$ Hz, 2H, Ar), 8.74 (s. 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 47.8, 55.1, 114.1, 126.0, 129.4, 131.6, 133.9, 149.1, 151.8, 152.6, 159.4; MS EI *m/z* (rel. %) 354/352 (M^+, 13/10), 275 (3), 273 (11), 122 (8), 121 (100), 78 (6), 77 (6); HRMS (EI) calcd. for $C_{13}H_{10}BrClN_4O$ 351.9727; found 351.9727.

8-Bromo-2,6-dichloro-9-[(4-methoxyphenyl)methyl]-9*H*-purine (2e)

Hexane, followed by EtOAc–hexane (1:6) and EtOAc–hexane (1:2), was used for flash chromatography; yield 154 mg (80%), pale yellow solid, mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H, OCH_3), 5.35 (s, 2H, CH_2), 6.82 (d, $J = 8.8$ Hz, 2H, Ar), 7.30 (d, $J = 8.8$ Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.1, 55.3, 114.4, 125.7, 129.7, 130.8. 134.6, 150.1, 153.1, 159.9; MS EI *m/z*

(rel. %) 390/388/386 (M^+, 3/7/4), 309 (1), 122 (11), 121 (100), 78 (8), 77 (7); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_4O$ 385.9337; found 385.9334.

8-Bromo-6-chloro-9-[(4-methylphenyl)methyl]-2-nitro-9*H*-purine (2f)

Hexane, followed by EtOAc–hexane (1:1) and EtOAc, was used for flash chromatography; yield 12 mg (6%), yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 5.49 (s, 2H, CH_2), 6.85 (d, $J = 8.7$ Hz, 2H, Ar), 7.39 (d, $J = 8.7$ Hz, 2H, Ar); MS EI m/z (rel. %) 399/397 (M^+, 11/9), 122 (12), 121 (100), 91 (5), 78 (8), 77 (8); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_5O_3$ 396.9577; found 396.9575.

6,6′-Dichloro-9,9′-di[(4-methoxyphenyl)methyl]-2-nitro-9*H*,9′*H*-[8,2′]-bipurinyl (5)

Isolated in the synthesis of **2f**; yield 6 mg (4%), yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2), 6.20 (s, 2H, CH_2), 6.69 (d, $J = 8.8$ Hz, 2H, Ar), 6.87 (d, $J = 8.8$ Hz, 2H, Ar), 7.15 (d, $J = 8.8$ Hz, 2H, Ar), 7.22 (d, $J = 8.8$ Hz, 2H, Ar), 8.17 (s, 1H, H-8′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.1, 48.9. 55.2, 55.3, 114.2, 114.8, 125.5, 127.1, 129.3, 129.7, 132.2, 132.7, 147.4, 149.3, 151.3, 152.1, 153.1, 153.7, 153,8, 159.5, 160.2; MS EI m/z (rel. %) 593/591 (M^+, 5/9), 122 (9), 121 (100), 77 (9); HRMS (EI) calcd. for $C_{26}H_{19}Cl_2N_9O_4$ 591.0937; found 591.0955.

9-[(4-Benzyloxyphenyl)methyl]-8-bromo-6-chloro-9*H*-purine (2g)

Hexane, followed by EtOAc–hexane (1:6) and EtOAc–hexane (1:2), was used for flash chromatography; yield 182 mg (84%), pale yellow solid, mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 2H, CH_2), 6.89–7.39 (m, 9H, Ar), 8.73 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.9, 70.0, 115.3, 126.5, 127.4, 128.1, 128.6, 129,7, 131.9, 134.2, 136.6, 149.5, 152.1, 152.9, 159.0; MS EI m/z (rel. %) 432/430/428 (M^+, 2/8/6), 386 (2), 384 (4), 92 (11), 91 (100); HRMS (EI) calcd. for $C_{19}H_{14}BrClN_4O$ 428.0040; found 428.0030.

8-Bromo-6-chloro-9-[(3,4,5-trimethoxyphenyl)methyl]-9*H*-purine (2h)

Hexane, followed by EtOAc–hexane (1:3) and EtOAc–hexane (1:1), was used for flash chromatography; yield 127 mg (76%), off-white solid, mp 145–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 6H, $2 \times OCH_3$), 3.78 (s, 3H, OCH_3), 5.37 (s, 2H, CH_2), 6.62 (s, 2H, Ar), 8.72 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.7, 56.1, 60.8, 105.5, 129.5, 131.8, 134.1, 138.3, 149.6, 152.1, 152.8, 153.5; MS EI m/z (rel. %) 416/414/412 (M^+, 10/49/30), 399 (6), 335 (8), 333 (23), 181 (100); HRMS (EI) calcd. for $C_{15}H_{14}BrClN_4O_3$ 411.9938; found 411.9918.

3,4,5-Trimethoxybenzaldehyde (4h)

Isolated in the synthesis of **2h**; yield 8 mg (8%), yellow solid, spectral data in accordance with those reported before.[17]

8-Bromo-6-chloro-9-[(3-methoxyphenyl)methyl]-9*H*-purine (2i)

Hexane, followed by EtOAc–hexane (1:6) and EtOAc–hexane (1:3), was used for flash chromatography; yield 44 mg (25%), pale yellow solid, mp 103–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, OCH_3), 5.47 (s, 2H, CH_2), 6.84–6.93 (m, 3H, Ar), 7.27–7.29 (m, 1H, Ar), 8.76 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.2, 55.2, 113.6, 113.9, 120.0, 130.1, 131.8, 134.2, 135.5, 149.5, 152.1, 152.9, 159.9; MS EI *m/z* (rel. %) 356/354/352 (M^+, 8/30/24), 275 (34), 274 (17), 273 (100), 121 (68); HRMS (EI) calcd. for $C_{13}H_{10}BrClN_4O$ 351.9727; found 351.9718.

6,6′-Dichloro-9,9′-di[(3-methoxyphenyl)methyl]-9*H*,9′*H*-[8,8′]-bipurinyl (3i)

Isolated in the synthesis of **2i**; yield 35 mg (26%), colorless solid, mp 218–220 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 6H, OCH_3), 6.21 (s, 4H, CH_2), 6.68–7.08 (m, 8H, Ar), 8.87 (s, 2H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.4, 55.1, 113.6, 114.0, 120.4, 129.6, 130.8, 137.2, 143.3, 152.2, 153.1, 153.4, 159.6; MS EI *m/z* (rel. %) 550/548/546 (M^+, 5/36/53), 429 (11), 427 (66), 425 (100), 240 (31), 121 (93); HRMS (EI) calcd. for $C_{26}H_{20}Cl_2N_8O_2$ 546.1086; found 546.1080.

8-Bromo-2,6-dichloro-9-[(3-methoxyphenyl)methyl]-9*H*-purine (2j)

Hexane, followed by EtOAc–hexane (1:6) and EtOAc–hexane (1:2), was used for flash chromatography; yield 108 mg (56%), pale yellow solid, mp 144–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.81–6.87 (m, 3H, Ar), 7.21–7.26 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.4, 55.3, 113.9, 114.0, 120.0, 130.2, 130.7, 134.7, 135.0, 150.2, 153.2, 154.0, 160.0; MS EI *m/z* (rel. %) 390/388/386 (M^+, 11/24/14), 307 (67), 122 (9), 121 (100), 91 (19); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_4O$ 385.9337; found 385.9338.

9,9′-Di[(3-methoxyphenyl)methyl]-2,2′,6,6′-tetrachloro-9*H*,9′*H*-[8,8′]-bipurinyl (3j)

Isolated in the synthesis of **2j**; yield 13 mg (8%), colorless solid, mp 251–254 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 6H, OCH_3), 6.14 (s, 4H, CH_2), 6.72–7.07 (m, 8H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.8, 55.2, 113.8, 114.1, 120.4, 129.8, 130.0, 136.7, 143.6, 153.1, 154.3, 154.8, 159.7; MS EI *m/z* (rel. %) 618/616/614 (M^+, 7/13/10), 497 (15), 495 (34), 493 (26), 240 (36), 121 (100); HRMS (EI) calcd. for $C_{26}H_{18}Cl_4N_8O_2$ 614.0307; found 614.0323.

8-Bromo-2,6-dichloro-9-[(2-methoxyphenyl)methyl]-9*H*-purine (2k)

Hexane, followed by EtOAc–hexane (1:2), was used for flash chromatography; yield 154 mg (80%), yellow solid, mp 190–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2), 6.83–6.95 (m, 3H, Ar), 7.25–7.32 (m, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 55.2, 110.5, 120.5, 121.5, 128.7, 129.9, 130.8, 135.5,

149.9, 152.9, 154.3, 156.9; MS EI *m/z* (rel. %) 390/388/386 (M^+, 5/11/6), 309 (23), 307 (35), 122 (9), 121 (100), 91 (48); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_4O$ 385.9337; found 385.9335.

8-Bromo-6-chloro-9-[(4-trifluoromethylphenyl)methyl]-9*H*-purine (2l)

Hexane, followed by EtOAc–hexane (1:2) and EtOAc–hexane (1:1), was used for flash chromatography; yield 16 mg (8%), pale yellow solid, mp 173–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (s, 2H, CH_2), 7.45 (d, $J = 8.1$ Hz, 2H, Ar), 7.60 (d, $J = 8.1$ Hz, 2H, Ar), 8.74 (s, 1H, H-2); MS EI *m/z* (rel. %) 392/390 (M^+, 31/24), 313 (25), 311 (73), 159 (100), 109 (24); HRMS (EI) calcd. for $C_{13}H_7BrClF_3N_4$ 389.9495; found 389.9484.

6,6′-Dichloro-9,9′-di[(4-trifluoromethylphenyl)methyl]-9*H*,9′*H*-[8,8′]-bipurinyl (3l)

Isolated in the synthesis of **2l**; yield 7 mg (4%), yellow wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 4H, CH_2), 7.46 (d, $J = 8.3$ Hz, 4H, Ar), 7.54 (d, $J = 8.3$ Hz, 4H, Ar), 8.91 (s, 2H, H-2); MS EI *m/z* (rel. %) 624/622 (M^+, 36/54), 465 (65), 463 (100), 159 (26), 109 (9); HRMS (EI) calcd. for $C_{26}H_{14}Cl_3F_6N_8$ 622.0623; found 622.0609.

8-Bromo-6-chloro-9-[(4-fluorophenyl)methyl]-9*H*-purine (2m)

Hexane, followed by EtOAc–hexane (2:3) and EtOAc, was used for flash chromatography; yield 21 mg (19%), pale yellow solid, mp 143–144 °C (lit.[19] 143–144 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.43 (s, 2H, CH_2), 6.95–7.05 (m, 2H, Ar), 7.33–7.40 (m, 2H, Ar), 8.73 (s, 1H, H-2); MS EI *m/z* (rel. %) 342/340 (M^+, 17/13), 263 (9), 261 (28), 110 (10), 109 (100); HRMS (EI) calcd. for $C_{12}H_7BrClFN_4$ 339.9527; found 339.9528.

6,6′-Dichloro-9,9′-di[(4-fluorophenyl)methyl]-9*H*,9′*H*-[8,8′]-bipurinyl (3m)

Isolated in the synthesis of **2m**; yield 6 mg (5%), colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 4H, CH_2), 6.84–6.88 (m, 4H, Ar), 7.41–7.44 (m, 4H, Ar), 8.90 (s, 2H, H–2); MS EI *m/z* (rel. %) 524/522 (M^+, 20/29), 417 (9), 415 (50), 413 (75), 216 (7), 109 (100); HRMS (EI) calcd. for $C_{24}H_{14}Cl_2F_2N_8$ 522.0687; found 522.0700.

8-Bromo-6-chloro-9-[(2-fluorophenyl)methyl]-9*H*-purine (2n)

Hexane, followed by EtOAc–hexane (1:2) and EtOAc, was used for flash chromatography; yield 32 mg (17%), pale yellow solid, mp 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (s, 2H, CH_2), 7.04–7.08 (m, 3H, Ar), 7.27–7.31 (m, 1H, Ar), 8.72 (s, 1H, H-2); MS EI *m/z* (rel. %) 342/340 (M^+, 22/17), 110 (9), 109 (100), 83 (15); HRMS (EI) calcd. for $C_{12}H_7BrClFN_4$ 339.9527; found 339.9537.

8-Bromo-2,6-dichloro-9-[(4-chlorophenyl)methyl]-9*H*-purine (2o)

Hexane, followed by EtOAc–hexane (1:8), EtOAc–hexane (1:2), and EtOAc, was used for flash chromatography; yield 64 mg (34%), yellow solid, mp 203–204 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.46 (s, 2H, CH_2), 7.29 (d, $J = 8.5$ Hz, Hz, 2H, Ar), 7.42 (d, $J = 8.5$ Hz, 2H, Ar); ^{13}C NMR (50 MHz, DMSO-d_6) δ 47.0, 128.7, 129.1, 130.8, 132.7, 133.6, 136.3, 148.2, 151.4, 154.4; MS EI m/z (rel. %) 394/392/390 (M^+, 11/17/9), 313 (10), 311 (11), 127 (42), 125 (100); HRMS (EI) calcd. for $C_{12}H_6BrCl_3N_4$ 389.8841; found 389.8832.

8-Bromo-6-chloro-9-[(3,4-dichlorophenyl)methyl]-9*H*-purine (2p)

Hexane, followed by EtOAc–hexane (1:8) and EtOAc–hexane (1:4), was used for flash chromatography; yield 37 mg (19%), yellow solid, mp 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H, CH_2), 7.16–7.20 (m, 1H, Ar), 7.30–7.46 (m, 2H, Ar), 8.73 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.1, 127.3, 130.0, 131.1, 131.8, 133.3, 133.7, 134.0, 149.8, 152.3, 152.8; MS EI m/z (rel. %) 394/392/390 (M^+, 18/27/14), 315 (15), 313 (45), 311 (47), 163 (11), 161 (65), 159 (100); HRMS (EI) calcd. for $C_{12}H_6BrCl_3N_4$ 389.8841; found 389.8834.

8-Bromo-6-chloro-9-[(3-chlorophenyl)methyl]-9*H*-purine (2q)

Hexane, followed by EtOAc–hexane (1:2) and EtOAc, was used for flash chromatography; yield 26 mg (15%), yellow wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (s, 2H, CH_2), 7.23–7.34 (m, 4H, Ar), 8.74 (s, 1H, H-2); MS EI m/z (rel. %) 360/358/356 (M^+, 9/20/12), 281 (6), 279 (34), 277 (52), 127 (35), 125 (100); HRMS (EI) calcd. for $C_{12}H_7BrCl_2N_4$ 355.9231; found 355.9227.

6,6′-Dichloro-9,9′-di[(3-chlorophenyl)methyl]-9*H*,9′*H*-[8,8′]-bipurinyl (3q)

Isolated in the synthesis of **2q**; yield 8 mg (6%), colorless solid, mp 245–246 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 4H, CH_2), 7.12–7.33 (m, 5H, Ar), 7.56 (br s, 2H, Ar), 8.91 (s, 2H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.1, 126.7, 128.5, 129.0, 130.9, 134.4, 137.5, 143.0, 152.6, 153.1, 153.7; MS EI m/z (rel. %) 558/556/554 (M^+, 20/40/30), 433 (32), 432 (20), 431 (97), 430 (21), 429 (100), 127 (28), 125 (79); HRMS (EI) calcd. for $C_{24}H_{14}Cl_4N_8$ 554.0096; found 554.0096.

8-Bromo-6-chloro-7-(phenylmethyl)-7*H*-purine (7a)

The reaction time after the addition of $BrCCl_2CCl_2Br$ was 2.30 h. Hexane, followed by EtOAc–hexane (1:3) and EtOAc–hexane (1:1), was used for flash chromatography, and the reaction was run in a 2-mmol scale; yield 148 mg (23%), yellow solid, mp 108–110 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75 (s, 2H, CH_2), 7.05–7.07 (m, 2H, Ph), 7.30–7.36 (m, 3H, Ph), 8.84 (s, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.5, 126.2, 126.3, 128.5, 129.2, 134.4, 140.1, 142.0, 152.9, 161.6; MS EI m/z (rel. %)

324/322 (M^+, 14/11), 280 (8), 278 (12), 245 (3), 91 (100); HRMS (EI) calcd. for $C_{12}H_8BrClN_4$ 321.9616; found 321.9618.

8-Bromo-2,6-dichloro-7-[4-methoxyphenyl)methyl]-7*H*-purine (7b)

The reaction time after the addition of $BrCCl_2CCl_2Br$ was 2.25 h. Hexane, followed by EtOAc–hexane (1:4) and EtOAc–hexane (1:1), was used for flash chromatography; yield 80 mg (41%), yellow solid, mp 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H, OCH_3), 5.65 (s, 2H, CH_2), 6.85 (d, $J = 8.6$ Hz, 2H, Ar), 7.03 (d, $J = 8.6$ Hz, 2H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.2, 55.3, 114.5, 123.5, 126.0, 127.9, 141.4, 142.6, 153.6, 159.7, 162.3; MS EI m/z (rel. %) 390/388/386 (M^+, 3/6/3), 344 (5), 342 (6), 122 (17), 121 (100), 78 (11), 77 (8); HRMS (EI) calcd. for $C_{13}H_9BrCl_2N_4O$ 385.9337; found 385.9340.

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