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## Synthesis and cytostatic activity of 7-arylsulfanyl-7-deazapurine bases and ribonucleosides†

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A series of 7-phenylsulfanyl- or 7-(2-thienyl)sulfanyl-7-deazapurine bases bearing diverse substituents at position 6 was prepared through C–H sulfenylation of 6-chloro-7-deazapurine followed by cross-coupling or nucleophilic substitutions. The corresponding ribonucleosides (as thia-analogues of known nucleoside cytostatics) were prepared by glycosylation of 6-chloro-7-arylsulfanyl-7-deazapurines followed by the same transformations at position 6. The 7-thienylsulfanyl-7-deazapurine bases **2b–2h** exerted micromolar cytostatic activities, whereas the nucleosides did not show significant biological effects.

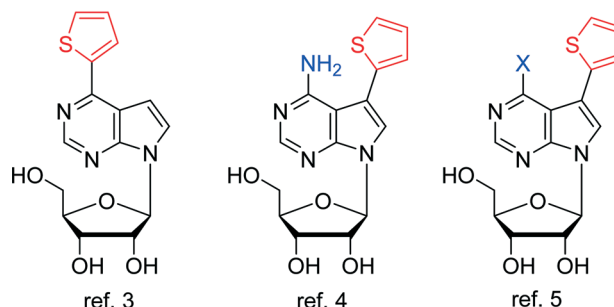
### 1. Introduction

Several base-modified purine nucleosides are important anti-tumor agents.<sup>1</sup> Also diverse substituted purine and deazapurine bases exert cytostatic effects, typically through inhibition of kinases and other ATP- or GTP-dependent enzymes.<sup>2</sup> Recently, we have discovered new types of nucleoside cytostatics: 6-hetaryl-7-deazapurine,<sup>3</sup> 7-hetaryl-7-deazaadenine<sup>4</sup> and 6-substituted 7-hetaryl-7-deazapurine<sup>5</sup> ribonucleosides. They all showed cytostatic effects at nanomolar concentrations and their mechanism of action is not yet fully understood. They are inhibitors of adenosine kinases,<sup>6,7</sup> but they are substrates at the same time and are phosphorylated to nucleoside triphosphates which then interfere with RNA synthesis or are incorporated to DNA and RNA. In all three series, the most active were derivatives bearing thiophene or furan (Chart 1).

C–H activation reactions are increasingly popular methods in organic synthesis<sup>8</sup> and were also applied in purines and deazapurines. In addition to relatively common and useful C–H arylations of purines reported by us<sup>9</sup> and by others,<sup>10</sup> we have recently reported C–H borylation<sup>11</sup> and C–H sulfenylation<sup>12</sup> of 7-deazapurines. The latter method gave

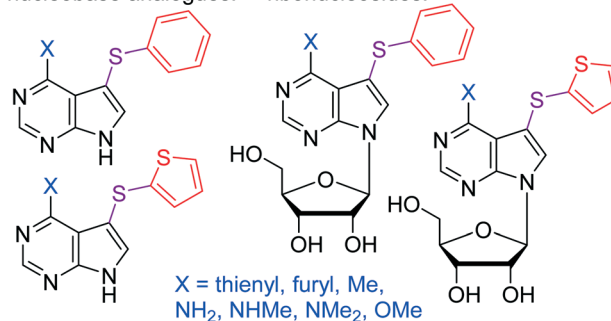
access to 7-arylsulfanyl-7-deazapurine bases,<sup>12</sup> which can be considered extended thia-analogues of 7-aryl-7-deazapurines that are components of the abovementioned nucleoside cytostatics.<sup>4,5</sup> Therefore, we decided to prepare a series of 7-phenylsulfanyl- and 7-(2-thienyl)sulfanyl-7-deazapurine bases and ribonucleosides for screening of their anticancer activity. These extended analogues should show whether the direct

Recently reported thienyl-deazapurine nucleoside cytostatics:



This work (extended thia-analogues):

nucleobase analogues:      ribonucleosides:



**Chart 1** Previously reported nucleoside cytostatics and the design of thia-analogues under study.

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conjugation of the (het)aryl group at position 7 is needed for the cytostatic activity of this class of 7-deazapurine nucleosides,<sup>4,5</sup> and in principle, they can also be metabolized to other sulfur-containing nucleosides.

## 2. Results and discussion

### 2.1. Chemistry

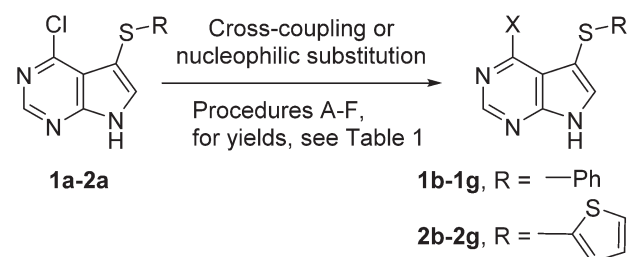
The proposed synthetic approach to our target 7-arylsulfanyl-7-deazapurines was based on recently developed direct C–H sulfenylation<sup>12</sup> of 6-chloro-7-deazapurine (correct IUPAC name: 4-chloro-7H-pyrrolo[2,3-d]pyrimidine) catalysed by CuI and 4,4-di-*tert*-butyl bipyridine (dtbpy) under oxygen atmosphere. This modified procedure (oxygen atmosphere and dtbpy) gave better results than previously published methods developed for related heterocycles.<sup>13</sup> By the reaction with diphenyldisulfide and bis(2-thienyl)disulfide, two modified 7-(het)arylsulfanyl-7-deazapurines **1a** and **2a** were synthesized in excellent yield (90% or 95%) (Scheme 1). After one-pot silylation by *N,O*-bis(trimethylsilyl)acetamide (BSA) of **1a** followed by glycosylation using commercially available 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- $\beta$ -D-ribofuranose, in analogy to the modified Vorbrüggen procedure,<sup>14</sup> the desired protected 7-phenylsulfanyl-7-deazapurine ribonucleoside intermediate **3a** was obtained in good yield of 49% (Scheme 1). In case of 7-thienylsulfanyl-7-deazapurine **2a**, the silylation was not completed under standard conditions and therefore 2 equiv. of BSA were used to fully dissolve the starting material, even though the yield of the following glycosylation to **4a** was only 30%, which was still sufficient to make multigram amounts of this key intermediate.

In order to synthesize a series of target 6-substituted 7-deazapurine nucleobase analogues, 6-chlorodeazapurine intermediates **1a** and **2a** were modified at position 6. The first goal was to introduce thiophene and furan substituents (previously reported<sup>3</sup> in cytostatic nucleosides). Since attempted Suzuki–Miyaura cross-coupling reactions with the corresponding thienyl- or furylboronic acids gave very low conversions (<10%), we further focused on the Stille

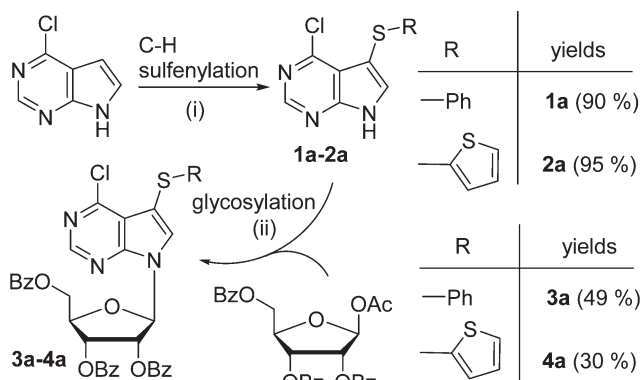
coupling. Thus the Stille reactions of **1a** or **2a** with thienyl- or furyl(tributyl)stannanes under standard conditions in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in DMF proceeded smoothly to give desired 6-hetaryl derivatives **1b–1c** and **2b–2c** in good yields (57–87%) (Scheme 2, Table 1, entries 1, 2, 7, and 8). A methyl group was introduced through Pd-catalysed cross-coupling of **1a** or **2a** with Me<sub>3</sub>Al to give **1d** and **2d** in good yields (entries 3 and 9). Finally, dimethylamino, methylamino and amino groups were introduced through aromatic nucleophilic substitution of 6-chloro-derivative **1a** or **2a** with amines or ammonia to give **1e–1f** and **2e–2f** in good yields (58–85%, entries 4–6, 10–12).

On the other hand, direct methoxylation of **1a–2a** by reaction with NaOMe in MeOH was not successful. Therefore, we first protected the NH at position 9 by a SEM group and then the methoxylation of **5a** or **6a** by MeONa proceeded quantitatively to give intermediates **5h** and **6h**. Final cleavage of the SEM groups by TFA afforded the desired 6-methoxy-7-deazapurines **1h** and **2h** in high yields (Scheme 3).

The target nucleoside analogues were prepared by analogous modifications of 6-chloro-7-(het)aryl-7-deazapurine nucleoside intermediates **3a** and **4a** (Scheme 4, Table 2). The Stille coupling reactions with thienyl- or furylstannanes gave the corresponding benzoylated 6-hetaryl-7-deazapurine nucleosides **3b** and **3c** and **4b** and **4c**, whereas the coupling with



**Scheme 2** Reagents and conditions, A: 2-thienylSnBu<sub>3</sub> (1.2 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5%), DMF, 100 °C, 18 h; B: 2-furylSnBu<sub>3</sub> (1.2 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5%), DMF, 100 °C, 18 h; C: Me<sub>3</sub>Al (3 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (5%), THF, 70 °C, 12 h; D: Me<sub>2</sub>NH in THF (3 equiv.), propan-2-ol, 70 °C, 24 h; E: aq. methylamine (40% [w/w]), dioxane, 120 °C, 18 h; F: aq. ammonia (25% [w/w]), dioxane, 120 °C, 18 h.

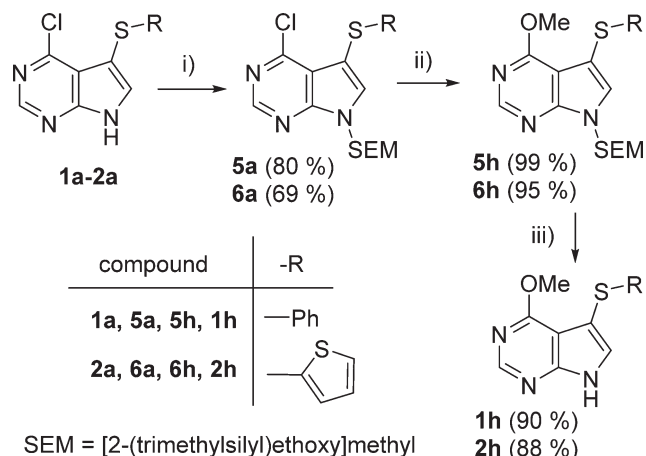


**Scheme 1** Reagents and conditions: i) RS-SR (1 equiv.), CuI (10%), dtbpy (20%), O<sub>2</sub>, DMF, 110 °C, 18 h. ii) 1. BSA (1 or 2 equiv.), MeCN, 15 min, rt, 2. TMSOTf (2 equiv.), sugar (1 equiv.), 80 °C, 6 h.

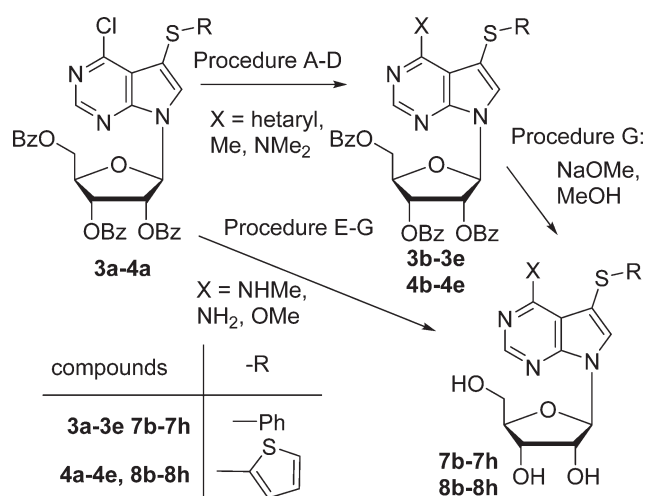
**Table 1** Yields of the transformations of 7-deazapurine bases

Entry	Procedure	Reagent	X–	R–	Product (yield %)
1	A	2-ThienylSnBu <sub>3</sub>	2-Thienyl–	Ph–	<b>1b</b> (80%)
2	B	2-FurylSnBu <sub>3</sub>	2-Furyl–	Ph–	<b>1c</b> (87%)
3	C	Me <sub>3</sub> Al	Me–	Ph–	<b>1d</b> (73%)
4	D	Me <sub>2</sub> NH	Me <sub>2</sub> N–	Ph–	<b>1e</b> (84%)
5	E	MeNH <sub>2</sub>	MeNH–	Ph–	<b>1f</b> (83%)
6	F	NH <sub>3</sub>	NH <sub>2</sub> –	Ph–	<b>1g</b> (85%)
7	A	2-ThienylSnBu <sub>3</sub>	2-Thienyl–	2-Thienyl–	<b>2b</b> (57%)
8	B	2-FurylSnBu <sub>3</sub>	2-Furyl–	2-Thienyl–	<b>2c</b> (72%)
9	C	Me <sub>3</sub> Al	Me–	2-Thienyl–	<b>2d</b> (66%)
10	D	Me <sub>2</sub> NH	Me <sub>2</sub> N–	2-Thienyl–	<b>2e</b> (63%)
11	E	MeNH <sub>2</sub>	MeNH–	2-Thienyl–	<b>2f</b> (58%)
12	F	NH <sub>3</sub>	NH <sub>2</sub> –	2-Thienyl–	<b>2g</b> (85%)





**Scheme 3** Reagents and conditions: i) NaH (60 wt%, 1.1 equiv.), SEM-Cl (1.1 equiv.), DMF, 0 °C to rt, 30 min; ii) 1 M MeONa in MeOH (2 equiv.), acetone, rt, 18 h; iii) 1. CF<sub>3</sub>COOH, rt, 18 h, 2. aq. ammonia (25% [w/w]), rt, 18 h.



**Scheme 4** Reagents and conditions, A: 2-thienylSnBu<sub>3</sub> (1.2 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5%), DMF, 100 °C, 18 h; B: 2-furylSnBu<sub>3</sub> (1.2 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5%), DMF, 100 °C, 18 h; C: Me<sub>3</sub>Al (3 equiv.), Pd(PPh<sub>3</sub>)<sub>4</sub> (5%), THF, 70 °C, 12 h; D: Me<sub>2</sub>NH in THF (3 equiv.), propan-2-ol, 70 °C, 24 h; E: aq. methylamine (40% [w/w]), dioxane, 120 °C, 18 h; F: aq. ammonia (25% [w/w]), dioxane, 120 °C, 18 h; G: 1 M MeONa in MeOH (1.5 equiv.), MeOH, rt, 18 h.

trimethylaluminum afforded 6-methyl derivatives 3d and 4d. The reactions with trimethylamine furnished 6-(dimethylamino)-7-deazapurine nucleosides 3e and 4e. Final Zemplén deprotection using sodium methoxide in methanol furnished free 6,7-disubstituted nucleosides 7b–7e and 8b–8e in 59–87% yields (Scheme 4, Table 2). Nucleophilic substitutions of protected nucleoside intermediate 3a or 4a with methylamine, ammonia or NaOMe proceeded with concomitant de-benzoylation to give directly unprotected 6-methylamino-, 6-amino or 6-methoxy-7-(het)arylsulfanyl-7-deazapurine ribonucleosides 7f–7h and 8f–8h in good yields.

## 2.2. Biological activity profiling

The *in vitro* cytotoxic/cytostatic activities of all final nucleobases 1b–1h and 2b–2h, as well as nucleosides 7b–7h and 8b–8h, were initially evaluated against seven cell lines derived from human solid tumors including lung (A549 cells) and colon (HCT116 and HCT116p53–/–) carcinomas, as well as leukemia cell lines (CCRF-CEM, CEM-DNR, K562 and K562-TAX) and, for comparison, non-malignant BJ and MRC-5 fibroblasts. Concentrations inhibiting the cell growth by 50% (IC<sub>50</sub>) were determined using a quantitative metabolic staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)<sup>15</sup> following a 3-day treatment. In addition, the anti-proliferative effect was tested against a human hepatocarcinoma Hep G2, human T-lymphoblastic promyelocytic leukemia HL-60 and cervical carcinoma HeLa S3 growing in liquid suspension. Cell viability was determined following a 3-day incubation using 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay.<sup>16</sup>

Selected results are summarized in Table 3 (for complete data including standard deviations, see Table S1 in the ESI†). Surprisingly, most of the nucleosides, 7 and 8, were entirely inactive in these assays with the exception of 6-amino-7-deazapurine nucleosides 7g and 8g showing moderate cytotoxic activities at >20 μM concentrations. Also none of the 7-phenylsulfanyl-7-deazapurine bases 1b–1h exerted any significant cytostatic activity. On the other hand, all the 7-(2-thienyl)sulfanyl-7-deazapurine bases bearing diverse

**Table 2** Yields of the transformations of 7-deazapurine nucleosides

Procedure	Reagent	X–	R–	Product (yield %)	Deprotection product (yield %)
A	ThienylSnBu <sub>3</sub>	2-Thienyl–	Ph–	3b (72%)	7b (75%)
B	FurylSnBu <sub>3</sub>	2-Furyl–	Ph–	3c (92%)	7c (78%)
C	Me <sub>3</sub> Al	Me–	Ph–	3d (55%)	7d (87%)
D	Me <sub>2</sub> NH	Me <sub>2</sub> N–	Ph–	3e (88%)	7e (87%)
E	MeNH <sub>2</sub>	MeNH–	Ph–	—	7f (90%)
F	NH <sub>3</sub>	NH <sub>2</sub> –	Ph–	—	7g (86%)
G	NaOMe	MeO–	Ph–	—	7h (75%)
A	ThienylSnBu <sub>3</sub>	2-Thienyl–	2-Thienyl–	4b (78%)	8b (59%)
B	FurylSnBu <sub>3</sub>	2-Furyl–	2-Thienyl–	4c (41%)	8c (57%)
C	Me <sub>3</sub> Al	Me–	2-Thienyl–	4d (67%)	8d (64%)
D	Me <sub>2</sub> NH	Me <sub>2</sub> N–	2-Thienyl–	4e (88%)	8e (65%)
E	MeNH <sub>2</sub>	MeNH–	2-Thienyl–	—	8f (75%)
F	NH <sub>3</sub>	NH <sub>2</sub> –	2-Thienyl–	—	8g (70%)
G	NaOMe	MeO–	2-Thienyl–	—	8h (77%)



**Table 3** Cytostatic activities of selected compounds

	IC <sub>50</sub> (μM)											
	A549	CCRF-CEM	CEM-DNR	HCT116	HCT116p53-	K562	K562-TAX	HepG2	HL60	HeLa S3	BJ	MRC-5
2b	16.19	10.55	17.67	13.03	5.06	5.14	21.664	>25	21.1	>25	23.38	54.48
2c	11.43	7.73	20.83	6.75	19.53	4.26	18.90	>25	7.63	8.49	22.06	32.87
2d	>50	>50	>50	38.12	29.10	13.99	>50	>25	>25	>25	>150	135.50
2e	19.80	14.63	35.25	11.01	27.54	3.83	22.14	>25	>25	>25	144.56	>150
2f	28.58	14.72	26.15	18.98	45.30	4.95	21.00	>25	13.5	17.6	132.24	148.21
2g	22.82	16.68	20.34	22.79	>50	17.88	17.92	>25	13.9	17.9	>150	135.71
2h	21.47	18.23	>50	17.15	>50	>50	43.95	>25	>25	23.9	122.60	148.13
7g	22.91	33.96	>50	20.80	22.41	23.09	29.62	>25	>25	>25	67.88	67.70
8g	43.76	64.66	>100	36.72	23.18	23.43	55.77	>25	>25	>25	93.59	138.24

substituents at position 6 showed significant cytostatic effects at micromolar concentrations. The most active were 6-hetaryl- (2b and 2c) and 6-methylamino and -dimethylamino (2e and 2f) derivatives having IC<sub>50</sub> values in the low micromolar range. Compounds 2e and 2f were non-toxic to BJ and MRC-5 fibroblasts showing a promising therapeutic index.

Since the nucleosides 7 and 8 were inactive with the exception of moderately active adenosine analogues 7g and 8g (thia-analogues of cytostatic 7-aryl-7-deazaadenosines<sup>4</sup>), it can be concluded that replacement of the (het)aryl group at position 7 by the extended (het)arylsulfanyl group is not tolerated by the biological target(s) of the previously developed nucleoside cytostatics.<sup>3–5</sup> Further studies will be necessary to explain the significant cytostatic effect of the 7-(thienylsulfanyl)-7-deazapurine bases which is apparently caused by a different mechanism (presumably by kinase inhibition).

In addition, all compounds were also tested on antiviral activity (HCV 1B and 2A replicon and RSV), antimicrobial activity (panel of gram-positive and gram-negative bacteria) and antifungal activity (several strains of *Candida* species) but did not show any significant activity in these assays.

### 3. Conclusions

In conclusion, we have developed a facile methodology for the synthesis of a series of 7-(het)arylsulfanyl-7-deazapurine bases and nucleosides bearing diverse substituents at position 6. It was based on Cu-catalysed C–H sulfenylation of 6-chloro-7-deazapurine followed by glycosidation and/or cross-coupling or nucleophilic substitutions. While the ribonucleoside analogues were almost entirely inactive, most of the 7-(thienylsulfanyl)-7-deazapurine bases showed significant cytostatic activities.

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### Notes and references

- Reviews: (a) W. B. Parker, J. A. Secrist III and W. R. Waud, *Curr. Opin. Invest. Drugs*, 2004, 5, 592–596; (b) C. M. Galmarini, F. Popowycz and B. Joseph, *Curr. Med. Chem.*, 2008, 15, 1072–1082; (c) W. B. Parker, *Chem. Rev.*, 2009, 109, 2880–2893.
- Reviews: (a) M. Legraverend and D. S. Grierson, *Bioorg. Med. Chem.*, 2006, 14, 3987–4006; (b) S. Tumkevicius and J. Dodonova, *Chem. Heterocycl. Compd.*, 2012, 48, 258–279.
- P. Nauš, R. Pohl, I. Votruba, P. Džubák, M. Hajdúch, R. Ameral, G. Birkuš, T. Wang, A. S. Ray, R. Mackman, T. Cihlar and M. Hocek, *J. Med. Chem.*, 2010, 53, 460–470.
- A. Bourderieux, P. Nauš, P. Perliková, R. Pohl, I. Pichová, I. Votruba, P. Džubák, P. Konečný, M. Hajdúch, K. M. Stray, T. Wang, A. S. Ray, J. Y. Feng, G. Birkus, T. Cihlar and M. Hocek, *J. Med. Chem.*, 2011, 54, 5498–5507.
- P. Nauš, O. Caletková, P. Konečný, P. Džubák, K. Bogdanová, M. Kolář, J. Vrbková, L. Slavětinská, E. Tloušťová, P. Perliková, M. Hajdúch and M. Hocek, *J. Med. Chem.*, 2014, 57, 1097–1110.
- P. Perliková, P. Konečný, P. Nauš, J. Snášel, I. Votruba, P. Džubák, I. Pichová, M. Hajdúch and M. Hocek, *Med. Chem. Commun.*, 2013, 4, 1497–1500.
- J. Snášel, P. Nauš, J. Dostál, A. Hnízda, J. Fanfrlík, J. Brynda, A. Bourderieux, M. Dušek, H. Dvořáková, J. Stolaříková, H. Zábranská, R. Pohl, P. Konečný, P. Džubák, I. Votruba, M. Hajdúch, P. Řezáčová, V. Veverka, M. Hocek and I. Pichová, *J. Med. Chem.*, 2014, 57, 8268–8279.
- C-H Activation, Topics in Current Chemistry*, ed. J.-Q. Yu and Z. Shi, Springer, 2010, vol. 292, pp. 1–380 (whole book).
- (a) I. Čerňa, R. Pohl, B. Klepetářová and M. Hocek, *Org. Lett.*, 2006, 8, 5389–5392; (b) I. Čerňa, R. Pohl and M. Hocek, *Chem. Commun.*, 2007, 4729–4730; (c) I. Čerňa, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2008, 73, 9048–9054; (d) I. Čerňa, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2010, 75, 2302–2308.
- (a) T. E. Storr, A. G. Firth, K. Wilson, K. Darley, C. G. Baumann and I. J. S. Fairlamb, *Tetrahedron*, 2008, 64,



- 6125–6137; (b) T. E. Storr, C. G. Baumann, R. J. Thatcher, S. De Ornellas, A. C. Whitwood and I. J. S. Fairlamb, *J. Org. Chem.*, 2009, **74**, 5810–5821; (c) S. Sahnoun, S. Messaoudi, J.-D. Brion and M. Alami, *Org. Biomol. Chem.*, 2009, **7**, 4271–4278; (d) B. Vaňková, V. Krchňák, M. Soural and J. Hlaváč, *ACS Comb. Sci.*, 2011, **13**, 496–500.
- 11 M. Klečka, R. Pohl, B. Klepetářová and M. Hocek, *Org. Biomol. Chem.*, 2009, **7**, 866–868.
  - 12 M. Klečka, R. Pohl, J. Čejka and M. Hocek, *Org. Biomol. Chem.*, 2013, **11**, 5189–5193.
  - 13 C–H sulfenylation: (a) Z. Li, J. Hong and X. Z. Li, *Tetrahedron*, 2011, **67**, 3690–3697; (b) G. L. Regina, V. Gatti, V. Famiglini, F. Piscitelli and R. Silvestri, *ACS Comb. Sci.*, 2012, **14**, 258–262; (c) L. H. Zou, J. Reball, J. Mottweiler and C. Bolm, *Chem. Commun.*, 2012, **48**, 11307–11309; (d) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang and X. Liu, *J. Org. Chem.*, 2011, **76**, 8999–9007; (e) Ch. Dai, Z. Xu, F. Huang, Z. Yu and Y.-F. Gao, *J. Org. Chem.*, 2012, **77**, 4414–4419; (f) X.-L. Fang, R.-Y. Tang, P. Zhong and J.-H. Li, *Synthesis*, 2009, **24**, 4183–4189.
  - 14 X. Ming and F. Seela, *Tetrahedron*, 2007, **63**, 9850–9861.
  - 15 (a) F. Denizot and R. Lang, *J. Immunol. Methods*, 1986, **89**, 271–277; (b) M. Hajduch, V. Mihal, V. Minarik, E. Faber, M. Safarova, E. Weigl and P. Antalek, *Cytotechnology*, 1996, **19**, 243–245.
  - 16 D. A. Scudiero, R. H. Shoemaker, K. D. Paull, A. Monks, S. Tierney, T. H. Nofziger, M. J. Currens, D. Seniff and M. R. Boyd, *Cancer Res.*, 1988, **48**, 4827–4833.

