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Direct C–H sulfenylation of purines and deazapurines†

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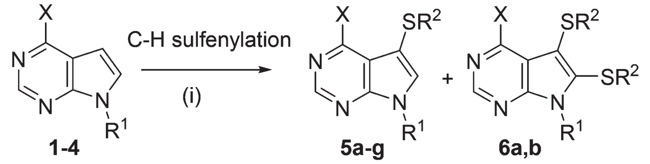
A general method for Cu-catalyzed C–H sulfenylation of purines, 7-deaza- and 9-deazapurines with aryl- or alkyldisulfides has been developed. In purines, the reaction occurs at position 8, in 7-deazapurines at position 7 and in 9-deazapurines at position 9, leading to new interesting arylsulfanyl derivatives of purine or deazapurine bases. The resulting 8-arylsulfanylpurines undergo Liebesking–Srogl coupling with arylstannanes or boronic acids, whereas the (arylsulfanyl)deazapurines are not reactive under these conditions.

Tri- and tetrasubstituted purines[1] and their analogues show a great variety of biological activities. However, compared to purines, 7-deazapurines (pyrrolo[2,3-*d*]pyrimidines) and 9-deazapurines (pyrrolo[3,2-*d*]pyrimidines) have been studied less systematically due to underdeveloped synthesis and substitution chemistry. Among the most important biological effects of deazapurines one should mention compound TWS119[2] which directs differentiation of neuronal cells in mice. Several types of 7-deazapurine nucleosides display antibiotic,[3] antiviral[4] or cytostatic[5] effects. In order to synthesize libraries of tri- and tetrasubstituted purines, a combination of inherently orthogonal cross-coupling reactions with C–H activations has been developed in our group.[6] 6,8,9-Trisubstituted 7-deazapurines were prepared by a "one pot" sequence of C–H borylation followed by Suzuki coupling.[7] In order to extend the portfolio of reactions and substituents available for modification of purines and deazapurines, we report here on direct C–H sulfenylations leading to hitherto unknown arylsulfanyl-derivatives and some follow-up reactions.

Direct C–H sulfenylations[8] have become quite popular in recent years since they lead to hetarylthioethers suitable for further functional group transformations by Liebeskind–Srogl cross-coupling[9] or oxidation and aminations.[10] Also some examples of biologically active hetarylthioesters were previously described.[11]

Our project started with the study of C–H sulfenylations of 7-deazapurines which are closely related to indoles. The model starting compound of choice was 6-phenyl-7-deazapurine (**1**). We started by testing several literature catalytic systems and conditions for direct C–H sulfenylation (Scheme 1).[8] The most efficient was the reaction of **1** with disulphides in the presence of copper(I) catalyst (by analogy to the literature[8a] but replacing DMSO with DMF) giving the desired 7-substituted product **5a** in excellent yield (96%, Table 1, entry 1). On a larger scale, a 7,8-bis(phenylsulfanyl) derivative **6a** was also isolated as a minor by-product (3%, entry 1). The reaction work-up by EDTA was very important to break up stable complexes of the product with copper (without such a work-up, the isolated yield of **5a** was only moderate, ~50%). These optimised conditions were then used for the synthesis of three other



Scheme 1 Reagents and conditions: (i) $R^2S–SR^2$ (0.75 equiv.), CuI (10%), air, DMF, 110 °C, 18–60 h.

Table 1 Direct C–H sulfenylation of 7-deazapurines

Entry	Start. compd.	R^1	X	R^2	Product (yield)
1	**1**	H	Ph–	Ph–	**5a** (96%) + **6a** (3%)
2[a]	**1**	H	Ph–	Me–	**5b** (71%) + **6b** (15%)
3	**1**	H	Ph–	4-MeO–Ph–	**5c** (91%)
4	**1**	H	Ph–	4-NO_2–Ph–	**5d** (47%)
5[b]	**2**	Bn	Ph–	Ph–	**5e** (20%)[b]
6[a]	**3**	H	Cl–	Ph–	**5f** (90%)
7	**4**	H	NH_2–	Ph–	**5g** (79%)

[a] 5 equiv. of $R^2S–SR^2$. [b] 2.5 equiv. of $R^2S–SR^2$ and recovery of the starting compound (71%).

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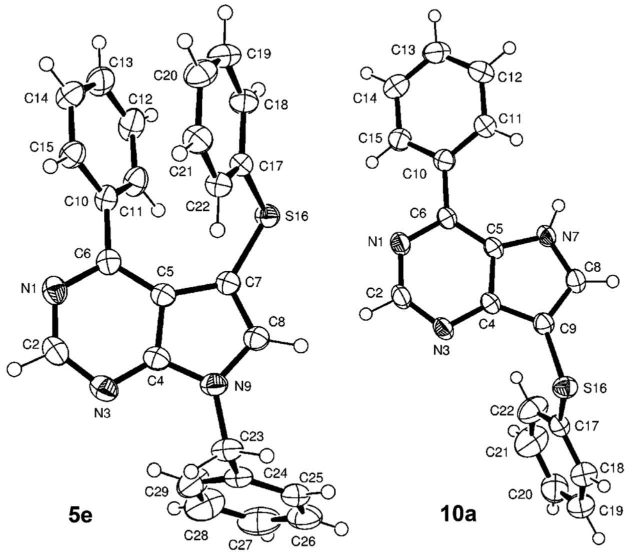
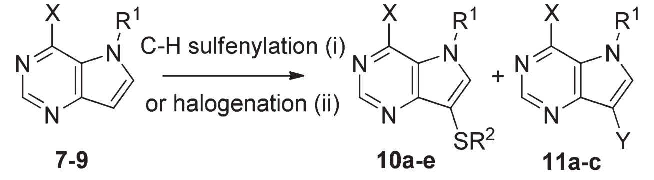


Fig. 1 ORTEP drawings of crystal structures of compounds **5e** (CCDC 926544) and **10a** (CCDC 926543).



Scheme 2 Reagents and conditions: (i) $R^2S–SR^2$ (1.5 equiv.), CuI (10%), air, bpy or dtbpy (0.2 equiv.), DMF, 110 °C, 48–90 h; (ii) CuI or $CuBr_2$ (1.1 equiv.), air, DMF, 110 °C, 18 h.

Table 2 Direct C–H sulfenylation of 9-deazapurines

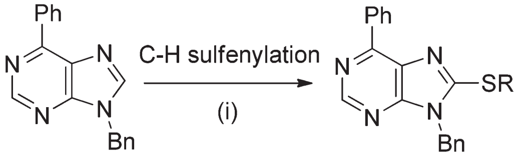
Entry	Start. compd.	Ligand	R^1	X	R^2 (or Y)	Product (yield)
1[a]	7	—	H	Ph	Ph	**10a** (14%) + **11a** (9%)
2	7	bpy	H	Ph	Ph	**10a** (98%)
3	7	bpy	H	Ph	Me	**10b** (30%)[c]
4	7	bpy	H	Ph	4-MeO–Ph	**10c** (85%)
5	7	bpy	H	Ph	$4\text{-}NO_2$–Ph	**10d** (50%)
6	8	bpy	Bn	Ph	Ph	No reaction
7	9	bpy	H	Cl	Ph	Complex mixture
8[b]	9	dtbpy	H	Cl	Ph	**10e** (90%)
9	7	dtbpy	H	Ph	Ph	**10a** (98%)
10	7	dtbpy	H	Ph	Me	**10b** (25%)
11	7	dtbpy	H	Ph	4-MeO–Ph	**10c** (41%)
12	7	dtbpy	H	Ph	$4\text{-}NO_2$–Ph	No reaction
13[d]	7	—	H	Ph	Y = I	**11a** (81%)
14[d]	7	—	H	Ph	Y = Br	**11b** (75%)
15[d]	9	—	H	Cl	Y = I	**11c** (65%)

[a] No bpy added. [b] 7 equiv. of $R^2S–SR^2$. [c] Recovery of the starting compound (40%). [d] Condition (ii) applied.

examples, 7-alkyl- or -arylsulfanyl derivatives **5b–d**. While the reactions with methyl and methoxyphenyl disulfide gave products **5b**, **c** in good yields (entries 2, 3), the yield of nitrophenylsulfanyl derivative **5d** was moderate. The reaction with 9-benzylated 6-phenyl-7-deazapurine **2** gives the 7-substituted product **5e** in poor yield (20%, entry 5) due to low conversion. The structure of **5e** was confirmed by X-ray (Fig. 1). Apparently, the free NH at position 7 is crucial for the efficiency of this reaction. Another interesting substrate was 6-chloro-7-deazapurine **3** that is suitable for further functional group transformations at position 6. In this case, the C–H sulfenylation also proceeded well to give the desired product **5f** in high (90%) yield (entry 6) without any trace of nucleophilic substitution at position 6. Also the reaction of 7-deazaadenine (**4**) proceeded under the same conditions to give 7-(phenylsulfanyl)-7-deazaadenine (**5g**) in good yield (entry 7) (Scheme 1).

The same C–H sulfenylation protocol was then tested on 9-deazapurines (pyrrolo[3,2-*d*]pyrimidines, Scheme 2). However, in this case a competitive iodination of the heterocycle by CuI occurred (Table 2, entry 1). The halogenation was suppressed by complexation of the copper catalyst by a 2,2′-dipyridine (bpy) ligand. The reaction of 6-phenyl-9-deazapurine (**7**) with diphenyl disulfide in the presence of CuI + bpy (entry 2) gave quantitatively the desired 9-phenylsulfanyl derivative **10a** (for confirmation of its structure by X-ray, see Fig. 1). The reaction with other disulfides allowed us to synthesize the target 9-alkyl- or -arylsulfanyl derivatives in moderate (**10b** and **10d**, 30% and 55%, respectively, entries 3, 5) or high yields (**10c**, 85%, entry 4). The reaction with 9-benzyl-6-phenyl-9-deazapurine **8** did not proceed at all (entry 6). The C–H sulfenylation of 6-chloro-9-deazapurine **9** under standard conditions gave a complex mixture of products (TLC, entry 7). Therefore, we tried the reaction in the presence of a more bulky and electron-rich ligand dtbpy (4,4′-di-*tert*-butyl-2,2′-dipyridine, for more details of the optimization, see ESI†) to give the desired product **10e** in good 90% yield (entry 8). The dtbpy ligand was then also tested in the reactions of **7** with diverse disulfides. The phenylsulfenylation proceeded with quantitative conversion (as with bpy) but in the case of other disulfides, the yields of products were lower than with bpy (entries 10–12). Therefore, the dtbpy ligand was only practical for the reaction of 6-chloro derivative **9**. On the other hand, using a stoichiometric amount of CuI or $CuBr_2$ in the absence of bpy led to the formation of 9-halogenated products **11a–c** in high yields (entries 8–10). The same reaction with CuCl or $CuCl_2$ proceeded as well but only in poor yield. Using the same catalytic system (CuI + bpy) for 7-deazapurine **1** gave the 7-substituted product **5a** in poor yield due to low conversion.

Our further efforts focused on the direct C–H sulfenylation of purines. Unfortunately, employing the same catalytic systems as above, no sulfenylation was observed. Using an alternative protocol based on a Lewis acid activation,[8e] the reaction proceeded to give 8-(phenylsulfanyl)purine **13a** in moderate ~40% yield. Finally, the sulfenylation in the presence of *t*BuOLi[8c] in dioxane at 130 °C for 120 h gave the desired product **13a** in acceptable 60% yield (Scheme 3, Table 3, entry 1). An analogous reaction with electron-rich bis(methoxyphenyl)disulphide proceeded well to give **13b** in 56% (entry 2), whereas the reaction with electron-poor bis(nitrophenyl)disulfide did not work.



12 13a-b

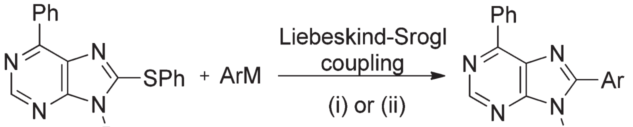
Scheme 3 Reagents and conditions: RS–SR (2.5 equiv.), *t*BuOLi (3 equiv.), 1,4-dioxane, 130 °C, 120 h.

Table 3 Direct C–H sulfenylations of purine **12**

Entry	X	R	Product (yield)
1	Ph–	Ph–	**13a** (60%)
2	Ph–	4-MeO–Ph–	**13b** (56%)
3	Ph–	4-NO_2–Ph–	No reaction

Having access to the arylsulfanyl derivatives of purines and deazapurines, we further explored their synthetic applications. The most obvious option was the Liebeskind–Srogl cross-coupling reaction.[9] The reactions of the 8-(phenylsulfanyl)purine **13a** with phenylboronic acid and diverse stannanes performed under standard conditions proceeded generally well to give the desired 8-aryl products **14a–14c** in high yields (57–83%, Scheme 4, Table 4).

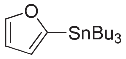
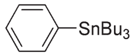
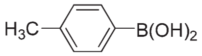
Surprisingly, analogous Liebeskind–Srogl reactions of 7-phenylsulfanyl-7-deazapurine **5a** or 9-phenylsulfanyl-9-deazapurine **10a** did not proceed at all. Neither stannanes nor boronic acids gave any reaction under a number of different catalytic systems (Cu, Pd, In) and conditions tried (including MW irradiation). This lack of reactivity of arylsulfanyl-deazapurines is probably due to the electron-rich nature of the deazapurine moiety which prevents efficient oxidative addition. Since no literature example of the Liebeskind–Srogl reaction of the related 3-(arylsulfanyl)indole was known, we have tried this reaction under the standard conditions and have confirmed that it does not proceed either. Apparently, this reaction is not applicable for electron-rich indole-type heterocycles.



13a 14a-c

Scheme 4 Reagents and conditions: (i) $ArSnBu_3$ (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol%), CuMeSal (2.2 equiv.), 50 °C, THF, 17 h; (ii) $ArB(OH)_2$, $Pd_2(dba)_3$ (4 mol%), $(2\text{-furyl})_3P$ (16 mol%), CuTc (1.3 equiv.), 50 °C, THF, 18 h.

Table 4 The Liebeskind–Srogl reactions of 8-(phenylsulfanyl)purine **13a**

Entry	Ar–M	Product (yield)
1		**14a** (70%)
2		**14b** (83%)
3		**14c** (54%)[a]

[a] Recovery of the starting compound (15%).

In conclusion, the Cu-catalyzed C–H sulfenylation of 7- and 9-deazapurines proceeded very well and selectively at position 7 or 9, respectively, to give novel and interesting (arylsulfanyl)-deazapurine derivatives. On the other hand, the C–H sulfenylation of purines was less efficient, and the conditions had to be changed. However, the 8-(arylsulfanyl)purines smoothly undergo the Liebeskind–Srogl cross-coupling reactions leading to 8-arylpurines, whereas the 7- and 9-arylsulfanylpurines were not reactive in these reactions. Since all these C–H sulfenylations can be performed with 6-chloro(deaza)purines, there is a potential in combination with classical cross-couplings in the synthesis of libraries of new di- and trisubstituted purines and deazapurine derivatives combining aryl(alkyl)sulfanyl and aryl or amino substituents for biological activity screening. Also there is a further potential in testing other reactivities of the (arylsulfanyl)deazapurines (oxidations, other couplings, *etc.*). Studies along these lines are under way in our laboratory.

Experimental

For a complete set of experimental procedures and characterization data, see ESI.†

Sulfenylation of 7-deazapurines. General procedure

A mixture of 7-deazapurines **1–4** (2 mmol), disulphides (1.5 mmol), and CuI (0.2 mmol, 10 mol%) in DMF (20 mL) was stirred at 110 °C under an air atmosphere for 18 hours until complete consumption of the starting material as monitored by TLC. The solution was then cooled to room temperature, diluted with EtOAc (30 mL), and washed with a 1 M solution of sodium salt of EDTA (20 mL). The aqueous solution was then extracted three times with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel.

4-Phenyl-5-(phenylsulfanyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (5a). 6-Phenyl-7-deazapurine **1** (390 mg, 2 mmol) and diphenyldisulfide (328 mg, 1.5 mmol) were used as starting compounds to give products **5a** (582 mg, 96%) and **6a** (25 mg, 3%) as white solids after chromatography eluting with hexane–EtOAc 5 : 1 to 1 : 1. Crystallization in hexane–EtOAc gave white needles. M.p. 184–186 °C. ^1H NMR (499.8 MHz, DMSO-d_6): 6.70 (m, 2H, H-*o*-SPh); 6.99 (m, 1H, H-*p*-SPh); 7.06 (m, 2H, H-*m*-SPh); 7.27 (m, 2H, H-*m*-Ph); 7.38 (m, 1H, H-*p*-Ph); 7.53 (m, 2H, H-*o*-Ph); 8.05 (d, 1H, $J_{6,NH}$ = 2.5, H-6); 8.88 (s, 1H, H-2); 12.86 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 99.90 (C-5); 115.26 (C-4a); 125.25 (CH-*p*-SPh); 126.04 (CH-*o*-SPh); 127.29 (CH-*m*-Ph); 128.80 (CH-*m*-SPh); 129.23 (CH-*p*-Ph); 129.86 (CH-*o*-Ph); 135.69 (CH-6); 137.04 (C-i-Ph); 138.47 (C-i-SPh); 151.53 (CH-2); 153.55 (C-7a); 159.40 (C-4). IR(KBr): 3104, 3059, 2988, 2862, 2818, 1598, 1581, 1551, 1478, 1435, 1322. HRMS (ESI) calculated for $C_{18}H_{14}N_3S$: 304.0902; found: 304.0901. Anal. calculated for $C_{18}H_{13}N_3S$ (303.08): C 71.26%, H 4.32%, N 13.85%, S 10.57%; found: C 71.07%, H 4.15%, N 13.57%, S 10.47%.

Sulfenylation of 9-deazapurines. General procedure

A mixture of CuI (0.2 mmol, 10 mol%) and 2,2′-bipyridine (0.4 mmol, 20 mol%) in DMF (10 mL) was stirred at rt for 15 minutes and then it was added to a mixture of 9-deazapurines **7–9** (2 mmol) and disulphides (3 mmol) in DMF (20 mL) and then was stirred at 110 °C under an air atmosphere for 48 hours until complete consumption of the starting material as monitored by TLC. The solution was then cooled to room temperature, diluted with EtOAc (30 mL), and washed with a 1 M solution of sodium salt of EDTA (20 mL). The aqueous solution was then extracted three times with EtOAc and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel.

4-Phenyl-7-(phenylsulfanyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (10a). 6-Phenyl-9-deazapurine **7** (390 mg, 2 mmol) and diphenyldisulfide (656 mg, 3 mmol) were used as starting compounds to give product **10a** (595 mg, 96%) as white solids after chromatography eluting with hexane–EtOAc 5 : 1 to 1 : 2. Crystallization in hexane–EtOAc gave white needles. M.p. 210–216 °C. ^{1}H NMR (499.8 MHz, DMSO-d_6): 7.10 (m, 3H, H-*o*,*p*-SPh); 7.22 (m, 2H, H-*m*-SPh); 7.61 (m, 1H, H-*p*-Ph); 7.63 (m, 2H, H-*m*-Ph); 8.11 (m, 2H, H-*o*-Ph); 8.29 (s, 1H, H-6); 8.95 (s, 1H, H-2); 12.56 (bs, 1H, NH). ^{13}C NMR (125.7 MHz, DMSO-d_6): 101.28 (C-7); 124.83 (C-4a); 125.30 (CH-*p*-SPh); 126.02 (CH-*o*-SPh); 128.99 (CH-*o*-Ph); 129.10, 129.15 (CH-*m*-Ph, CH-*m*-SPh); 130.61 (CH-*p*-Ph); 135.77 (C-i-Ph); 138.63 (C-i-SPh); 140.37 (CH-6); 148.88 (C-4); 151.29 (CH-2); 151.43 (C-7a). IR(KBr): 3066, 2835, 1594, 1542, 1505, 1490, 1480, 1429. HRMS (ESI) calculated for $C_{18}H_{14}N_3S$: 304.0902; found: 304.0902.

Sulfenylation of 9-benzyl-6-phenyl-9*H*-purine. General procedure

A 20 mL sealable tube equipped with a magnetic stirring bar was charged with all solid reaction components, 9-benzyl-6-phenyl-9*H*-purine **12** (286 mg, 1 mmol), disulfide (2.5 mmol), *t*BuOLi (240 mg, 3 mmol) and 1,4-dioxane (2 mL) *via* a syringe. The vessel was closed by a Teflon-coated screw cap under Ar and was placed in a pre-heated oil bath at 130 °C and stirred until complete consumption of the starting material as monitored by TLC, approx. 130 hours. It was cooled to room temperature and diluted with ethyl acetate (15 mL). The resulting solution was directly filtered through a filter paper and concentrated under reduced pressure.

9-Benzyl-6-phenyl-8-(phenylsulfanyl)-9*H*-purine (13a). Diphenyldisulfide (546 mg, 2.5 mmol) was used as the starting compound to give product **13a** (237 mg, 60%) as white crystals after chromatography eluting with hexane–EtOAc 5 : 1 to 1 : 2. M.p. 101–104 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): 5.50 (s, 2H, CH_2Ph); 7.27–7.35 (m, 5H, H-*o*,*m*,*p*-Bn); 7.37–7.41 (m, 5H, H-*m*,*p*-PhS); 7.45–7.50 (m, 3H, H-*m*,*p*-Ph); 7.59 (m, 2H, H-*o*-PhS); 8.74 (m, 2H, H-*o*-Ph); 8.96 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 46.59 (CH_2Ph); 127.75 (CH-*o*-Bn); 128.18 (CH-*p*-Bn); 128.50 (CH-*m*-Ph); 128.68 (C-i-PhS); 128.82 (CH-*m*-Bn); 129.03 (CH-*p*-PhS); 129.37 (CH-*m*-PhS); 129.68 (CH-*o*-Ph); 130.78 (CH-*p*-Ph); 131.16 (C-5); 132.91 (CH-*o*-PhS); 135.24 (C-i-Bn); 135.54 (C-i-Ph); 151.95 (CH-2); 152.37 (C-6); 152.92 (C-8); 154.46 (C-4). IR(KBr): 2921, 2851, 1580, 1561, 1495, 1459, 1429, 1258, 764. HRMS (ESI) calculated for $C_{24}H_{19}N_4S$: 395.1325; found: 395.1323.

Liebeskind–Srogl cross-coupling of 9-benzyl-6-phenyl-8-(phenylsulfanyl)-9*H*-purine with stannanes. General procedure

To the mixture of CuMeSal (47 mg, 0.22 mmol, 2.2 equiv.), Pd-$(PPh_3)_4$ (5.8 mg, 0.005 mmol, 0.05 equiv.) and 9-benzyl-6-phenyl-8-(phenylthio)-9*H*-purine **13a** (39 mg, 0.1 mmol, 1.0 equiv.) and stannane (0.12 mmol, 1.2 equiv.) in THF (2 mL) were added. The reaction mixture was stirred under nitrogen at 50 °C for 18 h, and then 10% aqueous NH_4OH (10 mL) was added and the mixture was stirred for an additional 10 min. The reaction mixture was filtered through a plug of Celite, and the filtrate was extracted with ethylacetate (3 × 15 mL). The organic layer was washed with brine (5 mL), dried over $NaSO_4$, and evaporated. The crude product was purified by column chromatography on silica gel.

9-Benzyl-8-(furan-2-yl)-6-phenyl-9*H*-purine (14a). 2-(Tri-*n*-butylstannyl)furan (38 μL, 0.12 mmol, 1.2 equiv.) was used as the starting compound to give product **14a** (25 mg, 70%) as white crystals after chromatography eluting with hexane–EtOAc 5 : 1 to 2 : 1. M.p. 135–141 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 5.86 (s, 2H, CH_2Ph); 6.59 (dd, 1H, $J_{4,3}$ = 3.6, $J_{4,5}$ = 1.8, H-4-furyl); 7.22 (m, 2H, H-*o*-Bn); 7.26 (m, 1H, H-*p*-Bn); 7.28 (m, 2H, H-*m*-Bn); 7.29 (dd, 1H, $J_{3,4}$ = 3.6, $J_{3,5}$ = 0.8, H-3-furyl); 7.52 (m, 1H, H-*p*-Ph); 7.58 (m, 2H, H-*m*-Ph); 7.64 (dd, 1H, $J_{5,4}$ = 1.8, $J_{5,3}$ = 0.8, H-5-furyl); 8.88 (m, 2H, H-*o*-Ph); 9.02 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 46.96 (CH_2Ph); 112.34 (CH-4-furyl); 114.88 (CH-3-furyl);126.85 (CH-*o*-Bn); 127.84 (CH-*p*-Bn); 128.62 (CH-*m*-Ph); 128.76 (CH-*m*-Bn); 129.79 (CH-*o*-Ph); 130.82 (CH-*p*-Ph); 131.05 (C-5); 135.75 (C-i-Ph); 136.16 (C-i-Bn); 144.70 (C-2-furyl); 144.93 (CH-5-furyl); 145.47 (C-8); 152.27 (CH-2); 153.64 (C-6); 154.18 (C-4). IR(KBr): 3068, 1605, 1603, 1562, 1497, 1454, 1334, 1321, 1016. HRMS (ESI) calculated for $C_{22}H_{17}ON_4$: 353.1397; found: 353.1397.

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