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Influence of 2-Substituent on the Activity of Imidazo[1,2-*a*] Pyridine Derivatives Against Human Cytomegalovirus

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Abstract—The synthesis of various 2-substituted imidazo[1,2-*a*]pyridine bearing a thioether side chain in position 3 was reported. The new compounds were characterized by ^{1}H and ^{13}C NMR spectra. A conformational study was obtained by X-ray crystallographic analysis for 2-biphen-4-ylimidazopyridine **7**. The antiviral activity against human cytomegalovirus (HCMV) was investigated. It was strongly influenced by the nature of C-2 substituent.

Introduction

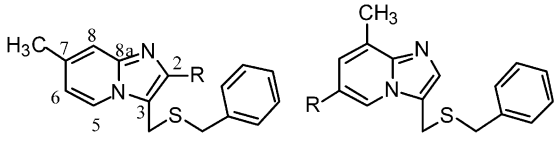
Human cytomegalovirus (HCMV) is a highly prevalent member of the herpesvirus family responsible for severe illness in newborns[1] and immunosuppressed patients, where it can lead to gastrointestinal infections, retinitis, pneumonitis, and encephalopathy.[2]

In previous communications, we have reported the synthesis and the antiviral activities of imidazo[1,2-*a*]pyridine derivatives bearing a 3-alkyl or 3-arylalkylthiomethyl side chain.[3–6] Some of these compounds were shown to be potent inhibitors of HCMV. In these studies, we were principally interested by studying the influence of the pyridinic substituent on the antiviral activity. It appeared that 7-methyl, 8-methyl and 6-bromo-8-methylimidazo[1,2-*a*] pyridine derivatives (**I**, **II**, **III**, Fig. 1) were potent inhibitors of HCMV. At this point, only little information on the influence of the 2-substitution was obtained. A phenyl group (compound **IV**) was found to diminish activity.[6] We have now synthesized and determined the antiviral activity of 2-alkyl, cycloalkyl, aryl and heteroaryl substituted derivatives. ^{1}H and ^{13}C NMR were determined together with X-ray crystal structure of one derivative. The biological activity is described too.

Results and Discussion

Chemistry

Condensation of 2-amino-4-picoline with the suitable bromoacetyl compound in refluxing ethanol in the usual manner gave the attempted imidazo[1,2-*a*]pyridine derivatives **1a**–**k** (Scheme 1), in moderate to good yield (not optimized, Table 1). Using formaldehyde in acetic acid medium, hydroxymethylation in position 3 gave compounds **2a**–**k**, generally in good yields (Table 1). Upon the nature of the 2-substituent, the reaction began smoothly at room (or eventually higher) temperature, and progressive heating was necessary in order to avoid the formation of by-products (Table 1). The thioethers **3**–**14** were obtained using benzyl or phenethylmercaptan in acetic acid medium at 100 °C. Yields and melting point were listed in Table 2. The structural determination of all the new structures was achieved by ^{1}H and ^{13}C spectroscopy and when necessary, for quaternary



I : R = H
IV : R = C_6H_5

II : R = H
III : R = Br

Figure 1.

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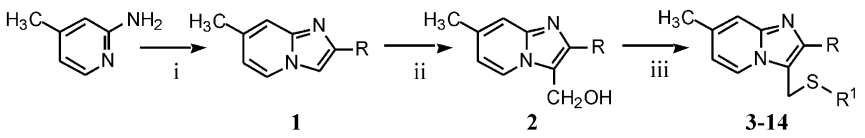

1 2 3-14

	R		R	R^1
		3	thien-2-yl	benzyl
1a, 2a	thien-2-yl	**4**	thien-2-yl	phenethyl
1b, 2b	furan-2-yl	**5**	furan-2-yl	benzyl
1c, 2c	napht-2-yl	**6**	napht-2-yl	benzyl
1d, 2d	biphen-4-yl	**7**	biphen-4-yl	benzyl
1e, 2e	pyridin-2-yl	**8**	pyridin-2-yl	benzyl
1f, 2f	pyridin-3-yl	**9**	pyridin-3-yl	benzyl
1g, 2g	pyridin-4-yl	**10**	pyridin-4-yl	benzyl
1h, 2h	trifluoromethyl	**11**	trifluoromethyl	benzyl
1i, 2i	t-butyl	**12**	t-butyl	benzyl
1j, 2j	adamantan-1-yl	**13**	adamantan-1-yl	benzyl
1k, 2k	1-methylcyclopropan-1-yl	**14**	1-methylcyclopopan-1-yl	benzyl

Scheme 1. Reagents and conditions: (i) α-halogenocarbonyl derivative, EtOH, 4 h, reflux; (ii) HCHO, AcOH, AcONa, 20 °C–reflux, 1–4 h; (iii) $C_6H_5CH_2SH$ or $C_6H_5(CH_2)_2SH$, AcOH, 100 °C, 4 h.

carbons, by LRHETCOR. For the final thioethers **3**–**14**, the spectroscopic data were given in Tables 2 and 3.

Antiviral assays

None of the synthesized compound showed appreciable activity against human immunodeficiency virus (HIV-1 and HIV-2) in MT-4 cell cultures (data not shown). The antiviral activity of compounds **3**–**14** against human cytomegalovirus are indicated in Table 4.

Crystal structure analysis

The biphenyl compound **7** gave suitable crystals. The solid-state conformation of compound **7** with thermal ellipsoid representation and the labeling of non-hydrogen atoms[7] is presented in Figure 2. It should be noted that the homologue of **7** in the 2-phenylimidazopyridine series was inactive.[6] Moreover, with regard to molecular modeling studies on imidazo[1,2-*a*]pyridine,[8] it seemed that the thioether side chain on C-3 is in an orientation perpendicular to the direction of the C(2)-H bond for active compounds. For compounds which presented poor antiviral activity, the thioether side chain conformation was parallel to the C-2 extra cyclic bond, as it was evident on the crystallographic data obtained for **7**. For these reasons, we did not look further into the activities for this compound. The bond lengths and bond angles are given in Tables 5 and 6, respectively. The interesting torsion angles which entirely define the molecule conformation are as follows:

N1–C2–C1′–C2′	−41.2 (3)°	C3–C9–S10–C11	78.0 (2)
C3′–C4′– C7′–C8′	147.5 (2)°	C9–S10–C11–C1″	67.3 (2)
N4–C3–C9–S10	65.0 (2)°	C10–C11–C1″–C2′	111.5 (2)

These data agree quite well with those obtained previously in the same series.[9,10]

Structure–activity relationship

Introduction of an alkyl group in position 2 (**12**, **13**) slightly enhanced the activity against HCMV, but also the cytotoxicity. The trifluoromethyl derivative **11** emerged as the most potent compound with an improvement of the antiviral activity by a factor 2- to 4-fold in comparison with **I**, and decreased cytotoxicity.

As reported for the 2-phenyl compound **IV**,[6] the furan-2-yl compound **5** was inactive, and the pyridin-3-yl derivative **9** was poorly active. In contrast, all the other compounds, with aryl group in 2 position, showed

Table 1. Physical data of **1**, conditions for the synthesis and physical data of **2**

	Yield %	Mp (°C)		Temperature (°C)	Time (h)	Yield (%)	Mp (°C)
1a	75	124–126 (lit.:[21] 129)	**2a**	Reflux	1	76	205–207
1b	37	149–151 (lit.:[22] 155)	**2b**	Room temperature	2	51	155–157
1c	54	199–201	**2c**	50	4	57	221–223
1d	77	221–223 (lit.:[23] 217)	**2d**	50	1	75	>260
1e	48	183–185	**2e**	Reflux	3	90	182–184
1f	13	72–74	**2f**	60	2	42	162–164
1g	12	165–167	**2g**	60	4	53	243–245
1h	40	145–146 (lit.:[24] 145)	**2h**	100	3	70	175–177
1i	36	96–98	**2i**	50	3	46	159–161
1j	67	147–146	**2j**	50	3	43	230–232
1k	39	113–115	**2k**	50	1	79	182–184

Table 2. Physical data and ^{1}H NMR spectral data of thioethers **3**–**14** in $CDCl_3$, chemical shift[a]

	Yield %	Mp (°C)	H-5	H-6	H-8	H alkyl	H aryl
3	95	90–92	7.70 $J_{5,6}=7.1$	6.61 $J_{5,6}=7.1$, $J_{6,8}=1.7$	7.26 br.s	2.40 (s, CH_3), 3.68 (s, SCH_2), 4.18 (s, CH_2S)	7.07 (dd, $J_{4',5'}=5.0$, $J_{3',4'}=3.6$, H-4′), 7.25 (m, $3H_{arom}$, H-5′), 7.29 (dd, $J_{3',4'}=3.6$, $J_{3',5'}=1.1$, H-3′), 7.34 (m, $2H_{arom}$)
4	70	93–95	7.91 $J_{5,6}=7.0$	6.65 $J_{5,6}=7.0$, $J_{6,8}=1.7$	7.38 br.s	2.40 (s, CH_3), 2.70 (m, $2CH_2$), 4.26 (s, CH_2S)	7.01 (m, $2H_{arom}$), 7.15 (dd, $J_{4',5'}=5.1$, $J_{3',4'}=3.6$, H-4′), 7.25 (m, H-5′, $2H_{arom}$), 7.38 (m, H-8,4″, H-5′), 7.51 (dd, $J_{3',4'}=3.6$, $J_{3',5'}=1.2$, H-3′)
5	72	149–151	7.83 $J_{5,6}=7.0$	6.88 $J_{5,6}=7.0$	7.35 s	2.42 (s, CH_3), 3.65 (s, SCH_2), 4.35 (s, CH_2S)	6.52 (dd, $J_{3',4'}=3.4$, $J_{4',5'}=1.8$, H-4′), 6.88 (d, 1H, $J_{3',4'}=3.4$, H-3′), 7.24 (m, $5H_{arom}$), 7.43 (d, $J_{4',5'}=1.8$, H-5′)
6	75	142–144	7.78 $J_{5,6}=7.0$	6.68 $J_{5,6}=7.0$, $J_{6,8}=1.8$	7.45br.s	2.46 (s, CH_3), 3.69 (s, SCH_2), 4.20 (s, CH_2S)	7.19 (m, $5H_{arom}$), 7.55 (m, H-3′,4′), 7.90 (m, H-5′,6′,7′,8′), 8.25 (s, H-1′)
7	42	136–138	7.78 $J_{5,6}=7.0$	6.68 $J_{5,6}=7.0$	7.45 br.s	2.46 (s, CH_3), 3.70 (s, SCH_2), 4.17 (s, CH_2S)	7.17 (m, $5H_{arom}$), 7.91 (m, $5H_{arom}$)
8	56	118–119	7.81 $J_{5,6}=7.0$	6.56 $J_{5,6}=7.0$	7.29 br.s	2.33 (s, CH_3), 3.60 (s, SCH_2), 4.72 (s, CH_2S)	7.10 (m, $6H_{arom}$), 7.68 (td, $J_{4',3'}=J_{4',5'}=7.8$, $J_{4',6'}=1.8$, H-4′), 8.14 (ddd, $J_{3',4'}=7.8$, $J_{3',5'}=1.2$, $J_{3',6'}=1.0$, H-3′), 8.41 (m, H-6′)
9	57	189–191	7.56 $J_{5,6}=7.0$	6.49 $J_{5,6}=7.0$	7.25 br.s	2.26 (s, CH_3), 3.56 (s, SCH_2), 3.91 (s, CH_2S)	7.20 (m, $5H_{arom}$, H-5′), 7.91 (d, $J_{4',5'}=8.0$, H-4′), 8.48 (d, $J_{5',6'}=4.8$, H-6′), 8.96 (br.s, H-2′)
10	37	135–137	7.51 $J_{5,6}=6.8$	6.45 $J_{5,6}=6.8$	7.19 br.s	2.21 (s, CH_3), 3.53 (s, SCH_2), 3.86 (s, CH_2S)	7.15 (m, $5H_{arom}$), 7.44 (d, $J_{2',3'}=J_{5',6'}=5.0$, H-3′,5′), 8.42 (d, $J_{2',3'}=J_{5',6'}=5.0$, H-2′,6′)
11	20	106–108	7.77 $J_{5,6}=7.0$	6.72 $J_{5,6}=7.0$	7.32 s	2.42 (s, CH_3), 3.70 (s, SCH_2), 4.12 (s, CH_2S)	7.26 (m, $5H_{arom}$)
12	73	66–68	7.40 $J_{5,6}=7.0$	6.50 $J_{5,6}=7.0$, $J_{6,8}=1.4$	7.33 br.s	1.45 (s, $3CH_3$), 2.35 (s, CH_3), 3.79 (s, SCH_2), 4.05 (s, CH_2S)	7.37 (m, $5H_{arom}$)
13	64	Oil	7.48 $J_{5,6}=7.0$	6.53 $J_{5,6}=7.0$, $J_{6,8}=1.6$	7.46 br.s	1.79 (m, 4CH), 2.10 (m, $6CH_2$), 2.38 (s, CH_3), 3.80 (s, SCH_2), 4.10 (s, CH_2S)	7.41 (m, $5H_{arom}$)
14	34	74–76	7.57 $J_{5,6}=6.9$	6.53 $J_{5,6}=6.9$, $J_{6,8}=1.5$	7.27 br.s	0.70 (m, CH_2), 0.99 (m, CH_2), 1.43 (s, CH_3), 2.36 (s, CH_3), 3.78 (s, SCH_2), 4.08 (s, CH_2S)	7.36 (m, $5H_{arom}$)

[a]σ are in ppm, H–H coupling constants J are in Hz. Multiplicity of coupling are given: s, singlet; br. s, broad singlet; d, doublet; dd, doublet of doublet; m, multiplet.

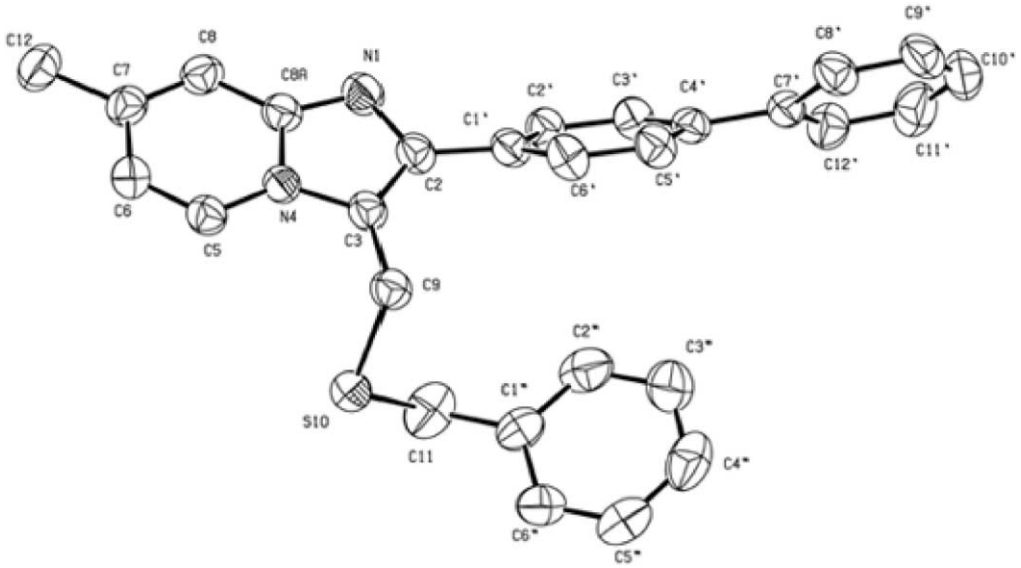

Figure 2. Ellipsoid representation and atomic labeling of **7** (probability 50%).

Table 3. ^{13}C NMR spectral data of thioethers **3–14** in $CDCl_3$[a]

	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	C-alkyl	C- aryl
3	137.3	114.3	122.5	114.9	135.3	115.7	144.8	20.8 (CH_3), 24.2 (CH_2S), 35.7 (SCH_2)	124.4 (C-3′), 125.0 (C-5′), 126.6 (C -4″), 127.3 (C-4′), 128.0 ($2C_{arom}$), 128.4 ($2C_{arom}$), 136.8 (C-1″), 137.8 (C-2′)
4	137.3	114.2	123.4	114.9	136.0	115.7	145.5	21.4 (CH_3), 25.4 (CH_2S), 33.0 (CH_2), 36.4 (CH_2)	125.1(C-3′), 125.6 (C-5′), 126.3 (C-4″), 127.8 (C -4′), 128.4 ($2C_{arom}$), 128.5 ($2C_{arom}$), 138.5 (C -1″), 140.0 (C-2′)
5	136.1	114.2	123.3	114.7	135.4	115.6	145.8	21.3 (CH_3), 24.4 (CH_2S), 35.6 (SCH_2)	107.9 (C-3′), 111.4 (C-4′), 126.8 (C-4″), 128.3 ($2C_{arom}$), 128.7 ($2C_{arom}$), 137.8 (C-1″), 141.9 (C-5′), 149.8 (C-2′)
6	143.7	114.5	122.9	114.6	135.4	115.5	145.4	21.1 (CH_3), 24.7 (CH_2S), 36.1 (SCH_2)	125.8 (C-6′, 7′), 126.1, 126.8, 127.0, 127.4 ($4C_{arom}$) 128.0, 128.2 ($4C_{arom}$), 128.5 (C-2″, 6″), 131.5, 132.6, 133.2 (C-2′,4a′,8a′), 137.6 (C-1″)
7	143.4	114.5	123.1	114.7	135.7	115.7	145.1	21.2 (CH_3), 24.7 (CH_2S), 36.2 (SCH_2)	126.9 ($2C_{arom}$), 127.0 ($1C_{arom}$), 127.2 ($2C_{arom}$), 128.4 ($2C_{arom}$), 128.6 ($2C_{arom}$), 128.7 ($5C_{arom}$), 133.0 (C-4′), 137.5 (C-1‴), 140.2, 140.6 (C-1′, 1″)
8	141.5	118.0	123.5	114.8	135.8	115.9	145.3	21.3 (CH_3), 24.7 (CH_2S), 35.6 (SCH_2)	121.9, 122.0 (C-3′, 5′), 126.6 (C-4″), 128.2 ($2C_{arom}$), 128.6 ($2C_{arom}$), 136.4 (C-4′), 138.3 (C-1″), 148.7 (C-6′), 154.3 (C-2′)
9	140.2	114.8	123.1	114.6	135.6	115.4	145.3	20.9 (CH_3), 24.2 (CH_2S), 36.0 (SCH_2)	122.8 (C-5′), 126.8 (C-4″), 128.1 ($2C_{arom}$), 128.3 ($2C_{arom}$), 129.9 (C-3′), 135.0 (C-4′), 137.1 (C-1″), 148.2 (C-6′), 148.7 (C-2′)
10	140.3	115.9	122.8	115.0	136.1	115.7	145.4	21.0 (CH_3), 24.1 (CH_2S), 36.2 (SCH_2)	122.0 (C-3′,5′), 127.1 (C-4″), 128.3, 128.6 (C-3′, 5′, 2″, 6″), 137.1 (C-1″), 141.5 (C-4′), 149.6 (C-2′,6′)
11	132.8 $J=36.7$ Hz	118.2	123.6	116.2	137.3	116.6	145.2	21.2 (CH_3), 23.6 (CH_2S), 36.2 (SCH_2)	122.3 (CF_3, $J=270$Hz), 127.1 (C-4′), 128.4, 128.6 ($4C_{arom}$), 137.1(C-1′)
12	152.2	111.9	121.9	113.6	133.8	114.9	143.5	20.7 (CH_3), 25.0 (CH_2S), 30.5 ($3CH_3$), 32.9 (C), 36.4 (SCH_2)	126.7 (C-4′), 128.1, 128.5 ($4C_{arom}$), 137.5 (C-1′)
13	152.1	112.0	121.9	113.5	133.8	115.0	143.7	20.7 (CH_3), 25.1(CH_2S), 28.3 ($3CH_2$), 35.2 (SCH_2), 36.4 (4CH), 41.9 ($3CH_2$)	126.7 (C-4′), 128.0, 128.5 ($4C_{arom}$), 137.6 (C-1′)
14	148.5	114.3	122.5	114.0	134.7	115.0	144.1	13.2 ($2CH_2$), 14.3 (C), 20.9 (CH_3), 24.1 (CH_3), 25.4 (CH_2S), 36.5 (SCH_2)	126.9 (C-4′), 128.2 ($2C_{arom}$), 128.6 ($2C_{arom}$), 137.6 (C-1′)

[a]Chemical shift δ are in ppm.

Table 4. Anti-HCMV activities and cytotoxic properties of test compounds in human embryonic lung (HEL) cells

Compd	Antiviral activity		Cytostatic and cytotoxic activity	
	HCMV AD-169 strain IC_{50} (μg/mL)	HCV Davis strain IC_{50} (μg/mL)[a]	Cell morphology MCC (μg/mL)[b]	Cell growth CC_{50} (μg/mL)[c]
I	3.5	3.5	ND[d]	45
II	0.12	0.12	50	>50
III	>20	>20	5	>50
3	2.7	7.0	>50	14
4	1.1	1.6	>5	14
5	>50	>50	>50	>50
6	>0.5	1.2	≥2	16
8	0.6	0.95	≥20	50
9	10	50	≥50	>50
10	3.2	>5	≥50	>50
11	0.95	1.5	≥50	>50
12	1.0	1.2	5	11
13	>0.5	>0.5	2	10
14	2.0	5.0	≥20	>50
Ganciclovir	1.3	5	>50	>50
Cidofovir	0.17	0.68	>50	50

[a]Compound concentration required to inhibit virus-induced cytopathicity by 50%.
[b]Minimum cytotoxic concentration that causes a micro-scopically detectable alteration of cell morphology.
[c]Cytostatic concentration required to reduce cell growth by 50%.
[d]Not determined.

Table 5. Bond lengths (Å), and standard-deviations for compound **7**

N1–C8a	1.327(3)	C2′–C3′	1.375(3)
N1–C2	1.369(3)	C3′–C4′	1.395(3)
C2–C3	1.383(3)	C4′–C5′	1.394(3)
C2–C1′	1.475(3)	C4′–C7′	1.480(3)
C3–N4	1.383(2)	C5′–C6′	1.374(3)
C3–C9	1.483(3)	C7′–C12′	1.386(3)
N4–C5	1.371(2)	C7′–C8′	1.396(3)
N4–C8a	1.392(2)	C8′–C9′	1.375(3)
C5–C6	1.347(3)	C9′–C10′	1.374(4)
C6–C7	1.423(3)	C10′–C11′	1.374(4)
C7–C8	1.361(3)	C11′–C12′	1.380(3)
C7–C12	1.500(3)	C1″–C6″	1.384(3)
C8–C8a	1.407(3)	C1″–C2″	1.388(3)
C9–S10	1.822(2)	C2″–C3″	1.383(4)
S10–C11	1.814(3)	C3″–C4″	1.356(4)
C11–C1″	1.495(3)	C4″–C5″	1.377(4)
C1′–C2′	1.391(3)	C5″–C6″	1.370(4)
C1′–C6′	1.394(3)		

improved antiviral potency. In particular, the thien-2-yl 3 and pyridin-4-yl **10** showed comparable activity with **I**. The napht-2-yl **6** and pyridin-2-yl **8** appeared to be as potent as **11** but **6** was also quite cytotoxic.

Conclusion

In this work, we have shown that the substituent at the 2 position strongly influences the activity of these compounds against human cytomegalovirus as well as their cytotoxicity. For the pyridin-2-, 3- and 4-yl derivatives, it was demonstrated that the position of the nitrogen plays a crucial role for an optimal interaction with the target virus (HCMV).

Experimental

General details

Melting points were determined on a Köfler hotstage apparatus and are uncorrected. Elemental analysis were performed by Microanalytical Center, ENSCM, Montpellier and the analytical results obtained were within $\pm 0.4\%$ of the theoretical values. NMR spectra were recorded on Brüker DPX 200 (SAVIT, 37200 Tours) or AM 400 WB spectrometer. The following α-halogenocarbonyl compound were synthesized according to cited references: 2-bromoacetylthiophene,[11] 2-bromoacetylpyridine,[12] 3-bromoacetylpyridine,[13] 4-bromoacetyl-pyridine,[12] 1-bromoacetyl-1-methylcyclopropane.[14]

General procedure for cyclisation to give (1)

To a solution of 2-amino-4-picoline (0.1 mol) in ethanol (100 mL) was added the α-halogeno carbonyl derivative (0.1 mol) and the resulting mixture was refluxed for 4 h. After cooling the solution was evaporated to dryness. The residue was treated with water, made alkaline with sodium carbonate and extracted with dichloromethane. The organic layers were dried over calcium chloride, filtered, and after evaporation under vacuo, the residue was chromatographed on neutral alumina eluted with dichloromethane.

Table 6. Bond angles (°) and standard-deviations for compound **7**

C8a–N1–C2	105.33(16)	C6′–C1′–C2	122.44(18)
N1–C2–C3	111.90(17)	C3′–C2′–C1′	121.11(17)
N1–C2–C1′	119.52(17)	C2′–C3′–C4′	121.71(18)
C3–C2–C1′	128.55(18)	C5′–C4′–C3′	116.91(18)
N4–C3–C2	104.50(16)	C5′–C4′–C7′	121.72(17)
N4–C3–C9	121.90(16)	C3′–C4′–C7′	121.35(17)
C2–C3–C9	133.49(18)	C6′–C5′–C4′	121.47(18)
C5–N4–C3	131.11(16)	C5′–C6′–C1′	121.36(18)
C5–N4–C8a	121.57(16)	C12′–C7′–C8′	117.54(19)
C3–N4–C8a	107.32(15)	C12′–C7′–C4′	121.33(17)
C6–C5–N4	119.22(18)	C8′–C7′–C4′	121.12(18)
C5–C6–C7	121.78(19)	C9′–C8′–C7′	121.0(2)
C8–C7–C6	118.25(19)	C8′–C9′–C10′	120.6(2)
C8–C7–C12	121.39(19)	C9′–C10′–C11′	119.3(2)
C6–C7–C12	120.35(19)	C10′–C11′–C12′	120.4(2)
C7–C8–C8a	120.91(18)	C11′–C12′–C7′	121.2(2)
N1–C8a–N4	110.93(16)	C6″–C1″–C2″	117.6(2)
N1–C8a–C8	130.82(18)	C6″–C1″–C11	121.6(2)
N4–C8a–C8	118.23(17)	C2″–C1″–C11	120.9(2)
C3–C9–S10	115.21(13)	C3″–C2″–C1″	121.1(2)
C11–S10–C9	101.79(11)	C4″–C3″–C2″	120.2(2)
C1″–C11–S10	114.90(16)	C3″–C4″–C5″	119.5(2)
C2′–C1′–C6′	117.41(18)	C6″–C5″–C4″	120.7(2)
C2′–C1′–C2	120.09(17)	C5″–C6″–C1″	120.9(2)

General procedure for hydroxymethylation to give (2)

A mixture of imidazo[1,2-*a*]pyridine (20 mmol), formaldehyde 37% in water (10 eqviv), acetic acid (3 mL) and sodium acetate (4.3 g) was stirred at room temperature or heated for the time reported in Table 2. After cooling, when necessary, the solution was made alkaline with 2 N sodium hydroxyde. The solution was extracted with dichloromethane and the organic layers dried over calcium chloride. After evaporation under vacuo the residue was chromatographed on neutral alumina eluted with dichloromethane/methanol (99:1 v/v).

General procedure for the thioethers (3–14)

To a solution of the alcohol (500 mg) in acetic acid (5 mL) was added the suitable thiol (0.9 eqviv). The resulting mixture was heated at 100 °C for 4 h. After cooling, the solution was made alkaline with 2 N sodium hydroxide and extracted with dichloromethane. After drying on calcium chloride the organic layer was evaporated under vacuo, and the residue was chromatographed on neutral alumina eluted with dichloromethane.

X-ray diffraction

Colorless crystals were grown by slow evaporation of dichlomethane solution at 293 K. The crystal used for X-ray measurement was lamellar, with as dimensions: $0.05\times0.28\times0.38$ mm. The studied compound, $C_{28}H_{24}N_2S$, $M_x = 420.55$ g mol^{-1} crystallizes in the triclinic system, space group P-1 ($Z = 2$). The unit cell parameters were obtained by least-square fit of the setting angles of 25 reflections and are as follow: $a = 9.399(1)$, $b = 10.274(2)$, $c = 12.324(3)$ Å, $\alpha = 101.99(2)$, $\beta = 101.57(1)$ and $\gamma = 104.36(1)°$ with a cell volume of 1087.1(4) Å^3. The calculated density equaled to 1.29 g cm^{-3}. The linear absorption coefficient was $\mu = 1.44$ mm^{-1} for the $\lambda(CuK_\alpha)$ radiation ($\lambda = 1.54178$ Å). The diffracted intensities were collected with a CAD-4

Enraf-Nonius diffractometer equipped with a graphite monochromator for $\theta_{max} = 60°$: $-10 \leq h \leq 10$, $0 \leq k \leq 11$, $-13 \leq l \leq 13$ and a $\omega - 2\theta$ scan. Three standard reflections were used to monitor the data collection and detect any decrease of intensity (5 1−9, 3 5−6, 4 4−1); the crystal absorption correction was performed using the Ψ scan technique.[15] There were 3191 independent reflections of which 2642 were considered as observed ($I \geq 2\sigma(I)$ and $R_{int} = 0.029$). The crystal structure was solved and refined by full-matrix anisotropic least-squares on F^2 with using the SHELX97 program.[16] Scattering factors were taken from the International Tables for Crystallography.[17] The hydrogen atoms were introduced in their theoretical positions and allowed to ride with the atoms to which they are attached. The final reliability factors are: $R = 0.038$, $wR = 0.096$ and the goodness of fit on F^2 was equal to 1.032. The weight was equal to: $w = 1/[\sigma^2(F_o^2) + (0.0383P)^2 + 0.3458P]$ where $P = (Fo^2 + 2Fc^2)/3$. The minimum and maximum residual density were:-0.180 and 0.196 e.Å^{-3}, respectively.

Antiviral activity assays

Human cytomegalovirus (HCMV) (AD-169, Davis) strains were exposed to human embryonic lung HEL cell cultures. Briefly, confluent cell cultures in microtiter trays were inoculated with 100 plaque forming units (PFU). After 1 h virus adsorption, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (400, 200, 100, ...μg/mL) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures. Inhibition of HCMV by the test compounds was compared with cidofovir and ganciclovir as the reference compounds. Antiviral activity is expressed as the compound concentration required to inhibit viral cytopathicity by 50% (IC_{50}).

Cytostatic activity assays

The cytostatic assays were performed as previously described.[18–20] Briefly, 100-μL aliquots of HEL cell suspensions were added to the wells of a 96-well microtiter plate containing 100 μL of varying concentrations of the test compounds. After 3-days incubation period at 37 °C in a humidified CO_2-controled incubator, the number of viable cells was determined using a Coulter Counter. Cytostatic activity is expressed as the compound concentration that reduced the number of viable cells by 50% (CC_{50}). The cytotoxicity measurements were based on microscopically visible morphological alterations of the HEL cell culture: cytotoxicity was defined as the minimum cytotoxic concentration (MCC) required to cause a microscopically detectable alteration of cell morphology.

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