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Notes

Synthesis of Imidazo[1,2-*a*]pyridines as Antiviral Agents

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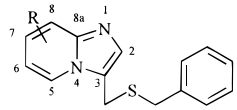
The synthesis of original imidazo[1,2-*a*]pyridines bearing a thioether side chain at the 3 position and their antiviral activity are reported. From the synthesized compounds, **4**, **15**, and **21** were highly active against human cytomegalovirus with a therapeutic index superior to 150. These compounds also showed pronounced activity against varicella-zoster virus. Their structure−activity relationship is discussed.

Introduction

Cytomegalovirus (CMV) is a β-herpesvirus responsible for severe illness in newborns[1] and immunosuppressed patients where it can lead to severe retinitis, pneumopathy, and encephalopathy.[2] The compounds currently used in the treatment of CMV infections are ganciclovir (Cymevene), foscarnet (Foscavir), and cidofovir (Vistide), although these compounds are not free of side effects.[3] The acyclic nucleoside phosphonate cidofovir represents a real advantage in the management of CMV infections because it must be administered only once a week (initially) or every 2 weeks (thereafter), and it does not easily lead to the development of virus drug resistance.[4] In previous communications, we have reported the synthesis of thioether derivatives in the imidazopyridine series as potential antiviral agents.[5] From these compounds, the 7- and 8-methyl-3-[(benzylthio)methyl]imidazo[1,2-*a*]pyridines **I** and **II** (Chart 1) showed a marked activity against CMV and varicella-zoster virus (VZV). However, these compounds were still relatively cytotoxic. We now report the synthesis and the antiviral activity of novel derivatives within this series of compounds.

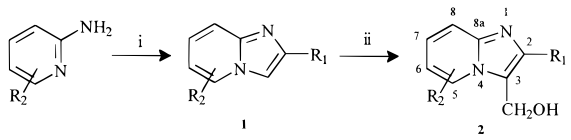
Chart 1



I: R = 7-CH_3

II: R = 8-CH_3

Scheme 1[a]



	R_1	R_2
a	H	7-Me
b	H	6-CF_3,8-Cl
c	H	6-Me
d	H	5,7-$(Me)_2$
e	H	5,8-$(Me)_2$
f	H	6-Br-8-Me
g	H	6-Me-8-Br
h	H	5-Me-6,8-$(Br)_2$
i	C_6H_5	7-Me
j	C_6H_5	8-Me
k	CH_3	H
l	CH_3	7-Me

[a] Reagents and conditions: (i) bromoacetaldehyde, chloroacetone or phenacyl bromide, EtOH, 4 h, reflux; (ii) HCHO, AcOH, AcONa, 4 h reflux except for **2i**,**j** (4 h room temperature).

Table 1. Yields and Melting Points for Original Intermediates

compd	yield,[a] %	mp, °C	compd	yield,[a] %	mp, °C
1f	78	40−41	**2f**	45	173−174
1h	92	175−176	**2g**	85	183−184
2c	9	136−137	**2h**	60	193−194
2d	30	144−145	**2i**	86	>260
2e	55	162−163	**2j**	92	>260

[a] After chromatography.

Chemistry

The starting substituted imidazo[1,2-*a*]pyridines (**1a**−**l**) were obtained according to known procedures (see General Details in Experimental Section) or by condensation of suitable 2-aminopyridine derivatives with bromoacetaldehyde in refluxing ethanol as described by

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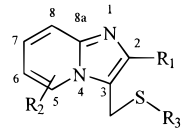
Table 2. ^{1}H NMR Spectral Data for New Intermediate Derivatives

compd	H-2	H-3	H-5	H-6	H-7	H-8	others
1f	7.62	7.55	8.17		7.07		2.63 (Me)
1h	7.56*	7.69*			7.56*		2.66 (Me)
2c	7.06		8.04		6.98	7.34	2.26 (Me); 4.84 (CH_2); 5.88 (OH)
2d	7.12			6.31		7.02	2.25 (Me); 2.88 (Me); 4.84 (CH_2); 4.87 (OH)
2e	7.19			6.44	6.88		2.49 (Me); 2.90 (Me); 4.89 (CH + OH)
2f	7.23		8.25		7.04		2.50 (Me); 3.40 (OH); 4.85 (CH_2)
2g	7.32		8.05		7.29		2.32 (Me); 4.87 (CH_2)
2h	7.47			7.62			3.09 (Me); 4.94 (CH_2)
2i			8.20	6.75		7.45	2.46 (Me); 5.14 (CH_2); 7.40 (3H); 7.78 (2H)
2j			8.14	6.78	7.05		2.66 (Me); 5.06 (CH_2); 7.40 (3H); 7.72 (2H)

Table 3. Structures and Physical Properties of Synthesized Thioethers



compd	R_1	R_2	R_3	yield,[a] %	mp, °C	compd	R_1	R_2	R_3	yield,[a] %	mp, °C
3	H	7-Me	cyclohexyl	90	111−112	**13**	H	5,7-$(Me)_2$	$CH_2C_6H_5$	70	oil
4	H	7-Me	$CH_2CH_2C_6H_5$	90	83−84	**14**	H	5,8-$(Me)_2$	$CH_2C_6H_5$	98	66−67
5	H	7-Me	cyclopentyl	91	87−88	**15**	H	8-Me-6-Br	$CH_2C_6H_5$	93	96−97
6	H	7-Me	CH_2CF_3	90	96−97	**16**	H	6-Me-8-Br	$CH_2C_6H_5$	92	97−98
7	H	7-Me	CH_2-*2*ClC_6H_4	87	70−71	**17**	H	5-Me-6,8-$(Br)_2$	$CH_2C_6H_5$	90	136−137
8	H	7-Me	CH_2-*4*ClC_6H_4	97	112−113	**18**	C_6H_5	7-Me	$CH_2C_6H_5$	62	111−113
9	H	7-Me	$CH_2CH_2CH_3$	83	oil	**19**	C_6H_5	8-Me	$CH_2C_6H_5$	55	74−76
10	H	7-Me	$CH(CH_3)_2$	81	oil	**20**	CH_3	7-Me	$CH_2C_6H_5$	54	107−109
11	H	6-CF_3-8-Cl	$CH_2C_6H_5$	50	oil	**21**	CH_3	H	$CH_2C_6H_5$	76	82−83
12	H	6-Me	$CH_2C_6H_5$	95	94−95						

[a] After chromatography.

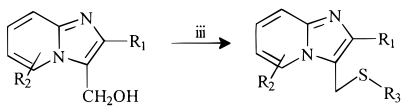
Table 4. ^{1}H NMR Spectral Data for Thioethers

compd	H-2	H-5	H-6	H-7	H-8	others
3	7.32	7.95	6.56		7.27	1.10−1.76 (11H); 2.30 (Me); 3.93 (CH_2)
4	7.42	7.97	6.66		7.38	2.39 (Me); 2.71 (4H); 7.06−7.28 ($5H_{arom}$)
5	7.31	7.92	6.54		7.25	1.33−1.80 ($8H_{cyclopentyl}$); 2.27 (Me); 2.66−2.80 (CH); 3.90 (CH_2)
6	7.35	7.84	6.59		7.25	2.27(Me); 2.69 (CH_2); 4.00 (CH_2)
7	7.39	7.80	6.52		7.28	2.27 (Me); 3.58 (CH_2); 3.86 (CH_2); 7.10 ($3H_{arom}$); 7.26 ($1H_{arom}$)
8	7.29	7.82	6.56		7.29	2.31 (Me); 3.38 (CH_2); 3.78 (CH_2); 7.09 (H-2′,6′); 7.12 (H-3′,5′)
9	7.36	7.98	6.63		7.32	0.85 (CH_3); 1.47 (CH_2); 2.25 (CH_2); 2.34 (Me); 3.92 (CH_2)
10	7.40	8.03	6.67		7.35	1.17 ($2CH_3$); 2.38 (Me); 2.62 (CH); 4.01 (CH_2)
11	7.56	8.30		7.39		3.52 (CH_2); 3.89 (CH_2); 7.21 ($5H_{arom}$)
12	7.44	7.75		7.05	7.53	2.34 (Me); 3.58 (CH_2); 3.88 (CH_2); 7.31 ($5H_{arom}$)
13	7.26		6.30		7.17	2.27 (Me); 2.78 (Me); 3.59 (CH_2);3.98 (CH_2); 7.26 ($5H_{arom}$)
14	7.32		6.38	6.84		2.58 (Me); 2.81 (Me); 3.65 (CH_2); 4.04 (CH_2)
15	7.40	7.98		7.06		2.56 (Me); 3.53 (CH_2); 3.81 (CH_2); 7.26 ($5H_{arom}$)
16	7.44	7.67		7.06		2.26 (Me); 3.52 (CH_2); 3.82 (CH_2); 7.27 ($5H_{arom}$)
17	7.35			7.48		2.88 (Me); 3.57 (CH_2); 3.92 (CH_2); 7.21 ($5H_{arom}$)
18		7.63	6.53		7.37	2.33 (Me); 3.60 (CH_2); 4.00 (CH_2); 7.14−7.45 ($8H_{arom}$); 7.77 ($2H_{arom}$)
19		7.77	6.73	7.01		2.67 (Me); 3.66 (CH_2); 4.11 (CH_2); 7.19−7.77 ($10H_{arom}$)
20		7.73	6.55		7.23	2.25 (Me); 2.34 (Me); 3.54 (CH_2); 3.87 (CH_2); 7.26 ($5H_{arom}$)
21		7.88	6.74	7.14	7.50	2.32 (Me); 3.58 (CH_2); 3.93 (CH_2); 7.27 ($5H_{arom}$)

Roe.[6] Direct hydroxymethylation was carried out according to the procedure of Teulade[7] modified as follows. A mixture of the imidazopyridine **1** with formaldehyde and sodium acetate in acetic acid media was heated at 100 °C for 4 h to give the suitable alcohol **2** in moderate to good yield. In the case of 2-phenyl compounds, the reaction occurred smoothly at room temperature and led to the hydroxymethyl derivative in 86−92% yield (Scheme 1, Tables 1 and 2).

Preparation of thioethers **3**−**21** was achieved by reaction of substituted (imidazo[1,2-*a*]pyridin-3-yl)-methanol derivatives with thiol in acetic acid media at 100 °C for 2 h according to the procedure of Del Corona[8] (Scheme 2). The structure, yields, and physical properties of these compounds are reported in Tables 3−5.

Scheme 2[a]



3-21

[a] Reagents and conditions: R_3SH, AcOH, 100 °C, 2 h.

Biological Assays

Antiviral activity was determined against a broad range of RNA and DNA viruses Table 6). The following structure−activity relationship (SAR) emerged:

1. Influence of the nature of the thioether side chain: This chain must contain a cyclic ring. Indeed, aliphatic compounds led to a dramatic decrease of the

Table 5. ^{13}C NMR Spectral Data of Thioethers

compd	C-2	C-3	C-5	C-6	C-7	C-8	C-8a	others
3	132.3	118.7	123.2	114.4	134.7	116.0	146.4	21.0 (Me); 23.2 (CH_2); 25.5 (CH_2); 25.6 ($2CH_2$); 32.8 ($2CH_2$); 42.5 (CH)
4	132.8	118.0	123.2	114.5	134.9	116.1	146.1	21.1 (Me); 24.9 (CH_2); 32.1 (CH_2); 35.7 (CH_2); 126.2 (C-4′); 128.3 ($4CH_{arom}$); 139.9 (C-1′)
5	131.9	118.4	122.9	114.1	134.3	115.6	146.1	20.7 (Me); 24.3 (CH_2); 24.7 (CH_2); 32.8 ($2CH_2$); 42.5 (CH)
6	134.1	116.0	123.0	115.0	135.5	116.3	147.1	21.3 (Me); 25.7 (CH_2); 32.1 (CH_2, J = 32.8 Hz); 125.9 (CF_3, J = 277.3 Hz)
7	132.6	117.6	122.8	114.1	135.5	115.6	146.2	20.7 (Me); 24.4 (CH_2); 32.5 (CH_2); 126.5 (C-5′); 128.0 (C-3′); 129.3 (C-4′); 130.0 (C-6′); 134.6 (C-1′); 135.0 (C-2′)
8	132.6	117.2	122.6	114.1	132.1	115.6	146.1	20.6 (Me); 23.7 (CH_2); 33.8 (CH_2); 127.9 (C-2′,6′); 129.5 (C-3′,5′); 134.5 (C-1′); 135.5 (C-4′)
9	132.8	118.4	123.3	114.6	135.0	116.2	146.7	13.3 (CH_3); 21.2 (Me); 22.3 (CH_2); 24.8 (CH_2); 33 (CH_2)
10	132.3	118.7	123.4	114.7	135.0	116.2	146.7	21.7 (Me); 22.8 ($2CH_3$); 24.0 (CH); 34.2 (CH_2)
11	135.3	124.6	122.2	116.4	119.1	122.6	143.3	23.8 (CH_2); 35.5 (CH_2); 127.3 (C-4′); 128.5 (C-3′,5′); 128.7 (C-2′,6′); 136.9 (C-1′); 123.0 (CF_3, J = 271.7 Hz)
12	133.2	121.6	121.7	118.2	127.0*	117.01	45.3	18.2 (Me); 23.9 (CH_2); 35.2 (CH_2); 127.2 (C-4′)*; 128.4 (C-3′,5′); 128.9 (C-2′,6′); 137.5 (C-1′)
13	135.7	120.3	134.8*	114.3	135.6	116.3	148.6	19.8 (Me); 20.8 (Me), 27.0 (CH_2); 35.1 (CH_2); 127.0 (C-4′); 128.5 (C-3′,5′); 128.9 (C-2′,6′); 137.5 (C-1′)
14	134.4	124.7	133.8	113.0	123.2	121.0	148.1	16.6 (Me); 19.4 (Me); 26.6 (CH_2); 34.8 (CH_2); 126.7 (C-4′); 128.1 (C-3′,5′); 128.6 (C-2′,6′); 137.2 (C-1′)
15	133.1	119.5	121.9	106.8	126.2	128.5	145.0	16.6 (Me); 23.8 (CH_2); 35.2 (CH_2); 127.0 (C-4′); 128.4 (C-3′,5′); 128.7 (C-2′,6′); 137.1 (C-1′)
16	133.2	120.1	121.7	120.9	129.2	110.7	142.6	17.8 (Me); 23.7 (CH_2); 35.0 (CH_2); 126.7 (C-4′); 128.1 (C-3′,5′); 128.5 (C-2′,6′); 137.0 (C-1′)
17	136.3	124.2	134.3	108.2	130.3	109.3	144.1	18.5 (Me); 27.1 (CH_2); 35.0 (CH_2); 126.9 (C-4′); 128.2 (C-3′,5′); 128.4 (C-2′,6′); 136.7 (C-1′)
18	143.6	114.1*	122.8	114.3*	135.2	115.4*	145.2	21.0 (Me); 24.5 (CH_2); 36.0 (CH_2); 126.7 (C-4′); 127.3 (C-4″); 128.0 (2CH); 128.1 (2CH); 128.3 (2CH); 128.5 (2CH); 134.0 (C-1″); 137.6 (C-1′)
19	143.6	115.1	121.5	111.7	123.0	127.0	145.1	16.8 (Me); 24.6 (CH_2); 36.0 (CH_2); 126.7 (C-4′); 127.3 (C-4″); 128.1 (2CH); 128.3 (4CH); 128.5 (2CH); 134.1 (C-1″); 137.6 (C-1′)
20	141.4	113.8	123.1	114.1	134.9	115.1	145.2	13.3 (Me); 21.2 (Me); 24.0 (CH_2); 35.5 (CH_2); 127.0 (C-4′); 128.5 (C-3′,5′); 128.7 (C-2′,6′); 137.6 (C-1′)
21	141.6	114.5	123.7	111.4	123.7	116.4	144.5	13.2 (Me); 23.8 (CH_2); 35.5 (CH_2); 126.9 (C-4′); 128.3 (C-3′,5′); 128.4 (C-2′,6′); 137.4 (C-1′)

Table 6. Anti-CMV and Anti-VZV Activities and Cytotoxic Properties of Test Compounds in Human Embryonic Lung (HEL) Cells

	50% virus-inhibitory concentration (μg/mL)[a]							
	CMV		VZV					
compd	AD-169 strain	Davis strain	OKA strain TK^+	YS strain TK^+	07/1 strain TK^-	YS/R strain TK^-	50% cytotoxic concentration (μg/mL)[b]	selectivity index[c]
I	3.5	3.5	15	17	*d*	10	45	13
II	0.2	0.2	0.9	0.3	0.4	>1	8	40
3	3	3.4	3.8	8.3	>5	5.7	>50	>17
4	0.33	0.35	0.2	0.5	0.95	0.66	>50	>151
5	5	6.3	18	>20	>5	13	12	2.4
6	40	42	>50	>50	>50	>50	>50	>1.2
7	0.5	0.7	1.8	>5	>5	>5	18	36
8	1.2	1.6	2	>5	>5	>5	19	16
9	12	14	>50	>50	41	29	>50	>4.2
11	>5	>5	6.6	8.8	>5	9.8	40	<8
12	0.3	0.5	0.74	6.4	2.58	1.2	23	77
14	1.2	>2	>2	>2	>2	>2	3	2.5
15	0.12	0.12	5.5	7	1.4	0.86	>50	>417
16	1.1	1.1	31	>50	9	4	>50	>45
17	>50	>50	>50	>50	>50	>20	>50	*d*
18	>20	>20	>20	>20	>50	>50	>50	*d*
19	1.2	>2	>2	>2	>2	2	13	11
20	3.4	3.5	10.5	>5	14.1	10	>50	>15
21	0.12	0.13	0.37	0.23	0.5	0.28	33	275
ganciclovir	0.5	0.5	*d*	*d*	*d*	*d*	>100	>200
acyclovir	*d*	*d*	0.82	0.95	>25	>40	>100	*d*
brivudin	*d*	*d*	0.0009	0.002	>50	>20	>50	*d*

[a] Compound concentration required to inhibit virus-induced cytopathogenicity by 50%. [b] Compound concentration required to inhibit cell proliferation by 50%. [c] Ratio of 50% cytotoxic concentration to 50% virus-inhibitory concentration [the latter based on the 50% inhibitory concentration for CMV (AD-169 strain)]. [d] Not determined.

anti-CMV and anti-VZV activity, while cycloalkyl groups gave antiviral activity in the range of that of **I**. From a comparison of **I** with **4**, it appears that the replacement of the benzyl by a phenylethyl group improves anti-CMV activity by 11-fold and anti-VZV activity by 15−75-fold. Finally, introduction of a chlorine atom ortho or para on the phenyl ring enhanced both antiviral activity and cytotoxicity.

2. Influence of the nature and the position of the substituent on the pyridinic moiety: The importance of a methyl group on the pyridinic moiety was confirmed. The dimethyl derivatives were less

potent. A bromine in the 8 position decreased the anti-CMV activity, while a bromine in the 6 position enhanced it. In both cases, a decrease in anti-VZV activity was observed. Both substitutions were accompanied by a marked decrease in cytotoxicity.

3. Influence of the substituent in the 2 position: This substitution had no marked effect. A 2-methyl group seemed compatible with antiviral activity only when the pyridinic moiety remained unsubstituted.

While several compounds (i.e., **4**, **15**, and **21**) proved quite promising as anti-CMV and anti-VZV agents, none showed appreciable activity against human immunodeficiency virus (HIV-1 and HIV-2) in cell culture (data not shown). Also, compounds **3**, **4**, **11**, **12**, **15**, **18**, **20**, and **21** were evaluated for their activity against herpes simplex virus type 1 (HSV-1) (strain KOS), HSV-2 (strain G), vaccinia virus, and vesicular stomatitis virus (VSV) in human embryonic skin muscle (E_6SM) cells; VSV, Coxsackie virus B4, and respiratory syncytial virus (RSV) in HeLa cells; and parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus in Vero cells. None of the compounds showed activity against these viruses at subtoxic concentrations.

Conclusions

Chemical modifications of the imidazo[1,2-*a*]pyridines enabled us to improve the therapeutic index of this new class of antiviral agents. From the reported series, compounds **4**, **15**, and **21** emerged as the most potent and selective inhibitors of CMV and VZV. Further studies are in progress to understand the mechanism and target of interaction of these compounds.

Experimental Section

General Details. Melting points were determined on a Totolli capillary apparatus and are uncorrected. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier. NMR spectra were recorded on a Brüker AC 100 or AM 400 WB spectrometer. Substituted 2-aminopyridines were purchased from Aldrich except for 5-bromo-3-methyl-2-aminopyridine,[9] 5-methyl-3-bromo-2-aminopyridine,[10] and 6-methyl-3,5-dibromo-2-aminopyridine.[11] Previously reported imidazo[1,2-*a*]pyridines synthesized by the described procedure were 7-methylimidazo[1,2-*a*]pyridine (**1a**),[12] 8-chloro-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine (**1b**),[5c] 6-methylimidazo[1,2-*a*]pyridine (**1c**),[12] 5,7-dimethylimidazo[1,2-*a*]pyridine (**1d**),[13] 5,8-dimethylimidazo[1,2-*a*]pyridine (**1e**),[6] 8-bromo-6-methylimidazo[1,2-*a*]pyridine (**1g**),[10] 7-methyl-2-phenylimidazo[1,2-*a*]pyridine (**1i**),[14] 8-methyl-2-phenylimidazo[1,2-*a*]pyridine (**1j**),[14] 2-methylimidazo[1,2-*a*]pyridine (**1k**),[13] 2,7-dimethylimidazo-[1,2-*a*]pyridine (**1l**),[15] (7-methylimidazo[1,2-*a*]pyridin-3-yl)-methanol (**2a**),[5a] and (8-chloro-6-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)methanol (**2b**).[5c]

Chemistry. General Procedure for Cyclization: A solution of 2-aminopyridine derivative (0.1 mol) and α-halogenocarbonyl compound (0.12 mol) was refluxed in ethanol (250 mL) for 4 h. After cooling, the solution was concentrated in vacuo and the residue diluted in water. The solution was made basic with sodium carbonate and extracted with dichloromethane. The dried organic layers were evaporated to dryness and the residue chromatographed on neural alumina eluted with dichloromethane.

General Procedure for Hydroxymethylation: To a solution of the heterocycle (3.45 mmol) in acetic acid (0.74 mL) were added sodium acetate (1.06 g, 13 mmol) and then a 37% formaldehyde solution in water (1.8 mL, 22 mmol), and the mixture was stirred at room temperature for **1i**,**j** and heated at 100 °C for the others until disappearance of starting material in TLC. After cooling (if necessary), the reaction media were diluted in water and made basic with sodium carbonate. After evaporation to dryness, the residue was chromatographed on neutral alumina eluted with dichloromethane−methanol (95/5 v/v).

General Procedure for Acyclonucleoside Analogues: A solution of alcohol (2 mmol) with the suitable thiol (1.8 mmol) in acetic acid (2 mL) was heated at 80 °C for 2 h. After cooling, the solution was made basic with sodium carbonate and extracted with dichloromethane. The organic layers were dried over calcium chloride and evaporated to dryness, and the residue was chromatographed on neutral alumina eluted with dichloromethane.

Biological Assays. All antiviral assays were performed as described before.[16−18]

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