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SYNTHESIS AND ANTIVIRAL ACTIVITY OF 3-SUBSTITUTED IMIDAZO[1,2-*a*]PYRIDINES.

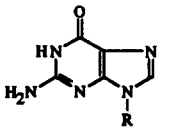
Ahmed Elhakmaoui, Alain Gueiffier*, Jean-Claude Milhavet, Yves Blache, Jean-Pierre Chapat
Laboratoire de Chimie Organique Pharmaceutique, URA-CNRS 1111, 15 Avenue C. Flahault, 34060 Montpellier Cédex, France

Olivier Chavignon, Jean-Claude Teulade
Département de Chimie Structurale et Pharmacochimie, Faculté de Pharmacie, Université d'Auvergne, 63001 Clermont-Ferrand, France

Robert Snoeck, Graciela Andrei and Erik De Clercq
Katholieke Universiteit Leuven, Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000, Leuven, Belgique

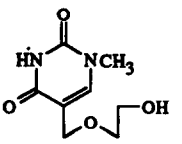
Abstract. A series of 3-substituted imidazo[1,2-*a*]pyridines was synthesized as potential antiviral agents. Compound 10b and, to a lesser extent, 10c showed activity against both TK^+ and TK^- strains of varicella-zoster virus.

Among the antiviral agents, acyclic nucleosides have received much attention. Acyclovir (ACV) 1, Ganciclovir (GCV) 2, iNDG 3 and Buciclovir 4 are active against herpes simplex virus (HSV), varicella-zoster virus (VZV) and/or cytomegalovirus (CMV).[1] Other compounds known as antiviral agents include (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), (*S*)-9-(2,3-dihydroxypropyl)adenine (DHPA), ribavirin and carbocyclic 3-deazaadenosine (C-c^{3}Ado).[1]



1 R = $CH_2O(CH_2)_2OH$
2 R = $CH_2OCH(CH_2OH)_2$
3 R = $CH_2OCH_2CH(OH)CH_2OH$
4 R = $CH_2CH_2CH(OH)CH_2OH$

Since the first synthesis of acyclo C-nucleosides by Igolen,[2] a number of acyclo-C-nucleosides have been reported.[3] From these, only 1-methylacyclopseudouridine 5 reported by Chu[4] showed activity against HSV-1.



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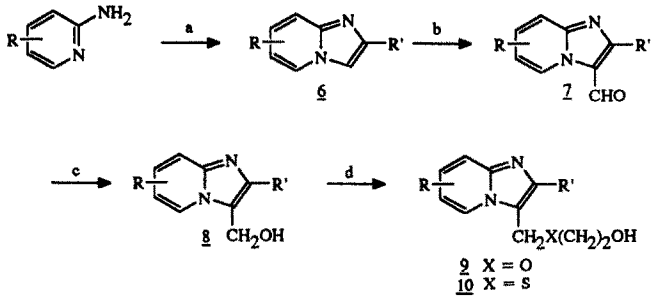
In continuation of our studies on bridgehead nitrogen heterocycles,[5] we became interested in the preparation of imidazo[1,2-*a*]pyridines possessing the acyclovir side chain and sulfur isoster in the 3-position. Condensation of suitably substituted 2-aminopyridines with α-halogenocarbonyl derivatives according the procedure of Tschitschibabin[6] gave the imidazo[1,2-*a*]pyridine 6a-c in 50-82% yield. Vilsmeier-Haack reaction gave the 3-formyl derivatives 7a-c (50-80% yield), which were reduced to the corresponding alcohols 8a-c (90-95%) using sodium borohydride. The chloromethyl derivative obtained by reaction with thionyl chloride gave the starting alcohol when the reaction mixture was basified; then, nucleophilic substitution with ethylene glycol or 2-mercaptoethanol was carried out in one pot in pyridine to give the desired derivatives 9a-c (30-70%) and 10a-c (65-95%).[7]



a: R = H R' = H
b: R = 7-CH_3 R' = H
c: R = H R' = C_6H_5

a. Phenacyl bromide or chloroacetaldehyde, EtOH, reflux; b. DMF, $POCl_3$, 90°C; c $NaBH_4$, MeOH, reflux; d. i:$SOCl_2$; ii: ethylene glycol (115°C, 4h) or 2-mercaptoethanol (90°C, 3h), pyridine.

The antiviral activity of 9b,c and 10b,c was investigated against various viruses (Tables 1-5). Compound 10b was active against both thymidine kinase-positive (TK^+) and -negative (TK^-) strains of varicella-zoster virus (VZV) at a 10-fold lower concentration than the cytotoxic concentration. Compound 10c was active against VZV at a 2- to 8-fold lower concentration than the cytotoxic concentration. None of the test compounds was active against CMV or HSV. Similarly, no selective activity was noted with any of the compounds against other viruses.

3-Thioesters of the acyclovir side chain of imidazo[1,2-*a*]pyridine may be regarded as a potential new class of anti-viral agents. Further studies, focused on the modification of the side chain and nature of the substituents in the heterocycle, are in progress

Table 1. Activity against varicella-zoster virus in human embryonic lung (HEL) cells.

Compound	Antiviral activity (IC_{50} (μg/ml))[a]				Cytotoxicity (μg/ml)	
	TK^+VZV		TK^-VZV			
	OKA strain	YS strain	O7/1 strain	YS/R strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
10c	28	35	26	10	>40	80
9c	>40	>40	>40	>40	>40	135
10b	10	6	4	7	40	70
9b	>40	>40	>40	>40	>40	>200
ACV	0.23	0.32	22	9	>40	>50

[a] Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.

Table 2. Activity against cytomegalovirus in human embryonic lung (HEL) cells.

Compound	Antiviral activity (IC_{50} (μg/ml))[a]		Cytotoxicity (μg/ml)	
	AD-169 strain	Davis strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
10c	20-25	25-40	>40	80
9c	>40	>40	100	130
10b	>10	>10	40	70
9b	>40	>40	>40	>200
GCV	2	1.5	>100	200

[a] Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.

Table 3. Cytotoxicity and antiviral activity in Vero cell cultures.

Compound	Minimum cytotoxic concentration[a] (μg/ml)	Minimum inhibitory concentration[b] (μg/ml)				
		Parainfluenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Semliki forest virus
10c	40	>10	>10	20	70	20
9c	400	70	>200	>200	>200	>200
10b	100	70	>40	70	>100	>100
9b	>200	>200	>200	>200	>200	>200
BVDU	>400	>400	>400	>400	>400	>400
DHPA	>400	20	40	>400	>400	>400
Ribavirin	>400	70	100	70	300	70
C-c^{3}Ado	>400	0.7	2	4	>400	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

Table 4. Cytotoxicity and antiviral activity in E_6SM cell cultures.

Compound	Minimum cytotoxic concentration[a] (µg/ml)	Minimum inhibitory concentration[b] (µg/ml)					
		Herpes simplex virus-1 (KOS)	Herpes simples virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK- B2006	Herpes simplex virus-1 TK- VMW1837
10c	>200	100	70	70	>40	>40	>40
9c	>200	>200	>200	>200	>100	>100	>100
10b	>200	>200	>100	>100	>100	>100	>200
9b	>400	>400	>400	>400	>400	>400	>400
BVDU	>400	0.004	20	0.2	>400	2	1
DHPA	>400	100	>400	40	40	200	100
Ribavirin	>400	>400	150	70	150	300	300
C-c^{3}Ado	>400	>400	300	0.7	0.7	200	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

Table 5. Cytotoxicity and antiviral activity in HeLa cell cultures.

Compound	Minimum cytotoxic concentration[a] (µg/ml)	Minimum inhibitory concentration[b] (µg/ml)		
		Vesicular stomatitis virus	Coxsackie virus B4	Polio virus-1
10c	>100	>100	>100	>100
9c	400	>200	>200	>200
10b	10	>10	>10	>10
9b	200	>200	>200	>200
BVDU	>400	>400	>400	>400
DHPA	>400	70	>400	>400
Ribavirin	>400	20	70	70
C-c^{3}Ado	>400	2	>400	>400

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

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References:

1. E. De Clercq, *Adv. Drug Res.*, **1988**, *17*, 1.
2. F. Babin, T. Huynh-Dinh, J. Igolen, *J. Heterocyclic Chem.*, **1983**, *20*, 1169.
3. C.K. Chu, S.J. Culter, *J. Heterocyclic Chem.*, **1986**,*23*, 289.
4. C.K. Chu, *J. Heterocyclic Chem.*, **1984**, *21*, 9.
5. A. Gueiffier, J.C. Milhavet, Y. Blache, O. Chavignon, J.C. Teulade, H. Viols, G. Dauphin, *Chem. Pharm. Bull.*, **1990**, *38(9)*, 2352; O. Chavignon, J.C. Teulade, A. Gueiffier, Y. Blache, H. Viols, J.P. Chapat, G. Dauphin, *J. Heterocyclic Chem.*, **1992**, *29*, 283
6. A.E. Tschitschibabin, *Ber.*, **1925**, *58*, 1704.
7. All compounds were fully characterized by ^1H and ^{13}C NMR, mass spectrometry and elemental analyses.

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