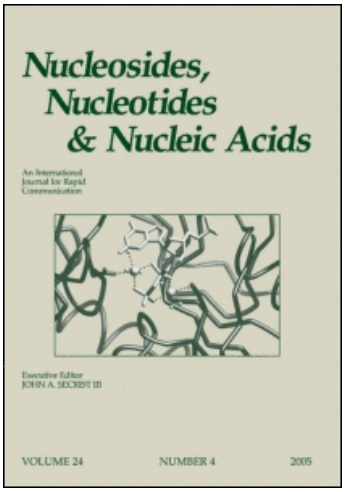


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Biological Activity of Some Dialkyl α-Anilinobenzylphosphonates and Their Palladium(II) Complexes

Lj. Tušek-Božić[a]; M. Ćurić[a]; J. Balzarini[b]; E. De Clercq[b]
[a] Department of Physical Chemistry, Ruder Bošković Institute, Zagreb, Croatia [b] Rega Institute for Medical Research, Katholieke Universiteit Leuven, Leuven, Belgium

To cite this Article Tušek-Božić, Lj. , Ćurić, M. , Balzarini, J. and De Clercq, E.(1995) 'Biological Activity of Some Dialkyl α-Anilinobenzylphosphonates and Their Palladium(II) Complexes', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 777 — 781
To link to this Article: DOI: 10.1080/15257779508012470
URL: http://dx.doi.org/10.1080/15257779508012470

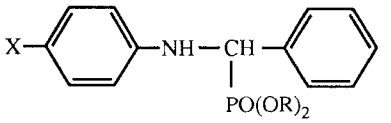
NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 777-781 (1995)

BIOLOGICAL ACTIVITY OF SOME DIALKYL α-ANILINOBENZYLPHOSPHONATES AND THEIR PALLADIUM(II) COMPLEXES

Lj. Tušek-Božić,[1]* M. Ćurić,[1] J. Balzarini[2] and E. De Clercq[2]
[1]Department of Physical Chemistry, Ruđer Bošković Institute, 41000 Zagreb, Croatia,
[2]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Abstract - Diethyl and dibutyl α-anilinobenzylphosphonates and [α-(4-benzeneazoanilino)benzyl]-phosphonates and their new palladium(II) halide complexes were evaluated for their cytostatic and antiviral activity in different cell systems.

Organophosphorus compounds such as derivatives of various aminophosphonic acids may be used as valuable models for biologically important nucleotide analogues[1] and their metal complexes as potential antitumoral and antiviral agents.[2] Continuing our investigations on new palladium(II) complexes with this class of phosphorus ligands,[3,4] here we describe complexes of various α-anilinobenzylphosphonates with detailed account of their biological properties.



1 L1: X=H; R=Et
2 L2: X=H; R=Bu
3 L3: X=Ph-N=N; R=Et
4 L4: X=Ph-N=N; R=Bu

Dialkyl esters of α-anilinobenzylphosphonic acid **1** and **2** and of [α-(4-benzeneazoanilino)benzyl]-phosphonic acid **3** and **4** were prepared as previously described.[5,6] For the preparation of their complexes, either adducts, $Pd(L)_2X_2$ (L = phosphorus ligand, X = Cl, Br), or cyclometallated derivatives, $[Pd(L\text{-}H)Cl]_2$, two general procedures were used. Palladium dichloride complexes **1a** and **2a**, as well as dichloride binuclear palladium complexes **3d** and **4d**, were obtained by reaction of the ligand and Na_2PdCl_4 in methanol at room temperature, while dichloride and dibromide complexes **3a**, **3b**, **3c**, **4a** and **4b** were prepared by reaction of $Pd(CH_3CN)_2Cl_2$ or $Pd(PhCN)_2Br_2$ with the appropriate ligand under refluxing in dichloromethane. Dihalide complexes with 1 : 2 metal-to-ligand ratio contain mutually *trans* N-bonded ligand through the anilinobenzyl nitrogen in α-anilinobenzylphosphonate complexes and through the azo nitrogen in [α-(4-benzeneazoanilino)benzyl]phosphonate complexes, respectively. Azobenzene containing ligands by *ortho*-metallation also form cyclopalladated complexes with the metal-metal chloro bridge. More details about preparation, identification and characterization of these complexes, which include comprehensive spectroscopic studies (IR, ^1H and ^{13}C NMR, UV-VIS and FAB-MS), accompanied by thermogravimetric, magnetic and conductometric measurements, will be desribed elsewhere.

The cytotoxicity and antiviral activity of the free organophosphorus ligands and their newly synthesized palladium(II) complexes are summarized in Tables 1-3. The antiviral assays were based on an inhibition of virus-induced cytopathogenicity in either E_6SM, HeLa, Vero or CEM cell cultures, following previously established procedures.[7,8] No specific antiviral effects were noted whether the compounds were originally dissolved in DMSO or MEM. Also, none of the compounds was inhibitory to replication of human immunodeficiency virus type 1 and type 2 [HIV-1(III_B) and HIV-2(ROD)] in human T-lymphocyte CEM

TABLE 1. Cytotoxicity and antiviral activity of dialkyl α-anilinobenzylphosphonates and their palladium(II) halide complexes against different viruses in human embryonic skin fibroblast (E_6SM) cell cultures.[a]

Compound		Minimum cytotoxic concentration[b] (μg/ml)		Minimum inhibitory concentration[c] (μg/ml)											
				Herpes simplex virus-1 (KOS)		Herpes simplex virus-2 (G)		Vaccinia virus		Vesicular stomatitis virus		Herpes simplex virus-1 TK⁻/B2006		Herpes simplex virus-1 TK⁻/VMW1837	
		DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]
1	L1	≥ 400	> 100	> 200	> 100	> 200	100	> 200	> 100	> 200	> 100	> 200	> 100	> 150	> 100
1a	$Pd(L1)_2Cl_2$	400	≥ 40	> 200	> 10	200	> 10	> 200	> 10	> 200	> 10	> 200	> 10	> 200	> 10
2	L2	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
2a	$Pd(L2)_2Cl_2$	40	≥ 40	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40
3	L3	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
3a	$Pd(L3)_2Cl_2$	40	≥ 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
3b	$Pd(L3)_2Br_2$-r	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
3c	$Pd(L3)_2Br_2$-o	10	≥ 100	> 4	> 100	> 4	> 100	> 4 (7)	> 100	> 4 (7)	> 100	> 4	> 100	> 4	> 100
3d	$[Pd(L3\text{-}H)Cl]_2$	100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
4	L4	≥ 40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4a	$Pd(L4)_2Cl_2$	> 100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
4b	$Pd(L4)_2Br_2$	100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
4c	$[Pd(L4\text{-}H)Cl]_2$	100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
BVDU		> 400	> 400	0.007	0.02	70	200	0.2	0.7	> 400	> 400	10	20	40	70
(S)-DHPA		> 400	> 400	> 400	> 400	300	> 400	20	20	20	7	100	> 400	200	> 400
Ribavirin		> 400	> 400	> 400	400	300	> 400	20	70	70	40	300	70	150	150
C-c^3 Ado		> 400	> 400	> 400	> 400	100	> 400	0.7	0.7	0.7	0.2	70	100	100	> 400

[a]Compounds were dissolved in either DMSO or cell culture medium (MEM), and then further diluted in MEM when evaluated for antiviral activity. [b]Required to cause a microscopically detectable alteration of normal cell morphology. [c]Required to reduce virus-induced cytopathogenicity by 50%.

[d]Highest concentration tested: 100 μg/ml.

TABLE 2. Cytotoxicity and antiviral activity of dialkyl α-anilinobenzylphosphonates and their palladium(II) halide complexes in African green monkey kidney (Vero) cell cultures.[a]

Compound	Minimum cytotoxic concentration[b] (μg/ml)		Minimum inhibitory concentration[c] (μg/ml)									
			Parainfluenza-3 virus		Reovirus-1		Sindbis virus		Coxsackie virus B4		Semliki forest virus	
	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]
1	≥ 400	> 100	> 200	> 100	> 200	> 100	> 200	> 100	> 200	> 100	> 200	> 100
1a	400	≥ 100	> 200	> 40	200	> 40	> 200	> 40	> 200	> 40	> 200	> 40
2	40	≥ 100	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40
2a	40	≥ 100	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40	> 10	> 40
3	≥ 100	≥ 100	20	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40	> 40
3a	≥ 100	> 100	20	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
3b	≥ 100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
3c	40	> 100	7	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
3d	≥ 40	> 100	> 40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4	100	> 100	> 40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4a	100	> 100	> 40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4b	≥ 40	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4c	100	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
BVDU	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
(S)-DHPA	> 400	> 400	70	70	70	70	> 400	> 400	> 400	> 400	> 400	> 400
Ribavirin	> 400	> 400	20	20	100	150	> 400	70	300	70	150	70
C-c[3] Ado	> 400	> 400	1	1	2	2	> 400	> 400	> 400	> 400	> 400	> 400

[a]Compounds were dissolved in either DMSO or cell culture medium (MEM), and then further diluted in MEM when evaluated for antiviral activity. [b]Required to cause a microscopically detectable alteration of normal cell morphology. [c]Required to reduce virus-induced cytopathogenicity by 50%. [d]Highest concentration tested: 100 μg/ml.

TABLE 3. Cytotoxicity and antiviral activity of dialkyl α–anilinobenzylphosphonates and their palladium(II) halide complexes in human cervix carcinoma (HeLa) cell cultures.[a]

Compound	Minimum cytotoxic concentration[b] (μg/ml)		Minimum inhibitory concentration[c] (μg/ml)					
			Vesicular stomatitis virus		Coxsackie virus B4		Polio virus-1	
	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]	DMSO	MEM[d]
1	200	> 100	150	> 100	> 100	> 100	> 100	> 100
1a	100	100	> 100	> 40	> 100	> 40	> 100	> 40
2	10	> 100	> 4	> 100	> 4	> 100	> 4	> 100
2a	≥ 4	> 100	> 4	> 100	> 4	> 100	> 4	> 100
3	10	> 100	> 10	> 100	> 10	> 100	> 10	> 100
3a	≥ 100	≥ 100	> 40	> 40	> 40	> 40	> 40	> 40
3b	≥ 40	> 100	> 40	> 100	> 40	> 100	> 40	> 100
3c	≥ 40	≥ 100	> 40	> 40	> 40	> 40	> 40	> 40
3d	200	> 100	> 100	> 100	> 100	> 100	> 100	> 100
4	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4a	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4b	40	> 100	> 10	> 100	> 10	> 100	> 10	> 100
4c	100	> 100	> 40	> 100	> 40	> 100	> 40	> 100
BVDU	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
(S)-DHPA	> 400	> 400	70	> 70	> 400	> 400	> 400	> 400
Ribavirin	≥ 100	≥ 200	20	> 20	40	20	70	70
C-c^3 Ado	> 400	> 400	1	> 2	> 400	> 400	> 400	> 400

[a]Compounds were dissolved in either DMSO or MEM, and then further diluted in MEM when evaluated for antiviral activity. [b]Required to cause a microscopically detectable alteration of normal cell morphology. [c]Required to reduce virus-induced cytopathogenicity by 50%. [d]Highest concentration tested: 100 μg/ml.

cells at subtoxic concentrations (> 40 μg/ml for **1** and **1a** or > 8 μg/ml for the other compounds). The test compounds have also been evaluated for their cytostatic activity against murine L1210, and human Molt/4F and CEM cells. The cytostatic activity varied widely from 5 to > 100 μg/ml depending the individual test compound and the tumor cell line studied. None of the palladium(II) halide complexes proved more cytostatic than the free organophosphorus ligands.

Acknowledgement- Financial support by the Ministry of Science and Technology of Republic Croatia (grant 1-07-165) is gratefully acknowledged.

REFERENCES

1. De Clercq, E. *Int. J. Immunopharmacol.*, **1991**, 13, 91; and references therein.
2. Klenner, T.; Keppler, B. K.; Münch, H.; Valenzuela-Paz, P. *Metal Ions in Biology and Medicine*, Collery, Ph.; Poirier, L. A.; Manfait, M.; Etienne J. C. Eds., John Libbey Eurotext, Paris, 1990; pp 369-371.
3. Tušek-Božić, Lj.; Matijašić, I.; Bocelli, G.; Calestani, G.; Furlani, A.; Scarcia, V.; Papaioannou, A. *J. Chem. Soc., Dalton Trans.* **1991**, 195.
4. Tušek-Božić, Lj.; Matijašić, I.; Bocelli, G.; Sgarabotto, P.; Furlani, A.; Scarcia, V.; Papaioannou, A. *Inorg. Chim. Acta* **1991**, 185, 229.
5. Fields, E. K.; *J. Am. Chem. Soc.* **1952**, 74, 1528.

6. Jagodić, V.; Tušek, Lj. J. *Org. Chem.* **1972**, 37, 1222.
7. De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis.* **1980**, 141, 563.
8. Balzarini, J.; Naesens, L.; Slachmuylders, J.; Niphuis, H.; Rosenberg, I.; Holy, A.; Schellekens, H.; De Clercq, E. *AIDS*, **1991**, 5, 21.