Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 7209–7219
Bioorganic & Medicinal Chemistry

Influence of 6 or 8-substitution on the antiviral activity of 3-phenethylthiomethylimidazo[1,2-*a*]pyridine against human cytomegalovirus (HCMV) and varicella-zoster virus (VZV)

Jean-Baptiste Véron,[a] Cécile Enguehard-Gueiffier,[a] Robert Snoeck,[b] Graciela Andrei,[b] Erik De Clercq[b] and Alain Gueiffier[a,*]

[a]*Laboratoire de chimie thérapeutique, Faculté de pharmacie, EA 3857, 31 avenue Monge, 37200 Tours, France*
[b]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium*

Received 10 October 2006; revised 13 March 2007; accepted 20 March 2007
Available online 24 March 2007

Abstract—The synthesis of original imidazo[1,2-*a*]pyridines bearing a phenethylthiomethyl side chain at the 3 position and a (hetero)aryl substituent on the 6 or 8 position, and their antiviral activities are reported. From the synthesized compounds, the 6-halogeno and 6-phenylimidazo[1,2-*a*]pyridine derivatives **4c**–**d** and **5b** were the most potent against human cytomegalovirus (CMV) and/or varicella-zoster virus (VZV), whereas several other congeners (i.e., **5e**, **5g**, **5i**, **5l**, **5n**, **5p**, **5q**, and **5t**), while less potent, were equally or more selective in their inhibitory activity against both VZV and CMV. These compounds showed similar activity against thymidine kinase competent (TK^+) and deficient (TK^-) VZV strains, demonstrating a mechanism of action independent of the viral thymidine kinase.

1. Introduction

Varicella-zoster virus (VZV) and human cytomegalovirus (HCMV) belong to the α- and β-herpesviridae, respectively. Like other herpesviruses, primary infection is followed by persistence of the virus in a latent form.[1] The HCMV primary infection rarely causes disease in immunocompetent individuals with the exception of a mononucleosis-like illness in some patients.[2] However, reactivation of the virus is of significant concern in immunocompromised individuals, such as HIV-infected or patients under immunosuppressive therapy after solid organ or allogeneic bone marrow transplantation.[3] Primary infection with VZV results in varicella (chickenpox), a common and extremely contagious acute infection, mild in healthy children but more severe in adults and immunocompromised persons. VZV establishes latency in neural tissues. Reactivation of latent VZV from dorsal root ganglia results in herpes zoster (shingles), a localized cutaneous eruption accompanied by neuralgic pain that occurs most commonly in older persons.[4]

Currently, five compounds are officially licensed for treatment of HCMV infection.[5] The principal indication for all these agents is HCMV retinitis in AIDS patients. Unfortunately, all these derivatives suffer from a number of drawbacks that limit their clinical usefulness. Thus, oral ganciclovir (GCV) was approved only as maintenance therapy and prophylaxis as the low bioavailability (around 5%) of the oral formulation was considered insufficient for induction therapy. There were concerns that inadequate viral suppression resulting from the lower systemic exposure from oral GCV could lead to emergence of drug resistance.[6] The side effects of GCV include hematologic abnormalities (primarily neutropenia, anemia, and thrombocytopenia) secondary to bone marrow suppression and probable long-term reproductive toxicity.[7] Valganciclovir (VGV), a prodrug of ganciclovir, has an improved oral bioavailability of around 60%.[8] Cidofovir (CDV) is available only as an IV formulation as its oral bioavailability is less than 5%. The drug needs only one administration per 1 or 2 weeks, as a result of its long intracellular half-life. The major limitation of CDV is severe renal toxicity.

Keywords: Antiviral drugs; Human cytomegalovirus (HCMV); Varicella-zoster virus (VZV); Imidazo[1,2-*a*]pyridine.
* Corresponding author. Tel.: +33 247 367 138; fax: +33 247 367 288; e-mail: alain-gueiffier@univ-tours.fr

0968-0896/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.bmc.2007.03.061

Patients receiving iv CDV (always as a second line therapy) must be given oral probenecid to protect against kidney failure and must be prehydrated before infusion.[6] The major dose-limiting toxicity of foscarnet (FOS) is renal impairment, underscoring the importance of adequate hydration and frequent monitoring of serum creatinine levels in patients receiving FOS. Renal impairment may lead to a number of cardiac or neurologic disorders, including seizures, that in several cases resulted in death.[7] FOS must be given intravenously three times daily.[5] Finally, fomivirsen has to be injected intraocularly, as a second-line therapy for local treatment of CMV retinitis in AIDS patients. The most frequent adverse effect is ocular inflammation (uveitis).[6,7]

As regards the treatment of VZV infections, four compounds are officially licensed: acyclovir, valaciclovir, famciclovir, and brivudin.[5] Famciclovir is an oral prodrug of penciclovir that presents a safety profile and antiviral activity spectrum largely similar to those of acyclovir. Finally, the in vitro inhibitory effect of brivudin on VZV by far exceeds that of acyclovir. In addition, brivudin has favorable oral bioavailability allowing only once-daily dosing.[6]

The antiviral activity and selectivity of acyclovir, ganciclovir, and related compounds is based on their specific activation by herpesvirus-encoded kinases (thymidine kinase TK for VZV and UL97 protein kinase for CMV) that convert these nucleoside analogues to their monophosphate metabolites. After initial conversion of the purine nucleoside analogues to their monophosphate, further activation to the di- and triphosphate is catalyzed by cellular enzymes involved in nucleotide metabolism. For brivudin, the monophosphate is converted to the diphosphate by HSV TK or VZV TK. These compounds after phosphorylation act as competitive inhibitor/alternate substrate with the substrate binding site of the DNA polymerase, resulting in inhibition of viral DNA synthesis.[6,9]

FOS and CDV are the only two antiherpes drugs known to inhibit viral DNA synthesis in a manner that is independent of viral thymidine kinase or protein kinase. FOS requires no metabolic activation; it interacts directly with the pyrophosphate binding site of the DNA polymerase. CDV requires a two-step activation by cellular kinases; its diphosphate inhibits the viral DNA polymerase.

Fomivirsen does not interfere with viral DNA synthesis but is a unique antiviral agent that inhibits CMV replication by an antisense mechanism. It prevents viral replication by binding to a complementary CMV mRNA sequence, thereby inhibiting translation of several CMV immediate early proteins.[6,9]

Thus, the main approved systemic drugs share a similar mechanism of action, targeting the viral DNA polymerase. The emergence of drug-resistant virus strains that carry alterations in the viral TK (VZV) or UL97 protein kinase (CMV) affects predominantly patients after long-term GCV or ACV therapy. Suppression of TK-deficient strains of VZV can only be achieved with TK-independent drugs such as FOS or CDV. These two drugs also retain full antiviral activity against GCV-resistant CMV strains carrying mutations in the CMV UL97 gene.

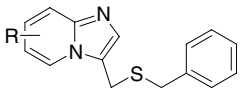
The extensive studies on the emergence of HCMV drug resistance strongly underscore that cross-resistance and drug-related toxicity can severely limit the therapeutic alternatives. Thus, development of new anti-HCMV drugs with novel mechanisms of action, less toxic, more effective, and orally bioavailable is urgently needed.[9,10] The human herpesvirus inhibitors in development have been recently largely reviewed.[9,11–14]

In our search in the chemistry and pharmacology of bridgehead heterocycles, we have reported that 7- and 8-methyl-3-phenylmethylthiomethylimidazo[1,2-*a*]pyridines **I**–**II** (Fig. 1) are potent inhibitors of HCMV and VZV.[15] We have now further investigated the influence of the thioether side chain and showed that phenethylthiomethyl group enhances the activity and diminishes the toxicity.[16] We have then demonstrated that many functionalities are tolerated in position 2 but in all cases, the unsubstituted compound remained the best inhibitor.[17] At this time, optimization of the pyridinic moiety was made problematic because of the lack of efficient methods of functionalization. Interestingly, in the past few years, optimization of various metallo-catalyzed coupling reactions in our laboratory[18–23] allowed us to introduce new functionalities on the pyridinic part of the scaffold, notably aryl and heteroaryl groups in position 6[18] and 8[22] via Suzuki–Miyaura cross-coupling reaction. The synthesis and biological evaluation of this new series of compounds is subject of the present article.

2. Results and discussion

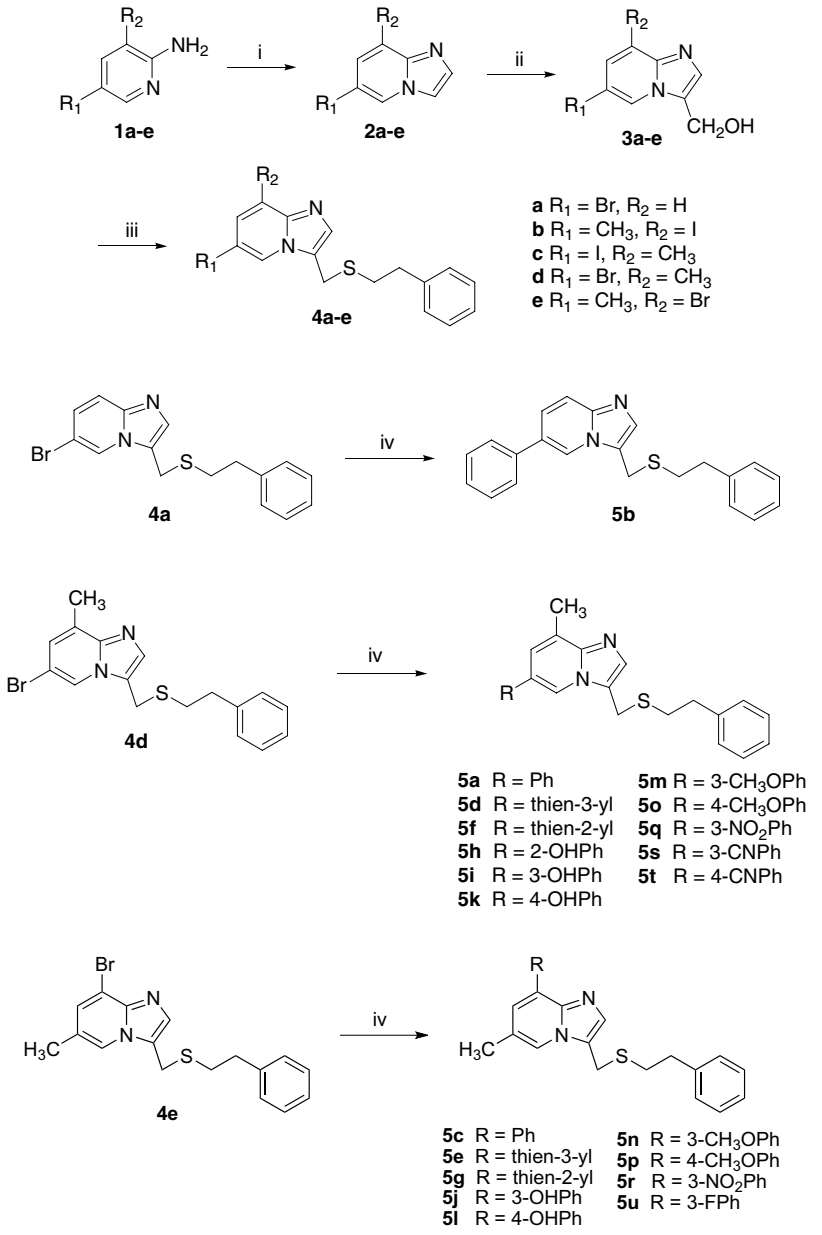
2.1. Chemistry

As shown in Scheme 1, the suitably halogenated 2-aminopyridines **1a**–**e**[24,25] were refluxed with chloroacetaldehyde in ethanol to give the imidazo[1,2-*a*]pyridines **2a**–**e**[16,25] in around 85% yields. Hydroxymethylation in position 3 of this scaffold was previously described using formaldehyde in acetic acid media in the presence of sodium acetate. In initial procedures, the reaction was performed in a Parr apparatus and isolation of the attempted product was made difficult because of the formation of a dimeric compound. Recently, we have shown that the reaction has to be performed at specific



I R = 7-CH_3
II R = 8-CH_3

Figure 1. Potent inhibitors of HCMV and VZV.



Scheme 1. Reagents: (i) $ClCH_2CHO$, C_2H_5OH; (ii) HCHO, CH_3COONa, CH_3COOH; (iii) $Ph(CH_2)_2SH$, CH_3COOH; (iv) $RB(OH)_2$, $Pd(PPh_3)_4$, NaOH or Na_2CO_3/DME, H_2O.

temperature depending upon the nature of substituent in position 2 in order to avoid the formation of the dimeric side product.[17] Concerning the 2-unsubstituted derivatives **2a**–**e**, a reaction temperature of 40 °C was required to give the corresponding alcohols **3a**–**e** within 24 h in about 80% yield. The thioether side chain was introduced using phenethylthiol in acetic media at 80 °C giving **4a**–**e** in moderate to good yield (41–90%).

In our previous studies on metallo-catalyzed coupling reactions, we reported that Suzuki reaction on 6 or 8-halogenoimidazo[1,2-*a*]pyridine occurred in various conditions. The reaction was efficient starting from the bromo or iodo derivatives using *tetrakis*(triphenylphosphine)palladium(0) as catalyst, and different bases, that is, NaOH, Na_2CO_3 or K_3PO_4 in 1,2-dimethoxyethane.[18,22] In this work, NaOH or Na_2CO_3 was used as base. The corresponding aryl or heteroaryl compounds **5a**–**u** were obtained in moderate to good yields, with the exception of the hydroxyphenyl compounds which were obtained in 35–51% yields, probably due to their poor solubility and the successive chromatographies required for the purification step.

2.2. Antiviral activity

All the synthesized compounds were inactive against parainfluenza-3 virus, reovirus-3, Sindbis virus, Coxsackie virus B4, Punta Toro virus in Vero cell cultures, against vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus in HeLa cell cultures,

and against herpes simplex virus type 1 (HSV-1) (KOS) and thymidine kinase-deficient (TK^-) (KOS) acyclovir-resistant (ACV^r) strains, HSV-2, and vesicular stomatitis in E_6SM cell cultures.

Compounds **5c**, **5f**, **5j**, and **5p** showed moderate activities against vaccinia virus [EC_{50} (50% effective concentration) = 9.6 μg/mL and a minimal cytotoxic concentration (MCC) of 80 μg/mL in E_6SM cell cultures].

The most interesting antiviral activities were obtained against CMV and VZV in human embryonic lung HEL cells (Table 1).

2.2.1. Anti-VZV activity. At first, it should be noted that contrarily to acyclovir and brivudin which require phosphorylation to exert their antiviral activity, our compounds showed the same range of activity against TK^+ and TK^- VZV strains, demonstrating a mechanism of action independent of the virus-encoded thymidine kinase.

With regard to the structure–activity relationship (SAR), the influence of the substitution position depends on the nature of the substituent. For the halogenated compounds **4b**–**d**, halogen atom is preferred in position 6 over position 8 for antiviral activity. However, these three compounds were rather cytotoxic since the MCC (minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology) values for those compounds were in the same range as their EC_{50} values. This toxicity seems to be diminished with the presence of a substituent in position 8 (methyl or phenyl) as seen with phenyl derivatives **5a**–**c**, when comparing **5b** with **5a** or **5c**. However, the 8-methyl also decreased the anti-VZV activity, that is, EC_{50} = 0.74 μg/mL (compound **5b**) compared to EC_{50} = 3.6 μg/mL (compound **5a**) against TK^+ VZV strains. Similar results were observed with the thienyl compounds **5d**–**g**, with the 6-thienyl derivatives, that is, **5d** and **5f** (EC_{50} = 1.7–4 μg/mL), being more potent than the 8-thienyl analogues, that is, **5e** and **5g** (EC_{50} = 7.8–8.9 μg/mL). A highly decreased toxicity was noted with a thienyl group in position 8 (MCC = 100 μg/mL for **5e** and **5g** compared to MCC ⩾ 4 and 20 μg/mL for **5d** and **5f**).

With regard to the 6-phenyl substitution pattern, a hydroxyl group was tolerated only in meta position (**5i**: EC_{50} = 2.4 μg/mL for TK^+ strain) while a total loss of activity was observed with the hydroxyl in *ortho* (**5h**) or *para* (**5k**) positions (EC_{50} > 20 μg/mL). On the contrary, the methoxy and cyano groups are preferred in *para* position (EC_{50} = 2.2–2.4 μg/mL for TK^+ strain) instead of *meta* (EC_{50} > 4 and 100 μg/mL for the TK^+ strain, respectively).

The compounds showing the highest anti-VZV potency (EC_{50} < 1.0 μg/mL) were the 6-iodo and 6-phenyl derivatives **4c** and **5b**, with EC_{50} values against TK^+ strain in the same range as acyclovir but with much higher potencies against the TK^- strain than the two references. However, these compounds inhibited VZV plaque formation at concentrations similar to those that alter cell morphology.

On the other hand, among compounds that inhibited VZV plaque formation at concentrations that resulted in no alteration of cell morphology, viz. **5e**, **5g**, **5i**, **5j**, **5l**, **5n**, **5p**, **5q**, and **5t**, while less potent (EC_{50} > 1.0 μg/mL) than **4c** and **5b**, had selectivity indexes (ratio of CC_{50} to EC_{50}) equal to or higher than 5.

2.2.2. Anti-CMV activity. As seen in table, the tested compounds can be classified in three groups depending on their range of anti-CMV activities: a group of totally inactive compounds (**5h**, **5k**, and **5r**) with an EC_{50} > 100 μg/mL, a group of moderately active compounds (**4b**, **5a**, **5d**–**5g**, **5i**, **5j**, **5l**, **5m**, **5o**–**5q**, **5s**–**5u**) with an EC_{50} between 2 and 4 μg/mL, and a group of two active compounds (**4c** and **4d**) with an EC_{50} < 1 μg/mL. It should be noted that some of the compounds inhibited mostly the Davis strain and not the AD-169 strain. The compounds (**5h**,**k**,**n**,**r**) that were inactive against CMV are also totally inefficient against VZV; thus, an *ortho*- or *para*-hydroxyphenyl group in the 6 position is deleterious for the antiviral activity as well as a 3-methoxy- or 3-nitrophenyl in the 8 position. Although compounds **4c** and **4d** showed the lowest EC_{50} values, compound **4c** only showed activity against the Davis strain but at concentrations close to those that altered cell morphology (MCC ⩾ 0.8). Compound **4d** showed EC_{50} values that were about 10-fold lower than MCC values, and the highest selectivity index (SI = 124).

The compounds showing the highest anti-CMV potency (**4c**, **4d** and **5b**) (EC_{50} < 1.0 μg/mL) were also the most cytotoxic (MCC values of the same order as EC_{50} values). On the other hand, a wealth of compounds, viz. **5a**, **5e**–**5g**, **5i**, **5m**, **5o**–**5q**, **5s**, and **5u**, which showed an EC_{50} of 2–4 μg/mL, had selectivity indexes (ratio CC_{50} to EC_{50}) similar to or in excess of 5.

3. Conclusion

In this work, we have shown that the substituent at the 6 or 8 position strongly influences the activity of these compounds against human cytomegalovirus and varicella-zoster virus as well as their cytotoxicity. From the synthesized compounds, the 6-halogeno and 6-phenylimidazo[1,2-*a*]pyridine derivatives **4c**, **4d** and **5b** were the most potent agents against CMV and/or VZV, whereas various other compounds, viz. **5e**, **5g**, **5i**, **5n**, **5p**, **5q**, and **5t**, were the most selective in their inhibitory activity against both VZV and CMV. All compounds showed similar activity against TK^+ and TK^- VZV strains, demonstrating a mechanism of action that is independent of the viral thymidine kinase.

Based on their potency and/or selectivity, any of the following compounds deserves to be further pursued in follow-up studies for their potential in the treatment of VZV and/or HCMV infections: **4c**, **4d**, **5a**, **5b**, **5e**–**5g**,

Table 1. Anti-CMV and -VZV activities and cytotoxic properties in human embryonic lung (HEL) cells

Compound	Antiviral activity EC_{50}[a] (μg/mL)				Cytotoxicity (μg/mL)	
	VZV		CMV		Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
	OKA strain TK^+	07/1 strain TK^-	AD-169 strain	Davis strain		
4b	2.6	2.6	>0.8	1.8	⩾4	>50
4c	0.68	0.43	>0.16	0.12	⩾0.8	>50
4d	0.48	1.1	0.32	0.13	⩾2	28
5a	3.6	>4	2.0	2.2	20	31
5b	0.74	>0.8	>0.8	>0.8	4	9.9
5c	>4	>4	>4	>4	20	33
5d	1.7	1.8	>0.8	1.8	⩾4	>50
5e	8.9	8.6	2.5	2.5	100	>50
5f	4	>4	2.2	2.2	20	32
5g	7.8	4	2.5	2.2	100	>50
5h	>20	>20	>100	>100	100	>50
5i	2.4	3.7	2.2	2.2	20	50
5j	1.6	2.9	>4	>4	20	11.4
5k	>20	>100	>100	>100	⩾100	>50
5l	1.7	2.7	2.2	2.2	20	13.7
5m	>4	>4	2.2	2.5	20	36
5n	8.3	10.3	10.9	10.9	100	>50
5o	2.4	>4	3.1	2.2	20	25.8
5p	2.0	3.1	2.2	2.2	20	19.6
5q	5.6	8.3	7.6	4	⩾100	43
5r	>20	>20	>100	>100	100	47
5s	>100	81	2.2	2.5	>100	>50
5t	2.2	2.0	1.8	2.5	⩾20	10.6
5u	>4	>4	2.2	2.2	20	35
Acyclovir	0.70	28	ND[d]	ND[d]	>400	>200
Brivudin	0.0038	362	ND[d]	ND[d]	>400	ND[d]
Ganciclovir	ND[d]	ND[d]	0.51	0.80	100	146
Cidofovir	ND[d]	ND[d]	0.10	0.12	⩾100	47

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU) for HCMV. Virus input was 20 plaque forming units (PFU) for VZV.
[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.
[d] Not determined.

5i, **5j**, **5m**–**5q**, and **5s**–**5u**. This abundance of possibilities will have to be narrowed down in the light of the future demands for antivirals (for anti-CMV compared to anti-VZV drugs), their in vivo efficacy and pharmacokinetics, and, eventually, safety/toxicity profile.

4. Experimental

4.1. General details

The melting points were determined in a capillary apparatus and are uncorrected. NMR experiments were performed at 200 MHz (^1H) and 50 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6 on Bruker DPX 200 instruments. Possible inversion of two values in the NMR spectra is expressed by an asterisk (*). *Tetrakis*(triphenylphosphine)palladium(0) was prepared as described in the literature.[26] The starting halogenated aminopyridine derivatives **1a**–**e** were prepared by iodination[24] or bromination[25] of commercially available aminopyridines. Previously reported imidazo[1,2-*a*]pyridines synthesized by the described procedure were 6-bromoimidazo[1,2-*a*]pyridine **2a**,[25] 6-bromo-8-methylimidazo[1,2-*a*]pyridine **2d**,[16] and 8-bromo-6-methylimidazo[1,2-*a*]pyridine **2e**,[25] 6-bromo-3-hydroxymethylimidazo[1,2-*a*]pyridine **3a**,[16] 6-bromo-3-hydroxymethyl-8-methylimidazo[1,2-*a*]pyridine **3d**,[16] 8-bromo-3-hydroxymethyl-6-methylimidazo[1,2-*a*]pyridine **3e**.[16]

4.2. Chemistry

4.2.1. General procedure for cyclization (2a–e). The appropriate 2-aminopyridine **1a**–**e** (27 mmol) and an aqueous solution of chloroacetaldehyde 45% (4.3 mL, 29,4 mmol) were refluxed in 50 mL of ethanol for 24 h. After cooling, the solution was concentrated to dryness, then diluted in water. The solution was made basic by addition of sodium carbonate and extracted with dichloromethane. The dried organic layers were evaporated to dryness and chromatographed on silica gel eluting with diethyl ether.

4.2.1.1. 8-Iodo-6-methylimidazo[1,2-*a*]pyridine (2b). Yield 85%. Mp 171–172 °C. ^1H NMR ($CDCl_3$) δ 7.90 (m, 1H, H_5), 7.62 (m, 2H, H_2, H_3), 7.53 (d, 1H, $J = 1.3$ Hz, H_7), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.31 (C8a), 137.20 (C7), 133.92 (C2), 124.23 (C5), 123.36 (C6), 114.48 (C3), 84.06 (C8), 18.04 (CH_3).

4.2.1.2. 6-Iodo-8-methylimidazo[1,2-*a*]pyridine (2c). Yield 89%. Mp 138 °C. ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H, H_5), 7.57 (d, 1H, J = 1.2 Hz, H_2), 7.52 (d, 1H, J = 1.2 Hz, H_3), 7.16 (s, 1H, H_7), 2.59 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.81 (C8a), 133.46 (C2), 131.17 (C7), 129.28 (C8), 128.88 (C5), 112.92 (C3), 75.89 (C6), 17.16 (CH_3).

4.2.2. General procedure for hydroxymethylation (3a–e). To a solution of imidazo[1,2-*a*]pyridine **2a**–**e** (32 mmol) in 8.5 mL of acetic acid was added sodium acetate (9.7 g, 0.118 mol) and then an aqueous solution of formaldehyde 37% (16 mL, 0.224 mol). The reaction mixture was stirred for 24 h at 40 °C. After cooling, the reaction mixture was diluted with water and made basic with sodium carbonate. The precipitate was filtered off and chromatographed on neutral alumina eluting with a mixture of CH_2Cl_2 and methanol (95:5).

4.2.2.1. 3-Hydroxymethyl-8-iodo-6-methylimidazo[1,2-*a*]pyridine (3b). Yield 81%. Mp 176–178 °C. ^{1}H NMR (DMSO-d_6) δ 8.23 (m, 1H, H_5), 7.67 (d, 1H, J = 1.2 Hz, H_7), 7.47 (s, 1H, H_2), 4.72 (s, 2H, CH_2), 3.38 (s, 1H, OH), 2.27 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 144.40 (C8a), 136.94 (C7), 132.66 (C2), 127.37 (C3), 123.79 (C5), 123.05 (C6), 85.19 (C8), 53.61 (CH_2), 18.00 (CH_3).

4.2.2.2. 3-Hydroxymethyl-6-iodo-8-methylimidazo[1,2-*a*]pyridine (3c). Yield 84%. Mp 218–220 °C. ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 1H, H_5), 7.45 (s, 1H, H_2), 7.33 (s, 1H, H_7), 5.30 (t, 1H, J = 5.4 Hz, OH), 4.79 (d, 2H, J = 5.4 Hz, CH_2), 2.47 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 144.99 (C8a), 132.30 (C2), 130.93 (C7), 129.02 (C8), 128.41 (C5), 126.11 (C3), 76.91 (C6), 53.35 (CH_2), 16.96 (CH_3).

4.2.3. General procedure to obtain thioether derivatives (4a–e). To a solution of imidazo[1,2-*a*]pyridine **3a**–**e** (12.4 mmol) in 12 mL of acetic acid was added phenethylmercaptan (1.5 mL, 11.2 mmol). The mixture was heated at 80 °C overnight. After cooling, the solution was diluted with water, made basic with sodium carbonate, and extracted with dichloromethane. The organic layers were dried and evaporated to dryness. The residue was chromatographed on neutral alumina eluting with dichloromethane.

4.2.3.1. 6-Bromo-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (4a). Yield 41%. Mp 107–109 °C. ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 1H, H_5), 7.58 (d, 1H, J = 9.5 Hz, H_8), 7.52 (s, 1H, H_2), 7.37–7.24 (m, 4H, H_7, Ph-3,4,5), 7.17 (m, 2H, Ph-2,6), 3.97 (s, 2H, CH_2), 2.80 (m, 2H, CH_2), 2.64 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 145.10 (C8a), 140.32 (Ph-1), 134,26 (C2), 128.95 (Ph-2,3,5,6), 128.18 (C7), 126.96 (Ph-4), 124.86 (C5), 119.98 (C3), 118.95 (C8), 107.51 (C6), 36.32 (CH_2), 33.02 (CH_2), 25.43 (CH_2). Anal. Calcd for $C_{16}H_{15}BrN_2S$: C, 55.34; H, 4.35; N, 8.07. Found: C, 55.12; H, 4.43; N, 8.17.

4.2.3.2. 8-Iodo-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (4b). Yield 78%. Mp 105–107 °C. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 1H, J = 1.3 Hz, H_5), 7.63 (d, 1H, J = 1.3 Hz, H_7), 7.53 (s, 1H, H_2), 7.41–7.22 (m, 3H, Ph-3,4,5), 7.16 (m, 2H, Ph-2,6), 3.93 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.12 (C8a), 140.35 (Ph-1), 136.94 (C7), 133.83 (C2), 128.95 (Ph-2,6*), 128.88 (Ph-3,5*), 126.88 (Ph-4), 123.19 (C6), 122.66 (C5), 121.06 (C3), 84.46 (C8), 36.27 (CH_2), 32.84 (CH_2), 25.74 (CH_2), 18.41 (CH_3). Anal. Calcd for $C_{17}H_{17}IN_2S$: C, 50.01; H, 4.20; N, 6.86. Found: C, 49.85; H, 4.29; N, 6.93.

4.2.3.3. 6-Iodo-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (4c). Yield 74%. Mp 99–100 °C. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1H, J = 0.8 Hz, H_5), 7.44 (s, 1H, H_2), 7.35–7.22 (m, 4H, H_7, Ph-3,4,5), 7.17 (m, 2H, Ph-2,6), 3.94 (s, 2H, CH_2), 2.82 (m, 2H, CH_2), 2.71–2.59 (m, 5H, CH_2, CH_3); ^{13}C NMR ($CDCl_3$) δ 147.75 (C8a), 140.38 (Ph-1), 133.10 (C2), 131.46 (C7), 129.45 (C8), 128.95 (Ph-2,3,5,6), 127.57 (C5), 126.92 (Ph-4), 119.83 (C3), 76.11 (C6), 36.36 (CH_2), 33.00 (CH_2), 25.53 (CH_2), 17.09 (CH_3). Anal. Calcd for $C_{17}H_{17}IN_2S$: C, 50.01; H, 4.20; N, 6.86. Found: C, 49.88; H, 4.19; N, 6.90.

4.2.3.4. 6-Bromo-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (4d). Yield 89%. Mp 66–68 °C. ^{1}H NMR ($CDCl_3$) δ 8.17 (m, 1H, H_5), 7.50 (s, 1H, H_2), 7.36–7.24 (m, 3H, Ph-3,4,5), 7.19–7.15 (m, 3H, Ph-2,6, H_7), 3.96 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.65 (s, 3H, CH_3), 2.64 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 145.59 (C8a), 140.37 (Ph-1), 133.47 (C2), 129.16 (C8), 128.92 (Ph-2,3,5,6), 126.92 (Ph-4, C7), 122.62 (C5), 120.24 (C3), 107.47 (C6), 36.35 (CH_2), 32.97 (CH_2), 25.53 (CH_2), 17.22 (CH_3). Anal. Calcd for $C_{17}H_{17}BrN_2S$: C, 56.51; H, 4.74; N, 7.75. Found: C, 56.77; H, 4.86; N, 7.81.

4.2.3.5. 8-Bromo-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (4e). Yield 90%. Mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 1H, H_5), 7.52 (s, 1H, H_2), 7.37 (d, 1H, J = 1.6 Hz, H_7), 7.33–7.21 (m, 3H, Ph-3,4,5), 7.15 (m, 2H, Ph-2,6), 3.94 (s, 2H, CH_2), 2.82 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 143.63 (C8a), 140.34 (Ph-1), 133.92 (C2), 130.10 (C7), 128.92 (Ph-2,6*), 128.88 (Ph-3,5*), 126.88 (Ph-4) 122.63 (C6), 121.79 (C5), 120.97 (C3), 111.66 (C8), 36.27 (CH_2), 32.88 (CH_2), 25.63 (CH_2), 18.59 (CH_3). Anal. Calcd for $C_{17}H_{17}BrN_2S$: C, 56.51; H, 4.74; N, 7.75. Found: C, 56.84; H, 4.89; N, 7.83.

4.2.4. General procedure for Suzuki cross coupling reactions (5a–u). Into a three-necked round-bottomed flask were introduced under argon, **4a** or **4d**–**e** (1 mmol), *tetrakis*(triphenylphosphine)palladium (58 mg, 0.05 mmol), the boronic acid (1.2 mmol), 8 mL of 1,2-dimethoxyethane, and NaOH (80 mg, 2 mmol) or Na_2CO_3 (212 mg, 2 mmol) solubilized in 8 mL of water. The reaction mixture was heated at 85 °C for 3 h. Reaction was followed by TLC. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried on $CaCl_2$, filtered, and evaporated to dryness.

4.2.4.1. 8-Methyl-6-phenyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5a). Compound **5a** was obtained following the general procedure using **4d** (362 mg, 1 mmol), phenylboronic acid (134 mg, 1.1 mmol), and NaOH as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 91%. Mp 72–73 °C. ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 1H, H_5), 7.62 (m, 2H, Ph′-2,6), 7.55 (s, 1H, H_2), 7.52-7.39 (m, 3H, Ph′-3,4,5), 7.34–7.15 (m, 6H, H_7, Ph), 4.05 (s, 2H, CH_2), 2.83 (m, 2H, CH_2), 2.73 (s, 3H, CH_3), 2.67 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 146.51 (C8a), 140.49 (Ph-1), 138.20 (Ph′-1), 133.50 (C2), 129,48 (Ph′-3,5), 128.97 (Ph-2,6*), 128.90 (Ph-3,5*), 128.20 (Ph′-4), 127.86 (C8), 127.56 (Ph′-2,6), 127.15 (C6), 126.87 (Ph-4), 124.47 (C7), 120.09 (C3), 119.89 (C5), 36.38 (CH_2), 32.93 (CH_2), 25.76 (CH_2), 17.55 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2S$: C, 77.06; H, 6.19; N, 7.81. Found: C, 77.38; H, 6.23; N, 7.99.

4.2.4.2. 6-Phenyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5b). Compound **5b** was obtained following the general procedure using **4a** (347 mg, 1 mmol), phenylboronic acid (134 mg, 1.1 mmol), and NaOH as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 58%. Oil. ^{1}H NMR ($CDCl_3$) δ 8.32 (dd, 1 H, J = 1.7–0.9 Hz, 1H, H_5), 7.74 (dd, 1H, J = 9.4–0.9 Hz, H_8), 7.63 (m, 2H, Ph′-2,6), 7.56 (s, 1H, H_2), 7.55–7.40 (m, 3H, Ph′-3,4,5), 7.34–7.14 (m, 6H, H_7, Ph), 4.05 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.66 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 146.09 (C8a), 140.46 (Ph-1), 137.88 (Ph′-1), 134.27 (C2), 129,56 (Ph′-3,5), 128.93 (Ph-2,3,5,6), 128.34 (Ph′-4), 127.54 (Ph′-2,6), 127.00 (C6), 126.90 (Ph-4), 125.40 (C7), 122,03 (C5), 119.79 (C3), 118,17 (C8), 36.35 (CH_2), 32.97 (CH_2), 25.61 (CH_2). Anal. Calcd for $C_{22}H_{20}N_2S$: C, 76.71; H, 5.85; N, 8.13. Found: C, 76.85; H, 5.81; N, 8.33.

4.2.4.3. 6-Methyl-8-phenyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5c). Compound **5c** was obtained following the general procedure using **4e** (362 mg, 1 mmol), phenylboronic acid (134 mg, 1.1 mmol), and NaOH as base. The reaction mixture was heated at 85 °C for 3 h and then phenylboronic acid (13 mg, 0.1 mmol) was again added. The heating was maintained for 3 h and the reaction mixture was stirred at room temperature overnight. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 92%. Mp 55–56 °C. ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 2H, Ph′-2,6), 7.93 (m, 1H, H_5), 7.58–7.40 (m, 4H, H_2, Ph′-3,4,5), 7.36–7.16 (m, 6H, H_7, Ph), 4.03 (s, 2H, CH_2), 2.86 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.47 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.22 (C8a), 140.47 (Ph-1), 136.61 (Ph′-1), 133.12 (C2), 130.25 (C8), 129.35 (Ph′-2,6), 129.01 (Ph-2,6* and Ph′-3,5), 128.92 (Ph-3,5*), 128.79 (Ph′-4), 126.97 (C7), 126.89 (Ph-4), 122.73 (C6), 121.43 (C5), 119.35 (C3), 36.37 (CH_2), 32.89 (CH_2), 25.67 (CH_2), 18.97 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2S$: C, 77.06; H, 6.19; N, 7.81. Found: C, 77.32; H, 6.17; N, 7.70.

4.2.4.4. 8-Methyl-3-phenethylthiomethyl-6-(thien-3-yl)imidazo[1,2-*a*]pyridine (5d). Compound **5d** was obtained following the general procedure using **4d** (362 mg, 1 mmol), thien-3-ylboronic acid (141 mg, 1.1 mmol), and NaOH as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 89%. Mp 108 °C. ^{1}H NMR ($CDCl_3$) δ 8.22 (m, 1H, H_5), 7.53 (s, 1H, H_2), 7.49 (m, 2H, Thio-2,4), 7.40 (dd, 1H, J = 3.9–2.5 Hz, Thio-5), 7.34–7.22 (m, 4H, Ph-3,4,5, H_7), 7.16 (m, 2H, Ph-2,6), 4.04 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.70 (s, 3H, CH_3), 2.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 146.53 (C8a), 140.47 (Ph-1), 138.94 (Thio-3), 133.52 (C2), 128.95 (Ph-2,6*), 128.88 (Ph-3,5*), 127.83 (C8), 127.25 (Thio-2), 126.85 (Ph-4), 126.33 (Thio-5), 123.75 (C7), 121.94 (C6), 121.08 (Thio-4), 120.09 (C3), 119.19 (C5), 36.35 (CH_2), 32.87 (CH_2), 25.62 (CH_2), 17.51 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2S_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.47; H, 5.48; N, 7.71.

4.2.4.5. 6-Methyl-3-phenethylthiomethyl-8-(thien-3-yl)imidazo[1,2-*a*]pyridine (5e). Compound **5e** was obtained following the general procedure using **4e** (362 mg, 1 mmol), thien-3-ylboronic acid (154 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 89%. Mp 91–92 °C. ^{1}H NMR ($CDCl_3$) δ 8.55 (dd, 1H, J = 3–1.3 Hz, Thio-2), 7.88 (m, 1H, H_5), 7.77 (dd, 1H, J = 5.1–1.3 Hz, Thio-4), 7.56 (s, 1H, H_2), 7.46 (dd, 1H, J = 5.1–3 Hz, Thio-5), 7.38–7.16 (m, 6H, H_7, Ph), 4.02 (s, 2H, CH_2), 2.86 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.45 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 144.13 (C8a), 140.54 (Ph-1), 136.91 (Thio-3), 133.39 (C2), 129.00 (Ph-2,6*), 128.92 (Ph-3,5*), 127.21 (Thio-4), 126.89 (Ph-4), 125.88 (Thio-2*), 125.83 (Thio-5*), 124.86 (C7), 124.59 (C8), 122.16 (C6), 120.93 (C5), 119.28 (C3), 36.39 (CH_2), 32.86 (CH_2), 25.66 (CH_2), 18.98 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2S_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.38; H, 5.49; N, 7.63.

4.2.4.6. 8-Methyl-3-phenethylthiomethyl-6-(thien-2-yl)imidazo[1,2-*a*]pyridine (5f). Compound **5f** was obtained following the general procedure using **4d** (362 mg, 1 mmol), thien-2-ylboronic acid (154 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with diethyl ether/petroleum ether (70:30). Yield 92%. Mp 72 °C. ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H, H_5), 7.52 (s, 1H, H_2), 7.35 (dd, 1H, J = 5.1–1.2 Hz, Thio-5), 7.33–7.12 (m, 8H, H_7, Ph, Thio-3,4), 4.02 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 146.38 (C8a), 140.89 (Thio-2), 140.47 (Ph-1), 133.50 (C2), 128.97 (Ph-2,6*), 128.91 (Ph-3,5*), 128.57 (C8), 128.10 (Thio-5), 126.88 (Ph-4), 125.57 (Thio-3*), 124.33 (Thio-4*), 123.71 (C7), 121,04 (C6), 120.26 (C3), 118.78 (C5), 36.39 (CH_2), 32.95 (CH_2), 25.67 (CH_2), 17.46 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2S_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.51; H, 5.59; N, 7.66.

4.2.4.7. 6-Methyl-3-phenethylthiomethyl-8-(thien-2-yl)imidazo[1,2-*a*]pyridine (5g). Compound **5g** was obtained following the general procedure using **4e**

(362 mg, 1 mmol), thien-2-ylboronic acid (154 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with ether/petroleum ether (70:30). Yield 52%. Mp 85–86 °C. ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, 1H, J = 3.8–1.2 Hz, Thio-3), 7.85 (m, 1H, H_5), 7.57 (s, 1H, H_2), 7.46 (dd, 1H, J = 5.1–1.2 Hz, Thio-5), 7.42 (d, 1H, J = 1.3 Hz, H_7), 7.36–7.16 (m, 6H, Thio-4, Ph), 4.00 (s, 2H, CH_2), 2.86 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 143.07 (C8a), 140.45 (Ph-1), 138.30 (Thio-2), 133.13 (C2), 128.97 (Ph-2,6*), 128.89 (Ph-3,5*), 128.07 (Thio-4), 127.72 (Thio-3), 126.94 (Thio-5), 126.87 (Ph-4), 124.33 (C7), 123.59 (C8*), 122.31 (C6*), 121.02 (C5), 119.54 (C3), 36.34 (CH_2), 32.84 (CH_2), 25.64 (CH_2), 18.91 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2S_2$: C, 69.19; H, 5.53; N, 7.68. Found: C, 69.25; H, 5.52; N, 7.70.

4.2.4.8. 6-(2-Hydroxyphenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5h). Compound **5h** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 2-hydroxyphenylboronic acid (165 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2, then by a mixture of CH_2Cl_2 and MeOH (99:1 then 98:2). Yield 66%. Mp 189–190 °C. ^{1}H NMR (DMSO-d_6) δ 9.83 (s, 1H, OH), 8.38 (s, 1H, H_5), 7.54 (s, 1H, H_2), 7.37 (m, 2H, PhOH-4 and H_7), 7.30–7.15 (m, 6H, PhOH-6, Ph), 7.01 (d, 1H, J = 7.9 Hz, PhOH-3), 6.93 (t, 1H, J = 7.4 Hz, PhOH-5), 4.24 (s, 2H, CH_2), 2.78 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.52 (s, 3H, CH_3); ^{13}C NMR (50 MHz, DMSO-d_6) δ 155.60 (PhOH-2), 145.66 (C8a), 141.28 (Ph-1), 133.32 (C2), 131.22 (PhOH-4), 129.82 (PhOH-6), 129.38 (Ph-2,6*), 129.13 (Ph-3,5*), 126.99 (Ph-4), 126.21 (C7), 125.95 (C8*), 125.14 (PhOH-1*), 123.97 (C6*), 122.52 (C5), 121.23 (C3), 120.33 (PhOH-5), 116.93 (PhOH-3), 36.06 (CH_2), 32.92 (CH_2), 24.79 (CH_2), 17.47 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.84; H, 5.83; N, 7.52.

4.2.4.9. 6-(3-Hydroxyphenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5i). Compound **5i** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 3-hydroxyphenylboronic acid (151 mg, 1.1 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with a mixture of CH_2Cl_2 and MeOH (98:2). Yield 37%. Mp 75 °C. ^{1}H NMR (DMSO-d_6) δ 8.47 (s, 1H, H_5), 7.56 (s, 1H, H_2), 7.41 (s, 1H, H_7), 7.36–7.14 (m, 8H, Ph, PhOH-2,5,6), 6.83 (d, 1H, J = 7.8 Hz, PhOH-4), 4.30 (s, 2H, CH_2), 2.75 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 2.71 (s, 3H, CH_3), OH not found; ^{13}C NMR (DMSO-d_6) δ 158.80 (PhOH-3), 145.89 (C8a), 141.25 (Ph-1), 139.36 (PhOH-1), 133.59 (C2), 130.91 (PhOH-5), 129.35 (Ph-2,6*), 129.11 (Ph-3,5*), 127.36 (C8), 126.98 (Ph-4), 125.91 (C6), 123.73 (C7), 121.70 (C3), 120.84 (C5), 118.39 (PhOH-6*), 115.52 (PhOH-4), 114.48 (PhOH-2*), 36.02 (CH_2), 32.80 (CH_2), 24.67 (CH_2), 17.49 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.98; H, 5.85; N, 7.51.

4.2.4.10. 8-(3-Hydroxyphenyl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5j). Compound **5j** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 3-hydroxyphenylboronic acid (151 mg, 1.1 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2 and then with a mixture of CH_2Cl_2 and MeOH (98:2). Yield 51%. Mp 78 °C. ^{1}H NMR (DMSO-d_6) δ 9.51 (s, 1H, OH), 8.21 (s, 1H, H_5), 7.64 (s, 1H, PhOH-2), 7.56 (s, 1H, H_2), 7.46 (d, 1H, J = 7.8 Hz, PhOH-6), 7.35–7.16 (m, 7H, H_7, Ph and PhOH-5), 6.84 (d, 1H, J = 7.5 Hz, PhOH-4), 4.20 (s, 2H, CH_2), 2.78 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 157.98 (PhOH-3), 143.73 (C8a), 141.27 (Ph-1), 138.17 (PhOH-1), 133.51 (C2), 130.04 (C8), 129.36 (Ph-2,6*), 129.13 (Ph-3,5*), 128.96 (PhOH-5), 127.01 (Ph-4), 126.13 (C7), 122.58 (C5), 122.03 (C6), 120.66 (C3), 120.55 (PhOH-6), 116.85 (PhOH-2), 115.97 (PhOH-4), 36.03 (CH_2), 32.88 (CH_2), 24.74 (CH_2), 18.70 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.94; H, 5.95; N, 7.47.

4.2.4.11. 6-(4-Hydroxyphenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5k). Compound **5k** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 4-hydroxyphenylboronic acid (165 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with a mixture of CH_2Cl_2 and MeOH (98:2). Yield 35%. Mp 210 °C. ^{1}H NMR (DMSO-d_6) δ 9.66 (s, 1H, OH), 8.40 (s, 1H, H_5), 7.60 (d, 2H, J = 8.5 Hz, PhOH-2,6), 7.53 (s, 1H, H_2), 7.40 (s, 1H, H_7), 7.30–7.16 (m, 5H, Ph), 6.90 (d, 2H, J = 8.5 Hz, PhOH-3,5), 4.30 (s, 2H, CH_2), 2.76 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 2.55 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 158.13 (PhOH-4), 145.64 (C8a), 141.29 (Ph-1), 133.42 (C2), 129.36 (Ph-2,6*), 129.12 (Ph-3,5*), 128.75 (PhOH-2,6), 128.60 (PhOH-1), 127.20 (C8), 126.99 (Ph-4), 125.89 (C6), 123.74 (C7), 121.48 (C3), 119.74 (C5), 116.69 (PhOH-3,5), 36.01 (CH_2), 32.79 (CH_2), 24.68 (CH_2), 17.50 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.82; H, 5.93; N, 7.46.

4.2.4.12. 8-(4-Hydroxyphenyl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5l). Compound **5l** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 4-hydroxyphenylboronic acid (165 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with a mixture of CH_2Cl_2 and MeOH (98:2). Yield 44%. Mp 184 °C. ^{1}H NMR (DMSO-d_6) δ 9.65 (s, 1H, OH), 8.14 (s, 1H, H_5), 8.03 (d, 2H, J = 8.6 Hz, PhOH-2,6), 7.55 (s, 1H, H_2), 7.31–7.18 (m, 6H, H_7, Ph), 6.88 (d, 2H, J = 8.6 Hz, PhOH-3,5), 4.20 (s, 2H, CH_2), 2.79 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.39 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.10 (PhOH-4), 144.69 (C8a), 140.44 (Ph-1), 132.24 (C2), 131.35 (C8), 130.25 (PhOH-2,6), 128.98 (Ph-2,3,5,6), 127.63 (C7), 127.15 (PhOH-1), 126.91 (Ph-4), 123.14 (C6), 120.66 (C5), 119.54 (C3), 117.01 (PhOH-3,5), 36.03 (CH_2), 32.81 (CH_2), 24.68 (CH_2), 18.77 (CH_3).

Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.78; H, 5.90; N, 7.49.

4.2.4.13. 6-(3-Methoxyphenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5m). Compound **5m** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 3-methoxyphenylboronic acid (183 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with CH_2Cl_2. Yield 87%. Mp 87–89 °C. ^{1}H NMR ($CDCl_3$) δ 8.18 (m, 1H, H_5), 7.54 (s, 1H, H_2), 7.41 (t, 1H, J = 8.1 Hz, PhOMe-5), 7.32–7.12 (m, 8H, H_7, Ph, PhOMe-2,6), 6.96 (ddd, 1H, J = 8.1–2.5–0.9 Hz, PhOMe-4), 4.02 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 2.85 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.71 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.55 (PhOMe-3), 146.48 (C8a), 140.48 (Ph-1), 139.66 (PhOMe-1), 133.38 (C2), 130.52 (PhOMe-5), 128.95 (Ph-2,6*), 128.89 (Ph-3,5*), 127.81 (C8*), 127.08 (C6*), 126.86 (Ph-4), 124.53 (C7), 120.15 (C3), 120.00 (PhOMe-6, C5), 113.58 (PhOMe-2), 113.30 (PhOMe-4), 55.82 (OCH_3), 36.38 (CH_2), 32.95 (CH_2), 25.75 (CH_2), 17.52 (CH_3). Anal. Calcd for $C_{24}H_{24}N_2OS$: C, 74.19; H, 6.23; N, 7.21. Found: C, 74.35; H, 6.27; N, 7.29.

4.2.4.14. 8-(3-Methoxyphenyl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5n). Compound **5n** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 3-methoxyphenylboronic acid (183 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99.5:0.5). Yield 95%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.92 (s, 1H, H_5), 7.59 (m, 2H, PhOMe-2,6), 7.56 (s, 1H, H_2), 7.44 (t, 1H, J = 8.1 Hz, PhOMe-5), 7.34–7.16 (m, 6H, H_7, Ph), 6.99 (dd, 1H, J = 8.1–1.7 Hz, PhOMe-4), 4.02 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 2.87 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 160.09 (PhOMe-3), 144.49 (C8a), 140.52 (Ph-1), 138.20 (PhOMe-1), 133.60 (C2), 130.18 (C8), 129.92 (PhOMe-5), 128.98 (Ph-2,6*), 128.90 (Ph-3,5*), 126.87 (Ph-4), 126.58 (C7), 122.37 (C6), 121.90 (PhOMe-6), 121.46 (C5), 119.26 (C3), 115.02 (PhOMe-2), 114.35 (PhOMe-4), 55.77 (OCH_3), 36.39 (CH_2), 32.89 (CH_2), 25.70 (CH_2), 18.93 (CH_3). Anal. Calcd for $C_{24}H_{24}N_2OS$: C, 74.19; H, 6.23; N, 7.21. Found: C, 74.58; H, 6.34; N, 7.19.

4.2.4.15. 6-(4-Methoxyphenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5o). Compound **5o** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 4-methoxyphenylboronic acid (168 mg, 1.1 mmol), and NaOH as base. The reaction mixture was heated at 85 °C for 3 h and then boronic acid (16 mg, 0.1 mmol) was again added. The heating was maintained for 3 h. Pure product was obtained by column chromatography on silica gel eluting with a mixture of ether and petroleum ether (50:50). Yield 88%. Mp 88 °C. ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H, H_5), 7.55 (d, 2H, J = 8.6 Hz, PhOMe-2,6), 7.53 (s, 1H, H_2), 7.34-7.15 (m, 6H, Ph, H_7), 7.06 (d, 2H, J = 8.6 Hz, PhOMe-3,5), 4.04 (s, 2H, CH_2), 3.91 (s, 3H, OMe), 2.85 (m, 2H, CH_2), 2.67 (m, 2H,CH_2), 2.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 159.88 (PhOMe-4), 146.33 (C8a), 140.51 (Ph-1), 133.34 (C2), 130.60 (PhOMe-1), 128.97 (Ph-2,6*), 128.89 (Ph-3,5*), 128.62 (PhOMe-2,6), 127.68 (C8), 126.85 (Ph-4), 124.53 (C7), 119.95 (C3), 119.24 (C5), 114.90 (PhOMe-3,5), 55.83 (OMe), 36.37 (CH_2), 32.90 (CH_2), 25.75 (CH_2), 17.55 (CH_3). C6 not found. Anal. Calcd for $C_{24}H_{24}N_2OS$: C, 74.19; H, 6.23; N, 7.21. Found: C, 74.42; H, 6.36; N, 7.25.

4.2.4.16. 8-(4-Methoxyphenyl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5p). Compound **5p** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 4-methoxyphenylboronic acid (183 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on neutral alumina eluting with a mixture of CH_2Cl_2 and MeOH (98:2). Yield 76%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 2H, J = 8.9 Hz, PhOMe-2,6), 7.87 (s, 1H, H_5), 7.56 (s, 1H, H_2), 7.35-7.16 (m, 6H, H_7, Ph), 7.07 (d, 2H, J = 8.9 Hz, PhOMe-3,5), 4.09 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 2.86 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 160.16 (PhOMe-4), 147.14 (C8a), 140.54 (Ph-1), 133.44 (C2), 130.56 (PhOMe-2,6), 129.87 (C8*), 129.27 (PhOMe-1*), 128.98 (Ph-2,6*), 128.89 (Ph-3,5*), 126.85 (Ph-4), 125.74 (C7), 122.46 (C6), 120.85 (C5), 119.22 (C3), 114.43 (PhOMe-3,5), 55.80 (OMe), 36.40 (CH_2), 32.89 (CH_2), 25.71 (CH_2), 18.95 (CH_3). Anal. Calcd for $C_{24}H_{24}N_2OS$: C, 74.19; H, 6.23; N, 7.21. Found: C, 74.41; H, 6.26; N, 7.22.

4.2.4.17. 8-Methyl-6-(3-nitrophenyl)-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5q). Compound **5q** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 3-nitrophenylboronic acid (200 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with a mixture of CH_2Cl_2/MeOH (98:2). 77% yield. Mp 108–109 °C. ^{1}H NMR ($CDCl_3$) δ 8.48 (m, 1H, $PhNO_2$-2), 8.29 (m, 2H, $PhNO_2$-4*, H_5), 7.94 (ddd, 1H, J = 7.9–1.1–0.7 Hz, $PhNO_2$-6), 7.69 (t, 1H, J = 7.9 Hz, $PhNO_2$-5), 7.58 (s, 1H, H_2), 7.34–7.14 (m, 6H, H_7, Ph), 4.07 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.68 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 149.24 ($PhNO_2$-3), 146.51 (C8a), 140.38 (Ph-1), 140.01 ($PhNO_2$-1), 133.94 (C2), 133.40 ($PhNO_2$-6), 130.49 ($PhNO_2$-5), 128.92 (Ph-2,6*), 128.88 (Ph-3,5*), 128.73 (C8), 126.88 (Ph-4), 124.85 (C6), 123.47 (C7), 122.92 ($PhNO_2$-4), 122.33 ($PhNO_2$-2), 120.55 (C3), 120.55 (C5), 36.32 (CH_2), 32.94 (CH_2), 25.71 (CH_2), 17.54 (CH_3). Anal. Calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H, 5.25; N, 10.41. Found: C, 68.64; H, 5.34; N, 10.52.

4.2.4.18. 6-Methyl-8-(3-nitrophenyl)-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5r). Compound **5r** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 3-nitrophenylboronic acid (200 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with ether and then ethyl acetate. Yield 79%. Mp 141–142 °C. ^{1}H NMR ($CDCl_3$) δ 8.86 (t, 1H, J = 1.9 Hz, $PhNO_2$-2), 8.49 (ddd, 1H, J = 7.9–1.9–1 Hz, $PhNO_2$-6),

8.30 (ddd, 1H, J = 7.9–1.9–1 Hz, $PhNO_2$-4), 8.00 (m, 1H, H_5), 7.71 (t, 1H, J = 7.9 Hz, $PhNO_2$-5), 7.57 (s, 1H, H_2), 7.34–7.16 (m, 6H, H_7, Ph), 4.04 (s, 2H, CH_2), 2.87 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 148.87 ($PhNO_2$-3), 143.99 (C8a), 140.43 (Ph-1), 138.48 ($PhNO_2$-1), 135.56 ($PhNO_2$-6), 133.87 (C2), 129.87 ($PhNO_2$-5), 128.97 (Ph-2,3,5,6), 127.64 (C8), 126.93 (Ph-4, C7), 124.15 ($PhNO_2$-2), 123.36 ($PhNO_2$-4), 122.55 (C5), 122.40 (C6), 119.80 (C3), 36.38 (CH_2), 32.93 (CH_2), 25.63 (CH_2), 18.94 (CH_3). Anal. Calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H, 5.25; N, 10.41. Found: C, 68.67; H, 5.32; N, 10.39.

4.2.4.19. 6-(3-Cyanophenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5s). Compound **5s** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 3-cyanophenylboronic acid (177 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99:1). Yield 83%. Mp 118–119 °C. ^1H NMR ($CDCl_3$) δ 8.20 (d, 1H, J = 0.9 Hz, H_5), 7.87 (s, 1H, PhCN-2), 7.84 (dt, 1H, J = 7.6–1.5 Hz, PhCN-6), 7.70 (dt, 1H, J = 7.67–1.5 Hz, PhCN-4), 7.63 (t, 1H, J = 7.6 Hz, PhCN-5), 7.56 (s, 1H, H_2), 7.32–7.12 (m, 6H, H_7, Ph), 4.05 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 2.72 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 146.47 (C8a), 140.37 (Ph-1), 139.58 (PhCN-1), 133.86 (C2), 131.86 (PhCN-6*), 131.58 (PhCN-2*), 131.02 (PhCN-4), 130.34 (PhCN-5), 128.92 (Ph-2*), 128.64 (Ph-3,5*), 128.64 (C8), 126.89 (Ph-4), 125.01 (C6), 123.50 (C7), 120.49 (C5), 118.97 (C3), 113.74 (PhCN-3), 36.30 (CH_2), 32.92 (CH_2), 25.71 (CH_2), 17.54 (CH_3). Anal. Calcd for $C_{24}H_{21}N_3S$: C, 75.16; H, 5.52; N, 10.96. Found: C, 75.24; H, 5.39; N, 10.87.

4.2.4.20. 6-(4-Cyanophenyl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (5t). Compound **5t** was obtained following the general procedure using **4d** (362 mg, 1 mmol), 4-cyanophenylboronic acid (177 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99:1). Yield 70%. Mp 102 °C. ^1H NMR ($CDCl_3$) δ 8.25 (s, 1H, H_5), 7.81 (d, 2H, J = 8.6 Hz, PhCN-3,5), 7.72 (d, 2H, J = 8.6 Hz, PhCN-2,6), 7.57 (s, 1H, H_2), 7.32–7.12 (m, 6H, H_7, Ph), 4.05 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 2.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 178.60 (CN), 146.27 (C8a), 142.64 (PhCN-1), 140.32 (Ph-1), 133.36 (C2), 133.28 (PhCN-3,5), 128.91 (Ph-2,3,5,6), 128.53 (C8), 128.10 (PhCN-2,6), 126.91 (Ph-4), 125.47 (C6), 123.75 (C7), 120.72 (C5), 119.05 (C3), 111.94 (PhCN-4), 36.29 (CH_2), 32.96 (CH_2), 25.70 (CH_2), 17.56 (CH_3). Anal. Calcd for $C_{24}H_{21}N_3S$: C, 75.16; H, 5.52; N, 10.96. Found: C, 75.32; H, 5.56; N, 10.98.

4.2.4.21. 8-(3-Fluorophenyl)-6-methyl-3-phenethylthiomethylimidazo[1,2- *a*]pyridine (5u). Compound **5u** was obtained following the general procedure using **4e** (362 mg, 1 mmol), 3-fluorophenylboronic acid (168 mg, 1.2 mmol), and Na_2CO_3 as base. Pure product was obtained by column chromatography on silica gel eluting with ether/petroleum ether (80:20). Yield 60%. Oil. ^1H NMR ($CDCl_3$) δ 7.95 (m, 1H, H_5), 7.79 (m, 2H, PhF-2,6), 7.56 (s, 1H, H_2), 7.49 (td, 1H, J = 8 Hz, 6 Hz, PhF-5), 7.36–7.23 (m, 4H, Ph-3,4,5, H_7), 7.20–7.09 (m, 3H, Ph-2,6, PhF-4), 4.02 (s, 2H, CH_2), 2.87 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.23 (J = 243.5 Hz, PhF-3), 144.18 (C8a), 140.51 (Ph-1), 138.97 (J = 8 Hz, PhF-1), 133.65 (C2), 130.36 (J = 8 Hz, PhF-5), 128.98 (Ph-2,6*), 128.90 (Ph-3,5*), 126.87 (Ph-4), 126.60 (C8), 125.03 (J = 2 Hz, PhF-6), 122.28 (C5), 121.92 (C6), 119.55 (C3), 116.36 (J = 22.5 Hz, PhF-2), 115.46 (J = 20.5 Hz, PhF-4), 36.39 (CH_2), 32.95 (CH_2), 25.62 (CH_2), 18.85 (CH_3). Anal. Calcd for $C_{23}H_{21}FN_2S$: C, 73.37; H, 5.62; N, 7.44. Found: C, 73.48; H, 5.63; N, 7.42.

4.3. Antiviral assays

Human cytomegalovirus (HCMV) AD169 and Davis strains were exposed to human embryonic lung (HEL) cell cultures. Briefly, confluent culture in microtiter plates was inoculated with 100 plaque forming units (PFU). After 2 h virus absorption, residual virus was removed and the cell cultures were incubated in the presence of varying concentrations 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. Varicella-zoster virus (VZV) Oka (TK^+) and 07/1 (TK^-) strains were grown on HEL cells. As described for HCMV, confluent cells were inoculated but with 20 PFU/well and the different dilutions of the tested compounds were added as for HCMV. After 5 days incubation at 37 °C in a 5% CO_2 atmosphere, the cells were fixed and stained. Viral plaque formation was recorded and compared to the untreated control. Acyclovir and brivudin were used as reference drugs.

Antiviral activity is expressed as the concentration of the compound required to inhibit viral cytopathicity by 50% (IC_{50}).

4.4. Cytostatic activity assays

The cytostatic assays were performed as previously described.[27–29] 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-controlled 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 measurement was based on microscopically visible morphological alterations of the HEL cell cultures: cytotoxicity was defined as the minimum cytotoxic concentration (MCC) required for causing a microscopically detectable alteration of cell morphology.

Acknowledgments

The authors thank SAVIT, Tours (France), for NMR spectrometry. We thank Mrs. Anita Camps, Frieda de Meyer, Anita van Lierde, and Lies Vandenheurck for excellent technical assistance. This work was supported by grants from the Belgian Fonds voor Wetenschappelijk Onderzoeck (FWO), Vlaanderen and the Geconcerteerde Onderzoeksacties (GOA), Vlaamse Gemeenschap.

References and notes

1. Stevens, J. G. *Microbiol. Rev.* **1989**, *53*, 318–332.
2. Vancikova, Z.; Dvorak, P. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* **2001**, *1*, 179–187.
3. Nichols, W. G.; Boeckh, M. *J. Clin. Virol.* **2000**, *16*, 25–40.
4. Gnann, J. W., Jr. *J. Infect. Dis.* **2002**, *186*(Suppl. 1), S91–S98.
5. De Clercq, E. *J. Clin. Virol.* **2004**, *30*, 115–133.
6. Naesens, L.; De Clercq, E. *Herpes* **2001**, *8*, 12–16.
7. Biron, K. K. *Antiviral Res.* **2006**, *71*, 154–163.
8. Baillie, G. M. *Am. J. Health Syst. Pharm.* **2005**, *62*, S14–S17.
9. De Clercq, E. *J. Antimicrob. Chemother.* **2003**, *51*, 1079–1083.
10. Baldanti, F.; Lurain, N.; Gerna, G. *Hum. Immunol.* **2004**, *65*, 403–409.
11. Borthwick, A. D. *Med. Res. Rev.* **2005**, *25*, 427–452.
12. Wathen, M. W. *Rev. Med. Virol.* **2002**, *12*, 167–178.
13. Bogner, E. *Rev. Med. Virol.* **2002**, *12*, 115–127.
14. Martinez, A.; Castro, A.; Gil, C.; Perez, C. *Med. Res. Rev.* **2001**, *21*, 227–244.
15. Gueiffier, A.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Kerbal, A.; Essassi, E. M.; Debouzy, J. C.; Witvrouw, M.; Blache, Y.; Balzarini, J.; De Clercq, E.; Chapat, J. P. *J. Med. Chem.* **1996**, *39*, 2856–2859.
16. Gueiffier, A.; Mavel, S.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Witvrouw, M.; Balzarini, J.; De Clercq, E.; Chapat, J. P. *J. Med. Chem.* **1998**, *41*, 5108–5112.
17. Mavel, S.; Renou, J. L.; Galtier, C.; Allouchi, H.; Snoeck, R.; Andrei, G.; De Clercq, E.; Balzarini, J.; Gueiffier, A. *Bioorg. Med. Chem.* **2002**, *10*, 941–946.
18. Enguehard, C.; Hervet, M.; Théry, I.; Renou, J.-L.; Fauvelle, F.; Gueiffier, A. *Helv. Chim. Acta* **2001**, *84*, 3610–3615.
19. Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 5614–5617.
20. Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 4367–4370.
21. Hervet, M.; Théry, I.; Gueiffier, A.; Enguehard-Gueiffier, C. *Helv. Chim. Acta* **2003**, *86*, 3461–3469.
22. Kazock, J.-Y.; Enguehard-Gueiffier, C.; Théry, I.; Gueiffier, A. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 154–159.
23. Enguehard-Gueiffier, C.; Théry, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042–6049.
24. Dolci, L.; Dolle, F.; Valette, H.; Vaufrey, F.; Fuseau, C.; Bottlaender, M.; Crouzel, C. *Bioorg. Med. Chem.* **1999**, *7*, 467–479.
25. Yamanaka, M.; Miyake, K.; Suda, S.; Ohhara, H.; Ogawa, T. *Chem. Pharm. Bull. (Tokyo)* **1991**, *39*, 1556–1567.
26. Coulson, D. R. *Inorg. Synth.* **1971**, *13*, 121–124.
27. De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. *J. Infect. Dis.* **1980**, *141*, 563–574.
28. De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. *Nature* **1986**, *323*, 464–467.
29. Balzarini, J.; Naesens, L.; Slachmuylders, J.; Niphuis, H.; Rosenberg, I.; Holy, A.; Schellekens, H.; De Clercq, E. *Aids* **1991**, *5*, 21–28.