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

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

[a] *PCMB EA 4244, Faculté de Pharmacie, Université François Rabelais, 31 avenue Monge, 37200 Tours, France*
[b] *Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium*

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ABSTRACT

The synthesis of original imidazo[1,2-*a*]pyridines bearing a thioether side chain at the 3 position and diversely substituted on the 6 or 8 position, and their antiviral activities are reported. From the synthesized compounds, the imidazo[1,2-*a*]pyridines bearing a 5 membered heterocycle (thiophene, furane or pyrrole) in the 6 position or a phenylthio group in the 6 or 8 position (**14**, **16**, **21**, **28**, **45**) were the most potent against human cytomegalovirus (CMV) and varicella-zoster virus (VZV), whereas several other congeners (i.e., **22**, **29** and **39**), while less potent, were more selective in their inhibitory activity against 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

In 1996, Alain Gueiffier and colleagues reported the antiviral activity of 8-methyl-3-benzylthiomethylimidazo[1,2-*a*]pyridine as potent inhibitor of human cytomegalovirus (HCMV) and varicella-zoster virus (VZV).[1] The antiviral activity optimization was pursued in this series, with the investigation of the role of the thioether side chain[2] or the 2-substituent.[3] It appeared that a phenethylthiomethyl group enhances the activity and diminishes the toxicity. Many functionalities were tolerated in position 2, but in all cases, the unsubstituted compound remained the best inhibitor. At this time, optimization of the pyridinic moiety substitution was just initiated, as a lack of efficient methods of functionalization made this investigation problematic. The development of new metallo-catalyzed coupling reactions in our laboratory allowed us to introduce new functionalities in the pyridinic part of the scaffold. We lately reported on the antiviral activity of 6- or 8-(hetero)aryl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine derivatives obtained via Suzuki-Miyaura coupling reactions.[4] The pharmacomodulation of positions 6 and 8 of the nucleus was pursued using Buchwald metallo-catalyzed cross-coupling reactions, for example, pallado-catalyzed aminations or copper-catalyzed couplings of amines, lactam, azoles, nitrile or thiophenols. The synthesis and biological evaluation of this new series of compounds is subject of the present article. Indeed, as has already been documented in previous papers,[1–4] development of new drugs against herpes viruses with novel mechanisms of action, that are less toxic, more effective, and orally bioavailable, is urgently needed.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, the halogenated imidazo[1,2-*a*]pyridines **4**–**9** were obtained through previously described procedures.[4] The suitably halogenated 2-aminopyridines **1a–d** were refluxed with chloroacetaldehyde in ethanol to yield around 85% of the imidazo[1,2-*a*]pyridines **2a–d**. Hydroxymethylation in position 3 of this scaffold was performed using formaldehyde in acetic media in the presence of sodium acetate at 40 °C. After 24 h of heating, about 80% yield of the corresponding alcohols **3a–d** were obtained. The thioether side chain was introduced using phenethylthiol in acetic media at 80 °C leading to **4**–**9** in moderate to good yield (41–90%).

The pharmacomodulation of positions 6 and 8 of the nucleus was performed using various metallo-catalyzed cross-coupling reactions (Table 1), for example, Suzuki-Miyaura coupling reactions, Buchwald pallado-catalyzed aminations or copper-catalyzed couplings of amines, lactam, azoles or thiophenols. The previously

* Corresponding author. Tel.: +33 247 367 140; fax: +33 247 367 288.
E-mail address: alain.gueiffier@univ-tours.fr (A. Gueiffier).

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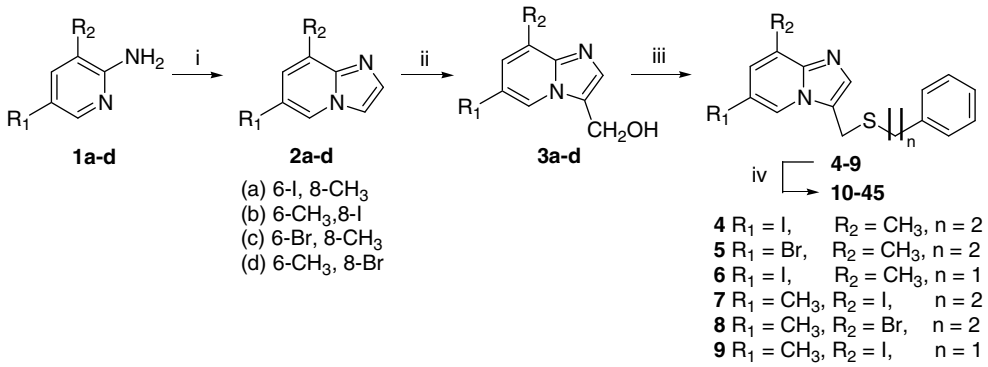

Scheme 1. General scheme leading to compounds **4**–**45**. Reagents and conditions: (i) $ClCH_2CHO$, C_2H_5OH, reflux 24 h; (ii) HCHO, CH_3COONa, CH_3COOH, 40 °C for 24 h; (iii) $Ph(CH_2)_2SH$ or $PhCH_2SH$, CH_3COOH, 80 °C overnight; (iv) $RB(OH)_2$, $Pd(PPh_3)_4$, NaOH, DME, H_2O, 85 °C or amine, $Pd_2(dba)_3$, rac-BINAP, *t*-BuONa, toluene, 112 °C; or amine, CuI, K_3PO_4, ethyleneglycol, isopropanol, 85 °C; or azole, CuI, K_3PO_4, *N*,*N*′-dimethylethylenediamine or ethyleneglycol, toluene, 112 °C; or NaCN, CuI, *N*,*N*′-dimethylethylenediamine, toluene, 112 °C; or thiophenol, CuI, K_2CO_3, *N*,*N*′-dimethylethylenediamine or ethyleneglycol, isopropanol.

described Suzuki conditions were applied to the iodinated imidazo[1,2-*a*]pyridine **4**, **6**, **7** or **9**, using *tetrakis*(triphenylphosphine)palladium (0) as catalyst and NaOH as base in 1,2-dimethoxyethane. Two substituted phenyl (4-vinylphenyl or 4-formylphenyl) and various heterocycles (indol-5-yl, thien-2- or -3-yl, and fur-2- or -3-yl) were thus introduced in positions 6 and 8 of the scaffold. After few hours of heating at 85 °C, the attempted coupling products **10**–**16** and **30**–**32** were obtained in 31–91% yields (not optimized).

Two cyclic amines (morpholine and pyrrolidine) were then introduced in the pyridine part of the scaffold using Buchwald palladium-catalyzed conditions.[5] The reaction was performed in a screw-capped tube in the presence of $Pd_2(dba)_3$ as catalyst, *tertio*-BuONa as base and *rac*-BINAP as ligand, in 2 mL of toluene at 112 °C.

Then, applying Buchwald copper-catalyzed coupling conditions to the diversely halogenated imidazo[1,2-*a*]pyridines led to the introduction of various substituents: an amine (4-methylpiperazine), a lactam (pyrrolidin-2-one), four azoles (pyrrole, imidazole, indole, and pyrrolo[2,3-*b*]pyridine), a nitrile and three thiophenols (4-chlorothiophenol, 4-hydroxythiophenol, and 4-aminothiophenol).[5–7] Depending on the nature of the coupling partner or the substitution position, many different methods were applied using CuI as catalyst, *N*,*N*′-dimethylethylenediamine or ethyleneglycol as ligands, K_3PO_4 or K_2CO_3 as bases, and isopropanol or toluene as solvents.

2.2. Anti-CMV activity

As seen in Tables 2 and 3, the tested compounds can be classified in three groups depending on their range of anti-CMV activities: a group of inactive compounds (**11**–**13**, **17**, **19**–**20**, **23**, **26**–**27**, **33**–**35**, **37**, and **41**) with an EC_{50} > 4 μg/mL, a group of moderately active compounds (**10**, **18**, **21**, **22**, **24**–**25**, **29**–**32**, **38**–**40**, **42**–**43**) with an EC_{50} between 1 and 4 μg/mL depending on the strain, and a group of four active compounds (**14**, **16**, **28**, **45**) with an EC_{50} < 1 μg/mL. It should be noted that many of the tested compounds inhibited mostly the Davis strain and, to a lesser extent, the AD-169 strain, as seen with **24** and **42**.

In previous work,[4] we reported on the influence of 6- or 8-substituted phenyl on the anti-CMV activity of the 3-phenethylthiomethylimidazo[1,2-*a*]pyridine series. From the anti-CMV results, we noticed that the 6-iodo or 6-bromo starting materials and the 6-phenyl analog showed the highest activities (EC_{50} < 1 μg/mL). However, most of the tested compounds were at least moderately active with EC_{50} values close to 2 μg/mL. The influence of the thien-2- or -3-yl substitution on positions 6 and 8 was also evaluated and led to moderately active compounds as well (EC_{50} values around 2 μg/mL).

In the present work, it appeared that the thienyl group can be replaced by a furyl, the highest anti-CMV potency being observed for the 6-(fur-3-yl) derivative **16** (EC_{50} > 0.8–0.27 μg/mL).

The presence of an oxygen atom in the 6 position is often noticed in compounds with a moderate or good anti-CMV activity (e.g., **16**, **28**). Nevertheless, some restrictions are associated with the exact location of this atom. Thus, we previously reported that a *para*- or *ortho*-hydroxyphenyl substituent in position 6 led to totally inactive compounds (EC_{50} > 100 μg/mL), whereas the *meta*-hydroxyphenyl analog was moderately active (EC_{50} = 2.2 μg/mL). In this work, the *para*-hydroxyphenylthio **28** presented an interesting anti-CMV activity with an EC_{50} of 0.8 μg/mL. This is also observed when comparing the fur-3-yl and fur-2-yl derivatives **15** and **16**, the latter being the more active. A hydrogen bonding between the oxygen in position 6 of our compounds and the active site may be postulated. As an example, the chlorine analog **27** of the hydroxyphenylthio **28** is inactive (EC_{50} > 4 μg/mL).

Nevertheless, a second polar atom or group in the 6 position seems to be deleterious for the activity as seen with compounds of which substitution is morpholine (**17**), *N*-methylpiperazine (**19**), pyrrolidinone (**20**) or imidazole (**23**).

Concerning the functionalization of the 8 position, a π–π interaction with the active site may be postulated, as all the aliphatic derivatives tested (**33**–**35**, **37**) appeared inactive (EC_{50} > 4–20 μg/mL), whereas the aromatic compounds **30**–**32**, **38**–**40**, **42** present a moderate anti-CMV activity (EC_{50} = 1.3–4 μg/mL). The nature of the heteroaromatic ring in position 8 influenced the activity to a lesser extent than in position 6. The best activity was displayed by the phenylthio derivative **45**.

As previously observed, the compounds showing the highest anti-CMV potency (**14**, **16**, **28**) (EC_{50} < 1 μg/mL) were also the most cytotoxic (MCC values of the same order as EC_{50} values). Only the 4-hydroxyphenylthio derivative **45** exhibited an interesting value of MCC > 100 μg/mL. On the other hand, a wealth of compounds, viz. **22**, **24**–**25**, **29**, **30**–**32**, **38**–**39**, and **42**–**43**, wich showed an EC_{50} of 1–4 μg/mL and no alteration of cell morphology at the active concentrations, had selectivity indexes (ratio of CC_{50} to EC_{50}) superior to 10.

2.3. Anti-VZV activity

As previously observed, contrarily to acyclovir and brivudin wich require phosphorylation to exert their antiviral activity, our

Table 1
Synthesis methods and yields for the obtention of compounds **10** to **45**

Cpd	R_1	R_2	*n*	Meth.	Yield (%)
10	4-Vinylphenyl	CH_3	2	A	31
11	4-Vinylphenyl	CH_3	1	A	73
12	4-Formylphenyl	CH_3	2	A	81
13	Indol-5-yl	CH_3	2	A	83
14	Thien-3-yl	CH_3	1	A	91
15	Fur-2-yl	CH_3	2	A	71
16	Fur-3-yl	CH_3	2	A	83
17	Morpholin-1-yl	CH_3	2	B	87
18	Pyrrolidin-1-yl	CH_3	2	B	84
19	*N*-Methylpiperazin-1-yl	CH_3	2	C	62
20	2-Oxopyrrolidin-1-yl	CH_3	2	D	90
21	Pyrrol-1-yl	CH_3	2	E	96
22	Pyrrol-1-yl	CH_3	1	E	93
23	Imidazol-1-yl	CH_3	2	E	20
24	Indol-1-yl	CH_3	2	D	62
25	Pyrrolo[2,3-*b*]pyridin-1-yl	CH_3	2	E	93
26	Cyano	CH_3	2	F	94
27	4-Chlorophenylthio	CH_3	2	G	96
28	4-Hydroxyphenylthio	CH_3	2	G	60
29	4-Aminophenylthio	CH_3	2	H	47
30	CH_3	Thien-3-yl	1	A	37
31	CH_3	Fur-2-yl	2	A	80
32	CH_3	Fur-3-yl	2	A	65
33	CH_3	Morpholin-1-yl	2	B	30
34	CH_3	Pyrrolidin-1-yl	2	B	80
35	CH_3	Pyrrolidin-1-yl	1	B	60
36	CH_3	*N*-Methylpiperazin-1-yl	2	C	35
37	CH_3	2-Oxopyrrolidin-1-yl	2	C	54
38	CH_3	Pyrrol-1-yl	2	E	94
39	CH_3	Pyrrol-1-yl	1	E	87
40	CH_3	Imidazol-1-yl	2	I	42
41	CH_3	Indol-1-yl	2	C	37
42	CH_3	Pyrrolo[2,3-*b*]pyridin-1-yl	2	E	48
43	CH_3	Cyano	2	F	94
44	CH_3	4-Chlorophenylthio	2	J	84
45	CH_3	4-Hydroxyphenylthio	2	J	21

Method A: $R(B(OH)_2$ (1.2 mmol), $Pd(PPh_3)_4$ (0.05 mmol), NaOH (2 mmol), DME (8 mL) and H_2O (4 mL) at 85 °C.
Method B: Amine (1.5 mmol), $Pd_2(dba)_3$ (0.01 mmol), *t*-BuONa (1.4 mmol), *rac*-BINAP (0.03 mmol) and toluene (2 mL) at 112 °C.
Method C: Amine (1.2 mmol) or azole or lactam (1.5 mmol), CuI (0.15 mmol), K_3PO_4 (2.1 mmol), ethylene glycol (2 mmol) and isopropanol (1 mL) at 85 °C.
Method D: Azole or lactam (1.5 mmol), CuI (0.15 mmol), K_3PO_4 (2.1 mmol), *N*,*N*′-dimethylethylenediamine (0.15 mmol) and toluene (2 mL) at 112 °C.
Method E: Azole (1.2 mmol), CuI (0.05 mmol), K_3PO_4 (2.1 mmol), *N*,*N*′-dimethylethylenediamine (0.15 mmol) and toluene (2 mL) at 112 °C.
Method F: CuI (0.1 mmol), NaCN (1.2 mmol), *N*,*N*′-dimethylethylenediamine (1 mmol) and toluene (2 mL) at 112 °C.
Method G: Thiophenol (1.2 or 1.5 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol), *N*,*N*′-dimethylethylenediamine (0.15 mmol) and isopropanol (1 mL) at 85 °C.
Method H: Thiophenol (1.5 mmol), CuI (0.20 mmol), K_2CO_3 (2 mmol), *N*,*N*′-dimethylethylenediamine (0.20 mmol) and isopropanol (1 mL) at 85 °C.
Method I: Azole (1.5 mmol), CuI (0.15 mmol), K_3PO_4, (2.1 mmol), *N*,*N*′-dimethylethylenediamine (0.30 mmol) and toluene (2 mL) at 112 °C.
Method J: Thiophenol (1.2 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol), ethylene glycol (2 mmol) and isopropanol (1 mL).

compounds showed the same range of activity or a higher activity against TK^- than TK^+ VZV strains, demonstrating a mechanism of action independent of the virus-encoded thymidine kinase (Tables 2 and 3).

The compounds that were moderately active against CMV (**16**, **22**, **29**, **39**, **45**) were also efficient against VZV with EC_{50} values around 2 μg/mL for the TK^- strain, that represent much higher potencies than the two references. Thus, small heteroaromatic rings such as fur-3-yl and pyrrol-1-yl are well tolerated in position 6. A phenylthio group introduced in position 6 or 8 led also to active compounds.

Moreover, compounds **22**, **29**, **39**, and **45**, inhibited VZV plaque formation at concentrations that resulted in no alteration of cell morphology, and had selectivity indexes (ratio of CC_{50} to EC_{50}) equal to or higher than 8.

3. Conclusion

In the present work, the impact of the substituent at the 6 or 8 position on the antiviral activity of the 3-phenethylthiomethylimidazo[1,2-*a*]pyridine was confirmed. From the synthesized compounds, eight (**14**, **16**, **21**–**22**, **28**–**29**, **39**, **45**) were the most potent against CMV and/or VZV. They present either a small heteroaromatic ring or a phenylthio group in position 6, or a phenylsulfanyl in position 8. On the other hand, **22**, **29, 39** and **45** were the most selective in their inhibitory activity against both VZV and CMV. All compounds showed similar or even greater activity against the TK^- VZV strain compared to the TK^+ strain, confirming a mechanism of action that is independent of the viral thymidine kinase.

Based on its potency and/or selectivity, the 4-hydroxyphenylthio derivative **45** deserves to be pursued in follow-up studies for its potential in the treatment of VZV and HCMV infections.

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. Signals are described as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q) and multiplet (m). Possible inversion of two values in the NMR spectra is expressed by an asterisk. Elemental analyses (C, H, N) were within ±0.4% of theory. *Tetrakis*(triphenylphosphine)palladium(0) was prepared as described in the literature.[8] The starting halogenated aminopyridine derivatives **1a**–**d** were prepared by iodination[9] or bromination[10] of commercially available aminopyridines.

The 6-iodo-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine **4**, 8-iodo-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine **7**, 6-bromo-8-methyl-3-phenethylthiomethyl-imidazo[1,2-*a*]-pyridine **5**, 8-bromo-6-methyl-3-phenethylthiomethylimidazo-[1,2-*a*]pyridine **8** were prepared by a multistep synthesis previously reported in the literature.[4]

4.2. Chemistry

4.2.1. 3-Benzylthiomethyl-6-iodo-8-methylimidazo[1,2-*a*]pyridine (6)

To a solution of **3a**[4] (2.66 g, 9.2 mmol) in 12 mL of acetic acid was added benzylmercaptan (1 mL, 8.3 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 CH_2Cl_2/petroleum ether (30:70). 84% yield. Mp 124–125 °C. ^1H NMR ($CDCl_3$) δ: 8.11 (m, 1H, H_5), 7.39 (s, 1H, H_2), 7.35–7.23 (m, 5H, Ph), 7.17 (d, 1H, J = 1.3 Hz, H_7), 3.82 (s, 2H, CH_2), 3.55 (s, 2H, CH_2), 2.56 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 145.62 (C8a), 137.70 (Ph-1), 133.36 (C2), 131.20 (C7), 129.29 (C8, Ph-2,6*), 128.96 (Ph-3,5*), 127.60 (Ph-4*), 127.43 (C5*), 119.64 (C3), 76.15 (C6), 35.78 (CH_2), 24.39 (CH_2), 17.11 (CH_3).

4.2.2. 3-Benzylthiomethyl-8-iodo-6-methylimidazo[1,2-*a*]pyridine (9)

To a solution of **3b**[4] (1.96 g, 6.8 mmol) in 10 mL of acetic acid was added benzylmercaptan (0.75 mL, 6.12 mmol). The mixture

Table 2
Anti-CMV and -VZV activities and cytotoxic properties in human embryonic lung (HEL) cells of compounds **10**–**29** substituted at position 6

Compound	R_1	R_2	*n*	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		
10	4-Vinylphenyl	CH_3	2			>4	2.9	20	14
11	4-Vinylphenyl	CH_3	1			>100	30	⩾100	59
12	4-Formylphenyl	CH_3	2			12.6	6.0	100	9.4
13	Indol-5-yl	CH_3	2			>20	>4	⩾20	26
14	Thien-3-yl	CH_3	1	>0.8	>0.8	>0.8	0.8	4	9.4
15	Fur-2-yl	CH_3	2	>4	>0.8	>0.8	>0.8	>4	40
16	Fur-3-yl	CH_3	2	2.4	>0.8	>0.8	0.27	>4	12
17	Morpholin-1-yl	CH_3	2	>20	>20	>20	>20	100	45
18	Pyrrolidin-1-yl	CH_3	2	>4	>4	4.0	2.0	20	12
19	*N*-Methylpiperazin-1-yl	CH_3	2	>4	>4	>20	4	20	32
20	2-Oxopyrrolidin-1-yl	CH_3	2	>100	>20	>20	>20	>100	89
21	Pyrrol-1-yl	CH_3	2	>4	>0.8	>0.8	1.3	⩾4	11
22	Pyrrol-1-yl	CH_3	1	>4	2.1	1.6	1.3	20	17
23	Imidazol-1-yl	CH_3	2	10.7	11.4	8.9	6.8	100	23
24	Indol-1-yl	CH_3	2	>20	>4	>4	1.8	>20	18
25	Pyrrolo[2,3-*b*]pyridin-1-yl	CH_3	2	>4	>4	2.0	1.4	20	16
26	Cyano	CH_3	2	>4	>4	8.9	8.9	20	14
27	4-Chlorophenylthio	CH_3	2	>4	>4	>4	>4	20	14
28	4-Hydroxyphenylthio	CH_3	2	>0.8	>0.8	>0.8	0.8	4	100
29	4-Aminophenylthio	CH_3	2	>4	2.2	1.8	1.8	20	23
Aciclovir				0.24	13	N.D.[d]	N.D.[d]	>400	137
Brivudin				0.0037	>50	N.D.[d]	N.D.[d]	400	122
Ganciclovir				N.D.[d]	N.D.[d]	0.51	0.80	100	146
Cidofovir				N.D.[d]	N.D.[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.

Table 3
Anti-CMV and -VZV activities and cytotoxic properties in human embryonic lung (HEL) cells of compounds **30**–**45** substituted at position 8

Compound	R_1	R_2	*n*	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		
30	CH_3	Thien-3-yl	1	7.3	6.5	4	2.1	100	100
31	CH_3	Fur-2-yl	2	6.6	7.9	2.5	2.7	100	41
32	CH_3	Fur-3-yl	2	20	>20	1.8	1.3	100	64
33	CH_3	Morpholin-1-yl	2	53.6	36.6	>4	8.2	>100	49
34	CH_3	Pyrrolidin-1-yl	2	35.7	>20	>20	20	>100	>100
35	CH_3	Pyrrolidin-1-yl	1	17.7	>4	10	5.2	⩾20	52
36	CH_3	*N*-Methylpiperazin-1-yl	2	N.D.[d]	N.D.[d]	N.D.[d]	N.D.[d]	N.D.[d]	N.D.[d]
37	CH_3	2-Oxopyrrolidin-1-yl	2	>4	>4	>4	>4	20	25
38	CH_3	Pyrrol-1-yl	2	>20	>20	1.8	1.8	100	26
39	CH_3	Pyrrol-1-yl	1	2.2	1.8	6.3	2.9	100	15
40	CH_3	Imidazol-1-yl	2	>4	>4	3.1	2.3	20	10
41	CH_3	Indol-1-yl	2	>20	>20	20	10.5	100	>100
42	CH_3	Pyrrolo[2,3-*b*]pyridin-1-yl	2	6.6	14	4	1.8	100	>100
43	CH_3	Cyano	2	16.4	>4	2.2	2.0	⩾20	>100
44	CH_3	4-Chlorophenylthio	2	>0.8	>0.8	>0.8	>0.8	4	100
45	CH_3	4-Hydroxyphenylthio	2	58	2.9	>0.8	0.8	>100	79
Aciclovir				0.24	13	N.D.[d]	N.D.[d]	>400	137
Brivudin				0.0037	>50	N.D.[d]	N.D.[d]	400	122
Ganciclovir				N.D.[d]	N.D.[d]	0.51	0.80	100	146
Cidofovir				N.D.[d]	N.D.[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.

was heated at 80 °C overnight. After cooling, the solution was worked up as for **6**. The residue was chromatographed on neutral alumina eluting with a CH_2Cl_2/petroleum ether (50:50) then with CH_2Cl_2. 81% yield. Mp 110–111 °C. ^1H NMR ($CDCl_3$) δ: 7.77 (s, 1H, H_5), 7.61 (s, 1H, H_7), 7.51 (s, 1H, H_2), 7.41–7.24 (m, 5H, Ph), 3.86 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 2.34 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 145.25 (C8a), 137.96 (Ph-1), 137.13 (C7), 134.16 (C2), 129.56 (Ph-2,6*), 129.14 (Ph-3,5*), 127.82 (Ph-4),

123.37 (C6), 122.78 (C5), 121.14 (C3), 84.56 (C8), 35.88 (CH_2), 24.86 (CH_2), 18.54 (CH_3).

4.2.3. General procedure for Suzuki cross-coupling reactions

Into a three necked round bottom flask was introduced under argon, iodinated imidazo[1,2-*a*]pyridines **4**, **6**, **7**, or **9** (1 mmol), *tetrakis*(triphenylphosphine)palladium (58 mg, 0.05 mmol), the boronic acid (1.1 or 1.2 mmol), 8 mL of 1,2-dimethoxyethane, and NaOH (80 mg, 2 mmol) solubilized in 4 mL of water. The reaction mixture was heated at 85 °C and 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. The residue was purified by column chromatography.

4.2.3.1. 8-Methyl-3-(phenethylthiomethyl)-6-(4-vinylphenyl)-imidazo[1,2-*a*]pyridine (10). The compound was obtained following the general procedure using **4** (320 mg, 0.78 mmol), 4-vinylphenylboronic acid (139 mg, 0.94 mmol). After 3 h at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (70:30). 31% yield. Mp 119–120 °C. ^{1}H NMR ($CDCl_3$) δ: 8.21 (m, 1H, H_5), 7.62–7.53 (m, 5H, H_2, Phvinyl-2,3,5,6), 7.36–7.15 (m, 6H, Ph, H_7), 6.81 (dd, 1H, ***J*** = 17.6–10.9 Hz, vinyl), 5.85 (dd, 1H, ***J*** = 17.6–0.8 Hz, vinyl), 5.35 (dd, 1H, ***J*** = 10.9–0.8 Hz, vinyl), 4.05 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.73 (s, 3H, CH_3), 2.66 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 146.62 (C8a), 139.56 (Ph-1*), 138.04 (Phvinyl-1,4*), 136.97 (vinyl-CH), 134.11 (C2), 129.74 (Ph-2,6). 129.32 (Ph-3,5), 128.15 (C8), 127.86 (Phvinyl-2,6*), 127.63 (Phvinyl-3,5*), 127.44 (Ph-4), 126.92 (C6), 124.32 (C7), 120.29 (C3), 119.97 (C5), 115.06 (vinyl-CH_2), 36.26 (CH_2), 33.02 (CH_2), 25.69 (CH_2), 17.53 (CH_3). Anal. Calcd for $C_{25}H_{24}N_2S$: C, 78.09; H, 6.29; N, 7.28. Found: C, 78.21; H, 6.19; N, 7.34.

4.2.3.2. 3-(Benzylthiomethyl)-8-methyl-6-(4-vinylphenyl)imidazo-[1,2-*a*]pyridine (11). The compound was obtained following the general procedure using **6** (394 mg, 1 mmol), 4-vinylphenylboronic acid (178 mg, 1.2 mmol). After 3 h at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (80:20). 73% yield. Mp 123–125 °C. ^{1}H NMR ($CDCl_3$) δ: 8.11 (m, 1H, H_5), 7.55 (m, 4H, Phvinyl-2,3,5,6), 7.52 (s, 1H, H_2), 7.34–7.26 (m, 6H, Ph, H_7), 6.80 (dd, 1H, ***J*** = 17.6–10.9 Hz, vinyl), 5.86 (dd, 1H, ***J*** = 17.6–0.8 Hz, vinyl), 5.35 (dd, 1H, ***J*** = 10.9–0.8 Hz, vinyl), 3.95 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 146.55 (C8a), 138.16 (Ph-1*), 137.62 (Phvinyl-1,4*), 136.79 (vinyl-CH), 133.93 (C2), 129.52 (Ph-2,6), 129.12 (Ph-3,5), 127.96 (C8), 127.71 (Phvinyl-2,6*), 127.44 (Phvinyl-3,5*, Ph-4), 126.70 (C6), 124.21 (C7), 120.16 (C3), 119.83 (C5), 114. 95 (vinyl-CH_2), 35.93 (CH_2), 24.89 (CH_2), 17.73 (CH_3). Anal. Calcd for $C_{24}H_{22}N_2S$: C, 77.80; H, 5.98; N, 7.56. Found: C, 77.83; H, 5.98; N, 7.54.

4.2.3.3. 4-(8-Methyl-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridin-6-yl)benzaldehyde (12). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), 4-formylphenylboronic acid (180 mg, 1.2 mmol). After 5 h at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (30:70). 81% yield. Mp 88–90 °C. ^{1}H NMR ($CDCl_3$) δ: 10.12 (s, 1H, CHO), 8.29 (m, 1H, H_5), 8.03 (d, 2H, ***J*** = 8.4 Hz, PhCHO-3,5), 7.79 (d, 2H, ***J*** = 8.4 Hz, PhCHO-2,6), 7.58 (s, 1H, H_2), 7.37 (m, 1H, H_7), 7.33–7.14 (m, 5H, Ph), 4.06 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.67 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 192.10 (CHO), 146.49 (C8a), 144.12 (PhCHO-1), 140.38 (Ph-1), 135.93 (PhCHO-4), 133.71 (C2), 130.89 (PhCHO-3,5), 128.94 (Ph-2,3,5,6), 128.36 (C8), 128.00 (PhCHO-2,6), 126.89 (Ph-4), 125.79 (C6), 123.81 (C7), 120.71 (C5), 120.49 (C3), 36.30 (CH_2), 32.94 (CH_2), 25.69 (CH_2), 17.57 (CH_3). Anal. Calcd for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25. Found C, 74.79; H, 5.69; N, 7.33.

4.2.3.4. 6-(Indol-5-yl)-8-methyl-3-phenethylthiomethylimidazo-[1,2-*a*]pyridine (13). The compound was obtained following the general procedure using **4** (226 mg, 0.55 mmol), indol-5-ylboronic acid (107 mg, 0.66 mmol). After 3 h at 75 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 83% yield. Mp 173–174 °C. ^{1}H NMR ($CDCl_3$) δ: 8.73 (br s, 1H, NH), 8.21 (m, 1H, H_5), 7.89 (m, 1H, indole), 7.55 (s, 1H, H_2), 7.54 (d, 1H, ***J*** = 6.7 Hz, indole), 7.45 (m, 2H, H_7, indole), 7.35–7.15 (m, 6H, Ph, indole), 6.68 (m, 1H, indole), 4.05 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.74 (s, 3H, CH_3), 2.68 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 145.41 (C8a), 140.18 (Ph-1), 135.72 (indole), 131.72 (C2), 129.47 (indole), 128.68 (Ph-2,6*), 128.60 (Ph-3,5*), 126.88 (C8), 126.57 (indole), 125.93 (Ph-4*), 125.48 (C7*), 121.64 (indole), 119.85 (C3), 119.46 (indole), 119.29 (C5), 111.79 (indole), 103.02 (indole), 36.09 (CH_2), 32.73 (CH_2), 25.48 (CH_2), 17.28 (CH_3), C6 not found. Anal. Calcd for $C_{25}H_{23}N_3S$: C, 75.53; H, 5.83; N, 10.57. Found: C, 75.51; H, 5.82; N, 10.55.

4.2.3.5. 3-Benzylthiomethyl-8-methyl-6-(thien-3-yl)imidazo[1,2-*a*]pyridine (14). The compound was obtained following the general procedure using **6** (394 mg, 1 mmol), thien-3-ylboronic acid (154 mg, 1.2 mmol). After 3 h at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 91% yield. Mp 113–114 °C. ^{1}H NMR ($CDCl_3$) δ: 8.13 (m, 1H, H_5), 7.50 (s, 1H, H_2), 7.48–7.46 (m, 2H, Thio-2,4), 7.37 (dd, 1H, ***J*** = 4.3–2.1 Hz, Thio-5), 7.35–7.27 (m, 6H, Ph, H_7), 3.95 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 2.69 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 146.34 (C8a), 139.00 (Ph-1), 137.98 (Thio-3), 133.67 (C2), 129.37 (Ph-2,6*), 128.98 (Ph-3,5*), 127.84 (C8), 127.59 (Thio-2), 127.24 (Ph-4), 126.44 (Thio-5), 123.86 (C7), 122.05 (C6), 121.13 (Thio-4), 119.94 (C3), 119.18 (C5), 35.73 (CH_2), 24.69 (CH_2), 17.50 (CH_3). Anal. Calcd for $C_{20}H_{18}N_2S_2$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.77; H, 5.25; N, 8.02.

4.2.3.6. 6-(Furan-2-yl)-8-methyl-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridine (15). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), fur-2-ylboronic acid (123 mg, 1.1 mmol). After 1 h at 85 °C, boronic acid was again added (56 mg, 0.5 mmol). After 2 h more at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 71% yield. Mp 112–113 °C. ^{1}H NMR ($CDCl_3$) δ: 8.36 (m, 1H, H_5), 7.53 (dd, 1H, ***J*** = 1.8–0.7 Hz, Furan-5), 7.51 (s, 1H, H_2), 7.35–7.46 (m, 6H, Ph, H_7), 6.68 (d, 1H, ***J*** = 3.4 Hz, Furan-3), 6.54 (dd, 1H, ***J*** = 3.4–1.8 Hz, Furan-4), 4.03 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.66 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 151.42 (Furan-2), 146.26 (C8a), 142.72 (Furan-5), 140.51 (Ph-1), 133.35 (C2), 128.96 (Ph-2,6*), 128.89 (Ph-3,5*), 128.03 (C8), 126.86 (Ph-4), 121.06 (C7), 120.54 (C3), 117.61 (C6), 117.51 (C5), 112.17 (Furan-4), 106.20 (Furan-3), 36.42 (CH_2), 32.97 (CH_2), 25.62 (CH_2), 17.45 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.32; H, 5.83; N, 8.12.

4.2.3.7. 6-(Furan-3-yl)-8-methyl-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridine (16). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), fur-3-ylboronic acid (123 mg, 1.1 mmol). After 1 h at 85 °C, boronic acid was again added (56 mg, 0.5 mmol). After 2 h more at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 83% yield. Mp 80–81 °C. ^{1}H NMR ($CDCl_3$) δ: 8.12 (m, 1H, H_5), 7.78 (m, 1H, Furan-5), 7.56 (t, 1H, ***J*** = 1.8 Hz, Furan-2), 7.52 (s, 1H, H_2), 7.34–7.14 (m, 6H, Ph, H_7), 6.73 (dd, 1H, ***J*** = 1.8–0.9 Hz, Furan-4), 4.03 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.69 (s, 3H, CH_3), 2.64 (s, 3H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 146.60 (C8a), 144.66 (Furan-2), 140.64 (Ph-1), 139.33 (Furan-5), 133.44 (C2), 129.14 (Ph-3,5*), 129.07 (Ph-2,6*), 128.26 (C8), 127.05 (Ph-4), 123.78 (C6), 123.59

(C7), 120.19 (C3), 118.78 (Furan-3), 118.74 (C5), 109.23 (Furan-4), 36.54 (CH_2), 33.04 (CH_2), 25.86 (CH_2), 17.61 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.47; H, 5.74; N, 8.03.

4.2.3.8. 3-Benzylthiomethyl-6-methyl-8-(thien-3-yl)imidazo-[1,2-*a*]pyridine (30). The compound was obtained following the general procedure using **9** (394 mg, 1 mmol), thien-3-ylboronic acid (154 mg, 1.2 mmol). After 3 h at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (50:50). 37% yield. Mp 90–91 °C. ^{1}H NMR ($CDCl_3$) δ: 8.55 (dd, 1H, J = 3–1.3 Hz, Thio-2), 7.78–7.75 (m, 2H, Thio-4, H_5), 7.55 (s, 1H, H_2), 7.46 (dd, 1H, J = 5.1–3 Hz, Thio-5), 7.38–7.29 (m, 6H, Ph, H_7), 3.94 (s, 2H, CH_2), 3.63 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 144.25 (C8a), 138.21 (Ph-1), 137.05 (Thio-3), 133.69 (C2), 129.64 (Ph-2,6*), 129.17 (Ph-3,5*), 127.79 (Ph-4), 127.38 (Thio-4), 126.03 (Thio-2*), 126.00 (Thio-5*), 125.07 (C7), 124.77 (C8), 122.33 (C6), 121.05 (C5), 119.34 (C3), 35.91 (CH_2), 24.81 (CH_2), 19.12 (CH_3). Anal. Calcd for $C_{20}H_{18}N_2S_2$: C, 68.53; H, 5.18; N, 7.99. Found: C, 68.69; H, 5.21; N, 7.95.

4.2.3.9. 8-(Furan-2-yl)-6-methyl-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridine (31). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), fur-2-ylboronic acid (135 mg, 1.2 mmol). After 3 h at 85 °C, boronic acid was again added (56 mg, 0.5 mmol). After 3 h more at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (10:90). 80% yield. Mp 95–96 °C. ^{1}H NMR ($CDCl_3$) δ: 7.85 (m, 1H, H_5), 7.74 (d, 1H, J = 3.4 Hz, Furan-3), 7.61–7.59 (m, 2H, H_7, Furan-5), 7.55 (s, 1H, H_2), 7.36–7.15 (m, 5H, Ph), 6.64 (dd, 1H, J = 3.4–1.8 Hz, Furan-4), 4.00 (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: 149.51 (C8a), 143.06 (Furan-5), 141.92 (Furan-2), 140.49 (Ph-1), 133.09 (C2), 128.98 (Ph-2,6*), 128.89 (Ph-3,5*), 126.87 (Ph-4), 122.19 (C8), 122.06 (C7), 120.85 (C5), 119.68 (C3*), 119.45 (C6*), 112.65 (Furan-3*), 112.50 (Furan-4*), 36.32 (CH_2), 32.82 (CH_2), 25.55 (CH_2), 18.95 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: C, 72.46; H, 5.80; N, 8.07.

4.2.3.10. 8-(Furan-3-yl)-6-methyl-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridine (32). The compound was obtained following the general procedure using **7** (300 mg, 0.74 mmol), fur-3-ylboronic acid (91 mg, 0.81 mmol). After 3 h at 85 °C, boronic acid was again added (56 mg, 0.5 mmol). After 3 h more at 85 °C and usual treatment, pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (10:90). 65% yield. Mp 92–93 °C. ^{1}H NMR ($CDCl_3$) δ: 8.76 (m, 1H, Furan-5), 7.79 (m, 1H, H_5), 7.54 (t, 1H, J = 1.7 Hz, Furan-2), 7.50 (s, 1H, H_2), 7.33–7.13 (m, 6H, Ph, H_7), 6.94 (dd, 1H, J = 1.7–0.8 Hz, Furan-4), 3.96 (CH_2), 2.82 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 143.80 (Furan-5), 143.58 (C8a), 143.45 (Furan-2), 140.53 (Ph-1), 132.98 (C2), 129.00 (Ph-2,6*), 128.91 (Ph-3,5*), 126.88 (Ph-4), 123.86 (C7), 122.14 (Furan-3*), 121.67 (C8*), 121.25 (C6*), 120.56 (C5), 119.42 (C3), 108.77 (Furan-4), 36.34 (CH_2), 32.85 (CH_2), 25.60 (CH_2), 18.94 (CH_3). Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04. Found: 72.35; H, 5.79; N, 8.02.

4.2.4. General procedure for palladium-catalysed aminations

Halogenated imidazo[1,2-*a*]pyridines **5**, **8** or **9** (1 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), *t*-BuONa (135 mg, 1.4 mmol), *rac*-BINAP (19 mg, 0.03 mmol), and amine if solid (1.5 mmol) were added to a screw-capped test tube. The tube was evacuated and back-filled with N_2. Amine if liquid (1.5 mmol), toluene (2 mL) were added successively by syringe. The tube was sealed with a teflon-lined cap and the reaction mixture was heated at 112 °C. After cooling at room temperature, the suspension was diluted with CH_2Cl_2 and was filtered through Celite. Solvent was evaporated and residue was purified by column chromatography.

4.2.4.1. 8-Methyl-6-(morpholin-1-yl)-3-(phenethylthiomethyl)imidazo[1,2-*a*]pyridine (17). The compound was obtained following the general procedure using **5** (361 mg, 1 mmol) and morpholine (130 μL, 1.5 mmol). The tube was heated for 20 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (40:60). 87% yield. Mp 76–77 °C. ^{1}H NMR ($CDCl_3$) δ: 7.46 (s, 1H, H_2), 7.42 (m, 1H, H_5), 7.35–7.22 (m, 3H, Ph-3,4,5), 7.16 (m, 2H, Ph-2,6), 6.97 (m, 1H, H_7), 3.98 (s, 2H, CH_2), 3.93 (t, 4H, J = 4.7 Hz, Morpholine), 3.12 (t, 4H, J = 4.7 Hz, Morpholine), 2.82 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 2.60 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 144.24 (C8a), 140.48 (Ph-1*), 140.07 (C6*), 132.85 (C2), 128.91 (Ph-2,6*), 128.82 (Ph-3,5*), 127.75 (C8), 126.78 (Ph-4), 120.00 (C7, C3), 108.15 (C5), 67.15 (Morpholine), 51.10 (Morpholine), 36.29 (CH_2), 32.72 (CH_2), 25.73 (CH_2), 17.54 (CH_3). Anal. Calcd for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.86; N, 11.43. Found: C, 68.60; H, 6.87; N, 11.46.

4.2.4.2. 8-Methyl-3-phenethylthiomethyl-6-(pyrrolidin-1-yl)-imidazo[1,2-*a*]pyridine (18). The compound was obtained following the general procedure using **5** (361 mg, 1 mmol) and pyrrolidine (123 μL, 1.5 mmol). The tube was heated for 20 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (40:60). 84% yield. Mp 131–132 °C. ^{1}H NMR ($CDCl_3$) δ: 7.42 (s, 1H, H_2), 7.35–7.14 (m, 5H, Ph), 7.09 (m, 1H, H_5), 6.80 (q, 1H, J = 1.1 Hz, H_7), 3.99 (s, 2H, CH_2), 3.31 (m, 4H, Pyrrolidine), 2.83 (m, 2H, CH_2), 2.62 (s, 3H, CH_3), 2.63 (m, 2H, CH_2), 2.08 (m, 4H, Pyrrolidine). ^{13}C NMR ($CDCl_3$) δ: 143.00 (C8a), 140.66 (Ph-1), 137.59 (C6), 132.20 (C2), 128.95 (Ph-2,6*), 128.82 (Ph-3,5*), 127.23 (C8), 126.74 (Ph-4), 118.83 (C3), 116.77 (C7), 101.81 (C5), 48.68 (Pyrrolidine), 36.39 (CH_2), 32.70 (CH_2), 25.91 (CH_2), 25.66 (Pyrrolidine), 17.64 (CH_3). Anal. Calcd for $C_{21}H_{25}N_3S$: C, 71.75; H, 7.17; N, 11.95. Found: C, 71.73; H, 7.18; N, 11.94.

4.2.4.3. 6-Methyl-8-(morpholin-1-yl)-3-(phenethylthiomethyl)-imidazo[1,2-*a*]pyridine (33). The compound was obtained following the general procedure using **8** (361 mg, 1 mmol) and morpholine (130 μL, 1.5 mmol). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted by CH_2Cl_2. 30% yield. Mp 108–110 °C. ^{1}H NMR ($CDCl_3$) δ: 7.58 (m, 1H, H_5), 7.41 (s, 1H, H_2), 7.35–7.22 (m, 3H, Ph-3,4,5), 7.16 (m, 2H, Ph-2,6), 6.34 (d, 1H, J = 1 Hz, H_7), 4.00 (t, 4H, J = 4.7 Hz, Morpholine), 3.95 (s, 2H, CH_2), 3.54 (t, 4H, J = 4.7 Hz, Morpholine), 2.83 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 141.35 (C8a), 140.94 (Ph-1*), 140.76 (C8*), 131.62 (C2), 129.20 (Ph-2,6*), 129.14 (Ph-3,5*), 127.10 (Ph-4), 122.89 (C6), 119.56 (C3), 116.11 (C5), 110.77 (C7), 67.60 (Morpholine), 50.71 (Morpholine), 36.58 (CH_2), 32.98 (CH_2), 25.81 (CH_2), 19.48 (CH_3). Anal. Calcd for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.86; N, 11.43. Found: C, 68.69; H, 6.87; N, 11.41.

4.2.4.4. 6-Methyl-3-phenethylthiomethyl-8-(pyrrolidin-1-yl)-imidazo[1,2-*a*]pyridine (34). The compound was obtained following the general procedure using **8** (361 mg, 1 mmol) and pyrrolidine (123 μL, 1.5 mmol). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with diethyl ether/petroleum ether (40:60). 80% yield. Mp 68–69 °C. ^{1}H NMR ($CDCl_3$) δ: 7.39 (s, 1H, H_2), 7.34–7.16 (m, 6H, Ph, H_5), 5.93 (s, 1H, H_7), 3.95 (s, 2H, CH_2), 3.81 (t, 4H, J = 6.7 Hz, Pyrrolidine), 2.82 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.32 (s,

3H, CH_3), 2.04 (m, 4H, Pyrrolidine). ^{13}C NMR ($CDCl_3$) δ: 140.70 (C8*), 140.50 (C8a*), 138.24 (Ph-1), 130.99 (C2), 129.00 (Ph-2,6*), 128.88 (Ph-3,5*), 126.80 (Ph-4), 123.62 (C6), 118.94 (C3), 111.14 (C5), 104.01 (C7), 50.38 (Pyrrolidine), 36.47 (CH_2), 32.83 (CH_2), 25.80 (Pyrrolidine, CH_2), 19.33 (CH_3). Anal. Calcd for $C_{21}H_{25}N_3S$: C, 71.25; H, 7.17; N, 11.95. Found: C, 71.20; H, 7.19; N, 11.96.

4.2.4.5. 3-Benzylthiomethyl-6-methyl-8-(pyrrolidin-1-yl)imidazo[1,2-*a*]pyridine (35). The compound was obtained following the general procedure using **9** (394 mg, 1 mmol) and pyrrolidine (123 μL, 1.5 mmol). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (70:30). 60% yield. Mp 86–87 °C. ^{1}H NMR ($CDCl_3$) δ: 7.38–7.29 (m, 5H, Ph), 7.36 (s, 1H, H_2), 7.22 (s, 1H, H_5), 5.91 (s, 1H, H_7), 3.85 (s, 2H, CH_2), 3.80 (m, 4H, Pyrrolidine), 3.61 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 2.04 (m, 4H, Pyrrolidine). ^{13}C NMR ($CDCl_3$) δ: 140.46 (C8a), 137.94 (Ph-1), 130.93 (C2), 129.22 (Ph-2,6*), 128.66 (Ph-3,5*), 127.22 (Ph-4), 123.24 (C6), 118.49 (C3), 110.81 (C5), 103.67 (C7), 50.08 (Pyrrolidine), 35.34 (CH_2), 25.50 (Pyrrolidine), 24.50 (CH_2), 19.01 (CH_3). C8 not found. Anal. Calcd for $C_{20}H_{23}N_3S$: C, 71.18; H, 6.87; N, 12.45. Found: C, 71.25; H, 6.84; N, 12.49.

4.2.5. General procedure for copper-catalysed couplings of amines, lactam, azoles or thiophenols

Halogenated imidazo[1,2-*a*]pyridines **4**, **6**, **7** or **9** (1 mmol), copper (I) iodide, base, and amine or azole or thiophenol if solids were added to a screw-capped test tube. The tube was evacuated and back-filled with N_2. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.1 mmol) or ethylene glycol (111 μL, 2 mmol), amine or azole or thiophenol if liquids (1.2 mmol) and isopropanol (1 mL) or toluene (2 mL) were added successively by syringe. The tube was sealed with a teflon-lined cap and the reaction mixture was heated at 85 °C with isopropanol or 112 °C with toluene. After cooling at room temperature, the suspension was diluted with CH_2Cl_2 and filtered through Celite. Solvent was evaporated and residue was purified by column chromatography.

4.2.5.1. 8-Methyl-6-(4-methylpiperazin-1-yl)-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (19). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), ethylene glycol (111 μL, 2 mmol), ***N***-methylpiperazine (133 μL, 1.2 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 62% yield. Mp 84–85 °C. ^{1}H NMR ($CDCl_3$) δ: 7.44 (s, 1H, H_2), 7.42 (m, 1H, H_5), 7.33–7.22 (m, 3H, Ph-3,4,5), 7.15 (m, 2H, Ph-2,6), 6.97 (m, 1H, H_7), 3.98 (s, 2H, CH_2), 3.16 (t, 4H, ***J*** = 4.8 Hz, Piperazine), 2.82 (m, 2H, CH_2), 2.68–2.58 (m, 6H, CH_2, Piperazine), 2.61 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 144.35 (C8a), 140.61 (Ph-1*), 140.14 (C6*), 132.93 (C2), 129.01 (Ph-2,6*), 128.92 (Ph-3,5*), 127.68 (C8), 126.87 (Ph-4), 120.50 (C7), 120.00 (C3), 108.31 (C5), 55.46 (Piperazine), 50.91 (Piperazine), 46.60 (CH_3), 36.44 (CH_2), 32.83 (CH_2), 25.88 (CH_2), 17.59 (CH_3). Anal. Calcd for $C_{22}H_{28}N_4S$: C, 69.44; H, 7.42; N, 14.72. Found: C, 69.48; H, 7.38; N, 14.69.

4.2.5.2. *N*-(8-Methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridin-6-yl)pyrrolidin-2-one (20). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), pyrrolidin-2-one (116 μL, 1.5 mmol), *N*,*N*′-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 90% yield. Mp 144–145 °C. ^{1}H NMR ($CDCl_3$) δ: 8.49 (dd, 1H, *J* = 2–0.7 Hz, H_5), 7.52 (s, 1H, H_2), 7.34–7.22 (m, 4H, H_7, Ph-3,4,5), 7.16 (m, 2H, Ph-2,6), 4.01 (s, 2H, CH_2), 3.92 (t, 2H, J = 7 Hz, Pyrrolidinone), 2.84 (m, 2H, CH_2), 2.72–2.58 (m, 7H, CH_2, CH_3, Pyrrolidinone), 2.26 (m, 2H, Pyrrolidinone). ^{13}C NMR ($CDCl_3$) δ: 174.85 (C = O), 144.94 (C8a), 140.52 (Ph-1), 133.56 (C2), 128.94 (Ph-2,6*), 128.86 (Ph-3,5*), 127.86 (C6*), 127.29 (C8*), 126.80 (Ph-4), 120.45 (C3), 118.82 (C7), 114.81 (C5), 49.41 (Pyrrolidinone), 36.32 (CH_2), 32.91 (CH_2*), 32.65 (Pyrrolidinone*), 25.63 (CH_2), 18.49 (Pyrrolidinone), 17.55 (CH_3). Anal. Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.03; H, 6.31; N, 11.54.

4.2.5.3. 8-Methyl-3-phenethylthiomethyl-6-(pyrrol-1-yl)imidazo[1,2-*a*]pyridine (21). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), pyrrole (84 μL, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with diethylether/petroleum ether (50:50). 96% yield. Mp 58–60 °C. ^{1}H NMR ($CDCl_3$) δ: 8.11 (m, 1H, H_5), 7.56 (s, 1H, H_2), 7.35–7.23 (m, 4H, H_7, Ph-3,4,5), 7.18 (m, 2H, Ph-2,6), 7.07 (t, 2H, ***J*** = 2.1 Hz, pyrrole-2,5), 6.43 (t, 2H, ***J*** = 2.1 Hz, pyrrole-3,4), 4.01 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.72 (s, 3H, CH_3), 2.66 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 145.81 (C8a), 140.59 (Ph-1), 134.12 (C2), 129.69 (C6), 129.12 (C8, Ph-2,3,5,6), 127.11 (Ph-4), 120.85 (C3, Pyrrole-2,5), 120.59 (C7), 114.96 (C5), 111.38 (Pyrrole-3,4), 36.54 (CH_2), 33.16 (CH_2), 25.90 (CH_2), 17.75 (CH_3). Anal. Calcd for $C_{21}H_{21}N_3S$: C, 72.59; H, 6.09; N, 12.09. Found: C, 72.64; H, 6.11; N, 12.12.

4.2.5.4. 3-Benzylthiomethyl-8-methyl-6-(pyrrol-1-yl)imidazo-[1,2-*a*]pyridine (22). The compound was obtained following the general procedure using **6** (394 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), pyrrole (84 μL, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (70:30). 93% yield. Mp 75–77 °C. ^{1}H NMR ($CDCl_3$) δ: 8.01 (m, 1H, H_5), 7.54 (s, 1H, H_2), 7.35–7.26 (m, 5H, Ph), 7.21 (m, 1H, H_7), 7.04 (t, 2H, ***J*** = 2.2 Hz, Pyrrole-2,5), 6.43 (t, 2H, ***J*** = 2.2 Hz, Pyrrole-3,4), 3.94 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 145.72 (C8a), 138.03 (Ph-1), 134.30 (C2), 129.61 (C6), 129.48 (Ph-2,6*), 129.15 (Ph-3,5*), 129.00 (C8), 127.79 (Ph-4), 120.81 (Pyrrole-2,5), 120.75 (C3), 120.45 (C7), 114.86 (C5), 111.31 (Pyrrole-3,4), 35.99 (CH_2), 24.84 (CH_2), 17.68 (CH_3). Anal. Calcd for $C_{20}H_{19}N_3S$: C, 72.04; H, 5.74; N, 12.60. Found: C, 72.11; H, 5.71; N, 12.61.

4.2.5.5. 6-(Imidazol-1-yl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (23). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), imidazole (82 mg, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 20% yield. Mp 130–132 °C. ^{1}H NMR ($CDCl_3$) δ: 8.15 (m, 1H, H_5), 7.84 (br s, 1H, Imidazole-2), 7.60 (s, 1H, H_2), 7.34–7.22 (m, 5H, H_7, Imidazole-5, Ph-3,4,5), 7.17–7.12 (m, 3H, Imidazole-4, Ph-2,6), 4.01 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.73 (s, 3H, CH_3), 2.68 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 145.83 (C8a), 140.27 (Ph-1), 136.76 (Imidazole-2), 134.36 (C2), 131.08 (Imidazole-5), 129.65 (C6), 128.91 (Ph-2,3,5,6), 126.94 (Ph-4), 125.78 (C8), 121.06 (C3), 120.12 (Imidazole-4), 119.66 (C7), 116.25 (C5), 36.24 (CH_2), 32.95 (CH_2), 25.63 (CH_2), 17.52 (CH_3). Anal. Calcd for $C_{20}H_{20}N_4S$: C, 68.93; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.82; N, 16.11.

4.2.5.6. 6-(Indol-1-yl)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (24). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), indole (175 mg, 1.5 mmol), ***N,N′***-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 62% yield. Mp 63–65 °C. ^{1}H NMR ($CDCl_3$) δ: 8.24 (m, 1H, H_5), 7.76 (m, 1H, Indole), 7.62 (s, 1H, H_2), 7.53 (m, 1H, Indole), 7.35 (d, 1H, J = 3.3 Hz, Indole), 7.34–7.14 (m, 8H, Ph, H_7, 2 H Indole), 6.77 (dd, 1H, J = 3.3–0.8 Hz, Indole), 4.01 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 2.68 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 145.71 (C8a), 140.37 (Ph-1), 136.85 (Indole quat.), 133.91 (C2), 129.56 (C6*), 128.95 (Ph-2,3,5,6), 128.59 (Indole), 127.59 (Indole quat.*), 126.94 (Ph-4), 123.21 (Indole), 122.66 (C7), 121.75 (Indole), 121.13 (Indole), 120.81 (C3), 118.46 (C5), 110.63 (Indole), 104.51 (Indole), 36.36 (CH_2), 33.05 (CH_2), 25.74 (CH_2), 17.57 (CH_3). C8 not found. Anal. Calcd for $C_{25}H_{23}N_3S$: C, 75.53; H, 5.83; N, 10.57. Found: C, 75.62; H, 5.87; N, 10.55.

4.2.5.7. 8-Methyl-3-phenethylthiomethyl-6-(pyrrolo[2,3-*b*]pyridin-1-yl)imidazo[1,2-*a*]pyridine (25). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), 7-azaindole (142 mg, 1.2 mmol), ***N,N′***-dimethylethylenediamine (16 μL, 0.15 mol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 93% yield. Mp 90–94 °C. ^{1}H NMR ($CDCl_3$) δ: 8.52 (m, 1H, H_5), 8.40 (dd, 1H, J = 4.7–1.5 Hz, azaindole), 8.02 (dd, 1H, J = 7.9–1.5 Hz, azaindole), 7.58 (s, 1H, H_2), 7.49 (d, 1H, J = 3.6 Hz, azaindole), 7.42 (m, 1H, azaindole), 7.32–7.14 (m, 6H, Ph, H_7), 6.69 (d, 1H, J = 3.6 Hz, azaindole), 4.03 (s, 2H, CH_2), 2.83 (m, 2H, CH_2), 2.73 (s, 3H, CH_3), 2.64 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 148.22 (azaindole), 145.56 (C8a), 144.24 (azaindole), 140.45 (Ph-1), 133.64 (C2), 129.80 (azaindole), 128.96 (Ph-2,6*), 128.90 (Ph-3,5*), 128.48 (azaindole), 128.41 (azaindole), 126.88 (Ph-4), 126.42 (C8), 122.32 (azaindole), 121.81 (C6), 120.82 (azaindole, C3), 118.33 (C5), 117.46 (C7), 102.52 (azaindole), 36.30 (CH_2), 33.00 (CH_2), 25.63 (CH_2), 17.64 (CH_3). Anal. Calcd for $C_{24}H_{22}N_4S$: C, 72.33; H, 5.56; N, 14.06. Found: C, 12.45; H, 5.64; N, 14.13.

4.2.5.8. 8-Methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridin-6-carbonitrile (26). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (19 mg, 0.10 mmol), sodium cyanide (59 mg, 1.2 mmol), ***N,N′***-dimethylethylenediamine (106 μL, 1 mmol) and toluene (2 mL). The tube was heated for 24 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 94% yield. Mp 75–76 °C. ^{1}H NMR ($CDCl_3$) δ: 8.48 (m, 1H, H_5), 7.60 (s, 1H, H_2), 7.37–7.24 (m, 3H, Ph-3,4,5), 7.18 (m, 3H, H_7, Ph-2,6), 3.98 (s, 2H, CH_2), 2.85 (m, 2H, CH_2), 2.65 (m, 5H, CH_2, CH_3). ^{13}C NMR ($CDCl_3$) δ: 145.99 (C8a), 139.91 (Ph-1), 134.49 (C2), 129.15 (C8), 128.89 (C5), 128.57 (Ph-2,6*), 128.49 (Ph-3,5*), 126.53 (Ph-4), 122.37 (C7), 121.33 (C3), 117.11 (CN), 98.21 (C6), 35.82 (CH_2), 32.67 (CH_2), 24.84 (CH_2), 16.89 (CH_3). Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.42; H, 5.53; N, 13.68.

4.2.5.9. 6-(4-Chlorophenylthio)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (27). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_2CO_3 (198 mg, 2 mmol), 4-chlorothiophenol (175 mg, 1.2 mmol), ***N,N′***-dimethylethylenediamine (16 μL, 0.15 mmol) and isopropanol (1 mL). The tube was heated for 24 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 96% yield. Mp 86–87 °C. ^{1}H NMR ($CDCl_3$) δ: 8.24 (m, 1H, H_5), 7.53 (s, 1H, H_2), 7.34–7.19 (m, 7H, Ph-3,4,5, PhCl-2,3,5,6), 7.15 (m, 2H, Ph-2,6), 7.01 (m, 1H, H_7), 3.96 (s, 2H, CH_2), 2.83 (m, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.60 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 146.25 (C8a), 140.40 (Ph-1), 135.43 (PhCl-1), 133.59 (C2), 133.10 (PhCl-4), 130.50 (PhCl-2,6), 129.77 (PhCl-3,5), 129.12 (C8), 128.96 (Ph-2,3,5,6), 128.31 (C7), 126.95 (Ph-4), 126.16 (C5), 120.54 (C3), 118.47 (C6), 36.40 (CH_2), 33.10 (CH_2), 25.59 (CH_2), 17.35 (CH_3). Anal. Calcd for $C_{23}H_{21}ClN_2S_2$: C, 65.00; H, 4.98; N, 6.59. Found: C, 65.12; H, 4.96; N, 6.64.

4.2.5.10. 6-(4-Hydroxyphenylthio)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (28). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (10 mg, 0.05 mol), K_2CO_3 (198 mg, 2 mmol), 4-hydroxythiophenol (190 mg, 1.5 mmol), ***N,N′***-dimethylethylenediamine (16 μL, 0.15 mmol) and isopropanol (1 mL). The tube was heated for 24 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 60% yield. Mp 139–140 °C. ^{1}H NMR (DMSO) δ: 9.81 (s, 1H, OH), 8.40 (s, 1H, H_5), 7.55 (s, 1H, H_2), 7.31–7.19 (m, 7H, Ph, PhOH-2,6), 6.99 (s, 1H, H_7), 6.80 (d, 2H, J = 8.2 Hz, Ph-3,5), 4.21 (s, 2H, CH_2), 2.74 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 2.44 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 158.45 (PhOH-4), 145.47 (C8a), 141.22 (Ph-1), 134.10 (PhOH-2,6), 133.57 (C2), 129.35 (Ph-2,6), 129.12 (Ph-3,5), 128.13 (PhOH-1), 126.99 (Ph-4, C7), 125.04 (C5), 123.63 (C8*), 121.81 (C6*), 120.68 (C3), 117.40 (PhOH-3,5), 36.01 (CH_2), 32.87 (CH_2), 24.55 (CH_2), 17.24 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS_2$: C, 67.95; H, 5.45; N, 6.89. Found: C, 97.93; H, 5.46; N, 6.89.

4.2.5.11. 6-(4-Aminophenylthio)-8-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (29). The compound was obtained following the general procedure using **4** (408 mg, 1 mmol), CuI (38 mg, 0.20 mmol), K_2CO_3 (198 mg, 2 mmol), 4-aminothiophenol (188 mg, 1.5 mmol), ***N,N′***-dimethylethylenediamine (22 μL, 0.20 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 47% yield. Oil. ^{1}H NMR ($CDCl_3$) δ: 7.99 (m, 1H, H_5), 7.47 (s, 1H, H_2), 7.34–7.23 (m, 3H, Ph-3,4,5), 7.29 (d, 2H, J = 8.7 Hz, $PhNH_2$-2,6), 7.16 (m, 2H, Ph-2,6), 6.96 (m, 1H, H_7), 6.65 (d, 2H, J = 8.7 Hz, $PhNH_2$-3,5), 3.92 (s, 2H, CH_2), 2.82 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 2.56 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 147.60 ($PhNH_2$-4), 145.98 (C8a), 140.54 (Ph-1), 134.73 ($PhNH_2$-2,6), 133.11 (C2), 128.99 (Ph-2,6*), 128.95 (Ph-3,5*), 128.06 ($PhNH_2$-1), 126.91 (Ph-4), 126.73 (C7), 123.16 (C8*), 122.34 (C5), 121.35 (C6*), 120.16 (C3), 116.18 ($PhNH_2$-3,5), 36.40 (CH_2), 33.09 (CH_2), 25.57 (CH_2), 17.37 (CH_3). Anal. Calcd for $C_{23}H_{23}N_3S_2$: C, 68.11; H, 5.72; N, 10.36. Found: C, 68.24; H, 5.69; N, 10.34.

4.2.5.12. 6-Methyl-8-(4-methylpiperazin-1-yl)-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (36). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), ethylene glycol (111 μL, 2 mmol), ***N***-methylpiperazine (133 μL, 1.2 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 35% yield. Mp 63–65 °C. ^{1}H NMR ($CDCl_3$) δ: 7.56 (m, 1H, H_5), 7.41 (s, 1H, H_2), 7.35–7.15 (m, 5H, Ph), 6.36 (m, 1H, H_7), 3.95 (s, 2H, CH_2), 3.59 (br s, 4H, Piperazine), 2.87–2.74 (m, 6H, Piperazine, CH_2), 2.62 (m, 2H, CH_2), 2.44 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). RMN ^{13}C ($CDCl_3$) δ: 141.42 (C8a*), 140.76 (Ph-1*), 140.57 (C8*), 131.63 (C2), 128.98 (Ph-2,6*), 128.89 (Ph-3,5*), 126.84 (Ph-4), 122.54 (C6), 119.15 (C3), 115.66 (C5), 110.58 (C7), 55.44 (Piperazine), 49.84 (Piperazine), 46.54 (CH_3), 36.36 (CH_2), 32.71 (CH_2), 25.62 (CH_2), 19.26 (CH_3). Anal. Calcd for $C_{22}H_{28}N_4S$: C, 69.44; H, 7.42; N, 14.72. Found: 69.49; H, 7.41; N, 14.76.

4.2.5.13. *N*-(6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridin-8-yl)pyrrolidin-2-one (37). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), ethylene glycol (111 μL, 2 mmol), pyrrolidin-2-one (116 μL, 1.5 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (20:80). 54% yield. Mp 106–107 °C. ^{1}H NMR ($CDCl_3$) δ: 7.83 (m, 1H, H_5), 7.44 (s, 1H, H_2), 7.36 (d, 1H, J = 1.3 Hz, H_7), 7.35–7.24 (m, 3H, Ph-3,4,5), 7.18 (m, 2H, Ph-2,6), 4.31 (m, 2H, Pyrrolidinone), 3.97 (s, 2H, CH_2), 2.86 (m, 2H, CH_2), 2.65 (m, 4H, CH_2, Pyrrolidinone), 2.41 (s, 3H, CH_3), 2.29 (m, 2H, Pyrrolidinone). ^{13}C NMR ($CDCl_3$) δ: 175.82 (C=O), 141.67 (C8a), 140.46 (Ph-1), 132.74 (C2), 128.96 (Ph-2,6*), 128.91 (Ph-3,5*), 127.50 (C8), 126.89 (Ph-4), 124.01 (C7), 122.18 (C6), 120.65 (C5), 119.74 (C3), 50.29 (Pyrrolidinone), 36.31 (CH_2), 32.88 (CH_2*), 32.10 (Pyrrolidinone*), 25.53 (CH_2), 19.25 (Pyrrolidinone), 18.86 (CH_3). Anal. Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.05; H, 6.32; N, 11.48.

4.2.5.14. 6-Methyl-3-phenethylthiomethyl-8-(pyrrol-1-yl)imidazo[1,2-*a*]pyridine (38). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), pyrrole (84 μL, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 60 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (20:80). 94% yield. Mp 109–110 °C. ^{1}H NMR ($CDCl_3$) δ: 7.82 (m, 1H, H_5), 7.65 (t, 2H, J = 2.2 Hz, Pyrrole-2,5), 7.55 (s, 1H, H_2), 7.37–7.23 (m, 3H, Ph-3,4,5), 7.18 (m, 2H, Ph-2,6), 7.09 (d, 1H, J = 1.3 Hz, H_7), 6.44 (t, 2H, J = 2.2 Hz, Pyrrole-3,4), 4.01 (s, 2H, CH_2), 2.87 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 140.76 (C8a*), 140.65 (Ph-1*), 133.74 (C2), 130.09 (C6), 129.14 (Ph-2,3,5,6), 127.13 (Ph-4), 122.41 (C8*), 121.76 (Pyrrole-2,5), 120.35 (C3*), 119.63 (C5), 117.35 (C7), 110.99 (Pyrrole-3,4), 36.57 (CH_2), 33.13 (CH_2), 25.80 (CH_2), 19.22 (CH_3). Anal. Calcd for $C_{21}H_{21}N_3S$: C, 72.59; H, 6.09; N, 12.09. Found: C, 72.64; H, 6.17; N, 12.05.

4.2.5.15. 3-Benzylthiomethyl-6-methyl-8-(pyrrol-1-yl)imidazo[1,2-*a*]pyridine (39). The compound was obtained following the general procedure using **9** (394 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), pyrrole (84 μL, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (70:30). 87% yield. Mp 95–96 °C. ^{1}H NMR ($CDCl_3$) δ: 7.70 (m, 1H, H_5), 7.64 (t, 2H, J = 2.2 Hz, Pyrrole-2,5), 7.52 (s, 1H, H_2), 7.38–7.28 (m, 5H, Ph), 7.07 (d, 1H, J = 1.3 Hz, H_7), 6.44 (t, 2H, J = 2.2 Hz, Pyrrole-3,4), 3.94 (s, 2H, CH_2), 3.64 (s, 2H, CH_2), 2.42 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 140.66 (C8a), 138.08 (Ph-1), 133.87 (C2), 129.98 (C8), 129.56 (Ph-2,6), 129.13 (Ph-3,5), 127.78 (Ph-4), 122.24 (C6), 121.70 (Pyrrole-2,5), 120.21 (C3), 119.49 (C5), 117.14 (C7), 110.89 (Pyrrole-3,4), 36.00 (CH_2), 24.73 (CH_2), 19.09 (CH_3). Anal. Calcd for $C_{20}H_{19}N_3S$: C, 72.04; H, 5.74; N, 12.60. Found: C, 72.22; H, 5.69; N, 12.64.

4.2.5.16. 8-(Imidazol-1-yl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (40). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), imidazole (102 mg, 1.5 mmol), ***N,N*′**-dimethylethylenediamine (32 μL, 0.30 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2. 42% yield. Mp 85–86 °C. ^{1}H NMR ($CDCl_3$) δ: 8.53 (br s, 1H, Imidazole-2), 7.90 (m, 1H, H_5), 7.80 (br s, 1H, Imidazole-4), 7.54 (s, 1H, H_2), 7.36–7.23 (m, 4H, H_7, Ph-3,4,5), 7.20–7.14 (m, 3H, Imidazole-5, Ph-2,6), 4.01 (s, 2H, CH_2), 2.87 (m, 2H, CH_2), 2.68 (m, 2H, CH_2), 2.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 140.35 (C8a*), 139.89 (Ph-1*), 137.63 (Imidazole-2), 133.77 (C2), 130.23 (Imidazole-5), 128.91 (Ph-2,3,5,6), 126.90 (Ph-4), 126.52 (C8), 121.96 (C6), 120.87 (C5), 120.82 (C3), 119.20 (Imidazole-4), 117.73 (C7), 36.31 (CH_2), 33.01 (CH_2), 25.53 (CH_2), 18.89 (CH_3). Anal. Calcd for $C_{20}H_{20}N_4S$: C, 68.93; H, 5.79; N, 16.08. Found: C, 69.02; H, 5.81; N, 16.06.

4.2.5.17. 8-(Indol-1-yl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (41). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (28 mg, 0.15 mmol), K_3PO_4 (447 mg, 2.1 mmol), indole (175 mg, 1.5 mmol), ethylene glycol (111 μL, 2 mmol) and isopropanol (1 mL). The tube was heated for 60 h at 85 °C. Pure product was obtained by column chromatography on silica gel eluted with CH_2Cl_2/methanol (99.5:0.5). 37% yield. Mp 102–104 °C. ^{1}H NMR ($CDCl_3$) δ: 7.94 (m, 1H, H_5), 7.90 (d, 1H, J = 3.4 Hz, indole), 7.73 (m, 1H, indole), 7.60 (m, 1H, indole), 7.54 (s, 1H, H_2), 7.37–7.17 (m, 8H, Ph, H_7, 2 H indole), 6.79 (dd, 1H, J = 3.4–0.8 Hz, indole), 4.03 (s, 2H, CH_2), 2.89 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 2.50 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 141.85 (C8a), 140.49 (Ph-1), 136.60 (indole quat.), 133.81 (C2), 130.05 (indole quat.), 129.49 (indole), 129.03 (Ph-2,6*), 128.99 (Ph-3,5*), 128.74 (C8), 126.97 (Ph-4), 122.79 (indole), 122.10 (C7*), 121.69 (C6*), 121.31 (indole*), 121.24 (indole*), 120.42 (C5), 111.34 (indole), 104.58 (indole), 36.42 (CH_2), 33.02 (CH_2), 25.62 (CH_2), 19.03 (CH_3). C3 not found. Anal. Calcd for $C_{25}H_{23}N_3S$: C, 75.53; H, 5.83; N, 10.57. Found: C, 75.51; H, 5.84; N, 10.52.

4.2.5.18. 8-(Pyrrolo[2,3-*b*]pyridin-1-yl)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (42). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_3PO_4 (447 mg, 2.1 mmol), 7-azaindole (142 mg, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (16 μL, 0.15 mmol) and toluene (2 mL). The tube was heated for 48 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (20:80). 48% yield. Mp 108–109 °C. ^{1}H NMR ($CDCl_3$) δ: 8.36 (dd, 1H, J = 4.7–1.6 Hz, azaindole), 8.31 (d, 1H, J = 3.8 Hz, azaindole), 7.99 (dd, 1H, J = 7.8–1.6 Hz, azaindole), 7.92 (s, 1H, H_5), 7.90 (m, 1H, azaindole), 7.48 (s, 1H, H_2), 7.33–7.23 (m, 3H, Ph-3,4,5), 7.21–7.13 (m, 3H, H_7, Ph-2,6), 6.70 (d, 1H, J = 3.8 Hz, azaindole), 3.98 (s, 2H, CH_2), 2.89–2.82 (m, 2H, CH_2), 2.69–2.60 (m, 2H, CH_2), 2.50 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 148.61 (azaindole), 143.59 (azaindole), 141.53 (C8a), 140.49 (Ph-1), 133.37 (C2), 130.23 (azaindole), 129.52 (azaindole), 128.99 (Ph-2,6*), 128.94 (Ph-3,5*), 127.02 (C8), 126.91 (Ph-4), 122.34 (azaindole), 122.26 (indole, C6), 120.37 (C5), 120.14 (indole, C3), 117.55 (C7), 102.02 (azaindole), 36.38 (CH_2), 32.91 (CH_2), 25.58 (CH_2), 19.12 (CH_3). Anal. Calcd for $C_{24}H_{22}N_4S$: C, 72.33; H, 5.56; N, 14.06. Found: C, 72.54; H, 53.46; N, 14.02.

4.2.5.19. 8-Cyano-6-methyl-3-phenethylthiomethylimidazo-[1,2-*a*]pyridine (43). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (19 mg, 0.10 mmol), sodium cyanide (59 mg, 1.2 mmol), ***N,N*′**-dimethylethylenediamine (106 μL, 1 mmol) and toluene (2 mL). The tube was heated for 24 h at 112 °C. Pure product was obtained by column chromatography on neutral alumina eluted with CH_2Cl_2/petroleum ether (80:20). 94% yield. Mp 122–123 °C. ^{1}H NMR ($CDCl_3$) δ: 8.12 (d, 1H, J = 1.4 Hz, H_5), 7.59 (s, 1H, H_2), 7.55 (d, 1H, J = 1.4 Hz, H_7), 7.35–7.23 (m, 3H, Ph-3,4,5), 7.17 (m, 2H, Ph-2,6), 3.98 (s, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 143.49 (C8a), 140.43 (Ph-1), 135.10

(C7*), 134.45 (C2*), 129.16 (Ph-2,3,5,6), 127.21 (C5*), 126.95 (Ph-4*), 121.85 (C6*), 121.21 (C3*), 115.53 (CN), 102.92 (C8), 36.45 (CH_2), 33.20 (CH_2), 25.55 (CH_2), 18.76 (CH_3). Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.31; H, 5.54; N, 13.68.

4.2.5.20. 8-(4-Chlorophenylthio)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (44). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_2CO_3 (198 mg, 2 mmol), 4-chlorothiophenol (175 mg, 1.2 mmol), ethylene glycol (111 μL, 2 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 80 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (30:70). 84% yield. Mp 56–58 °C. ^{1}H NMR ($CDCl_3$) δ: 7.75 (m, 1H, H_5), 7.50–7.45 (m, 3H, H_2, PhCl-2,6), 7.39–7.20 (m, 5H, PhCl-3,5, Ph-3,4,5), 7.13 (m, 2H, Ph-2,6), 6.59 (d, 1H, J = 1.4 Hz, H_7), 3.94 (s, 2H, CH_2), 2.80 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 143.36 (C8a), 140.43 (Ph-1), 135.44 (PhCl-2,6), 135.18 (PhCl-4), 133.34 (C2), 130.35 (C8), 130.17 (PhCl-3,5), 128.95 (Ph-2,6*), 128.87 (Ph-3,5*), 127.19 (PhCl-1), 126.85 (Ph-4), 125.46 (C7), 122.29 (C6), 120.42 (C5), 120.05 (C3), 36.31 (CH_2), 32.84 (CH_2), 25.49 (CH_2), 18.88 (CH_3). Anal. Calcd for $C_{23}H_{21}ClN_2S_2$: C, 65.00; H, 4.98; N, 6.59. Found: C, 64.98; H, 4.95; N, 6.60.

4.2.5.21. 8-(4-Hydroxyphenylthio)-6-methyl-3-phenethylthiomethylimidazo[1,2-*a*]pyridine (45). The compound was obtained following the general procedure using **7** (408 mg, 1 mmol), CuI (10 mg, 0.05 mmol), K_2CO_3 (198 mg, 2 mmol), 4-hydroxythiophenol (152 mg, 1.2 mmol), ethylene glycol (111 μL, 2 mmol) and isopropanol (1 mL). The tube was heated for 48 h at 85 °C. Pure product was obtained by column chromatography on neutral alumina eluted with ethyl acetate/petroleum ether (70:30). 21% yield. Mp 168–170 °C. ^{1}H NMR (DMSO) δ: 10.08 (s, 1H, OH), 8.01 (s, 1H, H_5), 7.52 (s, 1H, H_2), 7.45 (d, 2H, J = 8.4 Hz, PhOH-2,6), 7.28–7.17 (m, 5H, Ph), 6.94 (d, 2H, J = 8.4 Hz, PhOH-3,5), 6.24 (s, 1H, H_7), 4.17 (s, 2H, CH_2), 2.77 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (DMSO) δ: 159.88 (PhOH-4), 141.93 (C8a*), 141.26 (Ph-1), 138.19 (PhOH-2,6), 132.77 (C2), 130.03 (PhOH-1), 129.37 (Ph-2,6*), 129.13 (Ph-3,5*), 127.01 (Ph-4), 122.00 (C8*), 121.75 (C7), 121.34 (C6*), 120.08 (C5), 117.98 (PhOH-3,5), 117.74 (C3), 36.00 (CH_2), 32.82 (CH_2), 24.59 (CH_2), 18.80 (CH_3). Anal. Calcd for $C_{23}H_{22}N_2OS_2$: C, 67.95; H, 5.45; N, 6.89. Found: C, 98.02; H, 5.44; N, 6.92.

4.3. Antiviral assays

Human cytomegalovirus (CMV) AD-169 and Davis strains were exposed to human embryonic lung (HEL) cell cultures. Briefly, confluent cultures in microtiter plates were 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 CMV 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. For VZV, confluent cells were inoculated with 20 PFU/well and the different dilutions of the tested compounds were added as for CMV. 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% (EC_{50}).

4.4. Cytostatic activity assays

The cytostatic assays were performed as previously described.[11–13] 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.

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