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Original article

Synthesis and antileishmanial activity of (1,3-benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives

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Abstract

(1,3-Benzothiazol-2-yl) amino-9-(10H)-acridinone derivatives were synthesized via a procedure based on the Ullman reaction and were assessed for their in vitro antileishmanial and anti-HIV activities. Two derivatives, 4-(6-nitro-benzothiazol-2-ylamino)-10H-acridin-9-one and 1-(6-amino-benzothiazol-2-ylamino)-10H-acridin-9-one, revealed a selective antileishmanial activity, mainly due to amastigote-specific toxicity. Results suggested that:

- the addition of a benzothiazole group on a parent amino-9-(10*H*)-acridinone ring could enhance antileishmanial abilities,
- the presence of a 6-amino-benzothiazole group on position 2 amino chain or a 6-nitro-benzothiazole group on position 4 amino chain was essential for specific anti-amastigote properties.

Keywords: Acridinones; Antileishmanial activity; Anti-amastigote activity

1. Introduction

It has been established for many years that the planar structure of tricyclic rings conferred to acridine derivatives the ability to intercalate in DNA and interfere with various metabolic processes in both prokaryotic and eukaryotic cells [1,2]. During the past decade, natural and synthetic compounds of the acridine family have been investigated for their bactericidal [3] and antitumoral [4,5] activities, and a few molecules have been selected for antibacterial or anticancer chemotherapy. Recently, various derivatives of the acridine series also demonstrated powerful inhibitory activities towards *Plasmodium* [6,7], *Trypanosoma* [8] and *Leishmania* [9,10] parasites as well as potent antiviral properties [11]. In preceding studies, we established that both acridine and nitro- or amino-benzothiazole derivatives could exert interesting antileishmanial activities [12,13]. In the present study, we synthesized 16 acridin-9-(10*H*)-ones substituted with amino or (1,3-benzothiazol-2-yl)-amino groups and evaluated their in vitro antileishmanial activities. In the meantime, we investigated their antiviral abilities towards the human immunodeficiency virus.

2. Chemistry

Compounds **A1, A2, A3** and **A4** were prepared with various amino anilines following a classical synthetic route (Fig. 1) of amino acridone as described by Ullman and modified by us [14,15]. The aromatic nucleophilic substitution of 2-chlorobenzothiazole and the corresponding amino acridone were done in phenol, to give compounds of the **B** series (**B1, B2, B3** and **B4**). In the case of **B4**, the reaction

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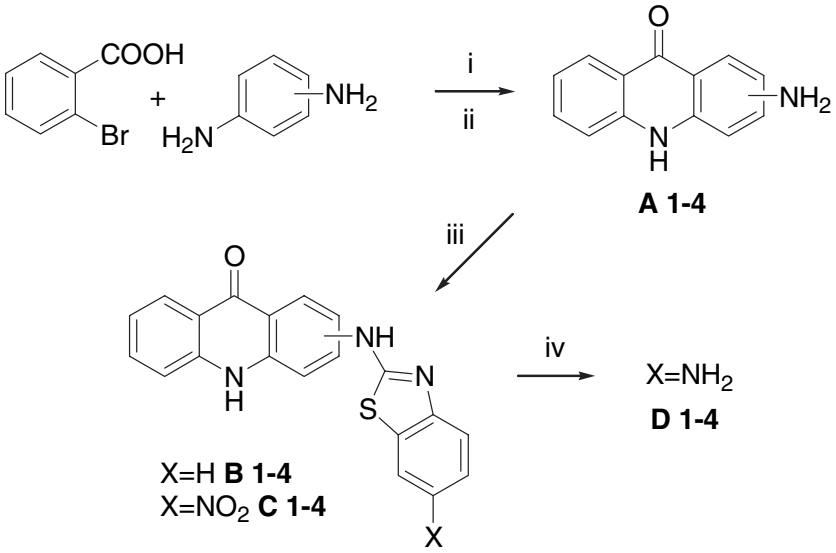


Fig. 1. Chemical procedure for the synthesis of acridine derivatives. Reagents and conditions: i: DME, Cu/Zn, ultrasound, 80 °C, 2 h; ii: H_2SO_4, 120 °C, 2 h; iii: 80 °C (4 or 12 h); iv: DMF, H_2, Pd/C, 40 psi, 60 °C, 5 h.

occurred with poor yield, even with longer reaction times (24/48 h). This could be due to the intramolecular hydrogen bond formed by the amino group in position 4 of the acridine ring and the imino-proton of acridone. With 2-chloro-6-nitrobenzothiazole [16], we obtained the corresponding compounds of the **C** series (**C1, C2, C3** and **C4**) by the same way. We could notice that the reaction time was considerably reduced and compounds were obtained with convenient yields (73–86%), versus the above mentioned way. The nitro group enhanced the reactivity of the chlorine in position 2. Reductions of nitro derivatives to amino (compounds **D1, D2, D3** and **D4**) were done in DMF under 40 psi with Pd/C catalyst [17]. All compound structures have been completely and unequivocally assigned by NMR spectroscopy and have been already published [18].

3. Pharmacology

Acridine antileishmanial activity was assessed towards parasites of the species *Leishmania infantum* responsible for kala-azar, the most severe visceral form of leishmaniasis. Both extracellular and intracellular parasitic forms were employed for the measurement of $IC_{50\ promastigotes}$ and $IC_{50\ amastigotes}$, corresponding, respectively, to the concentrations of acridine derivatives required to induce a 50% inhibition of parasite growth or a 50% decrease of infected macrophages. An antileishmanial potential was also defined for the establishment of structure–activity relationships, it was calculated by the ratio: $1/IC_{50\ amastigotes}$.

In order to evaluate the specificity of chemical compounds for *Leishmania* parasites, we investigated their antiproliferative activity towards human monocytes. Cytotoxicity was expressed by $IC_{50\ monocytes}$, corresponding to the concentration of acridine compounds responsible for a 50% decrease of monocyte growth. A cytotoxic potential was calculated by the ratio: $1/IC_{50\ monocytes}$. The specificity index (SI) corresponded to the following ratio:

$$SI = IC_{50\ monocytes}/IC_{50\ amastigotes}.$$

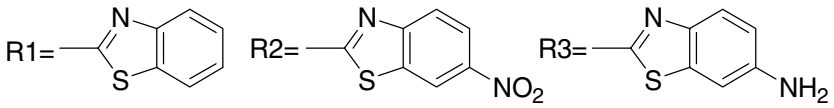
Anti-HIV activity was performed on MT-4 cells infected with the human immunodeficiency virus strains HIV-1 III_B and HIV-2 ROD. Antiviral activity was expressed by $IC_{50\ HIV}$ defined as the concentration of compound required to protect 50% of the virus-infected cells against viral cytopathicity. In parallel, a cytotoxic concentration $LC_{50\ MT\text{-}4}$ was defined as the concentration of compound that reduced by 50% the viability of mock-infected cells.

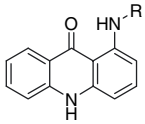
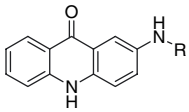
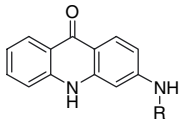
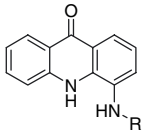
4. Results and discussion

Complete data concerning antiproliferative, antileishmanial and antiviral activities are reported in Table 1 and illustrated in Fig. 2. Almost all the (1,3-benzothiazol-2-yl) amino-9-(10*H*)-acridinone compounds revealed weak antiproliferative or cytotoxic abilities toward human monocytes and MT-4 cells, since none of $IC_{50\ monocytes}$ and $LC_{50\ MT\text{-}4}$ was lower than 10 μM. Amino-9-(10*H*)-acridinone compounds (**A1, A2, A3** and **A4**) exhibited the highest antiproliferative properties, with $IC_{50\ monocytes}$ from 12.5 to 36.8 μM, suggesting that the position of the amino group on the parent molecule did not greatly influence cytotoxicity of the compounds. However, addition of a substituted benzothiazole group to amino-acridines (compounds of the **B, C** and **D** series) whatever its position, decreased the cytotoxic potential of the derivatives.

Concerning antileishmanial activity, results revealed that the efficiency of the acridine compounds greatly depended on both the nature and the position of the substituted benzothiazole group. Among amino-9-(10*H*)-acridinone derivatives of the **A** series, only position 1 and 2 amino substituted

Table 1
Pharmacological activities of chemical compounds



Rings	R	Numbers	Toxicity towards MT-4 cells CC_{50} (μM)	Toxicity towards monocytes IC_{50} (μM)	Antileishmanial activity IC_{50} (μM)		
					Promastigotes	Amastigotes	SI
	H	**A1**	11.5	12.5	78.6	3.8	3.3
	R1	**B1**	>200	29.3	8.4	6.6	4.4
	R2	**C1**	>200	38.4	>200	Tox	–
	R3	**D1**	>200	223.1	20.1	4.3	51.9
	H	**A2**	–	14.3	21.0	4.7	3.0
	R1	**B2**	27.9	28.6	3.1	2.3	12.4
	R2	**C2**	>200	152.9	>200	>200	–
	R3	**D2**	105.3	32.4	15.3	Tox	–
	H	**A3**	78.2	36.8	46.6	>200	–
	R1	**B3**	88.1	227.4	11.3	15.2	15.0
	R2	**C3**	>200	351.4	>200	>200	–
	R3	**D3**	>200	364.1	25.2	26.3	13.8
	H	**A4**	>200	18.2	>200	Tox	–
	R1	**B4**	–	54.2	23.4	26.6	2.1
	R2	**C4**	>200	124.6	>200	2.5	49.8
	R3	**D4**	108.1	46.3	10.2	11.9	3.8
Amphotericin **B**				15.6	0.08	0.02	780

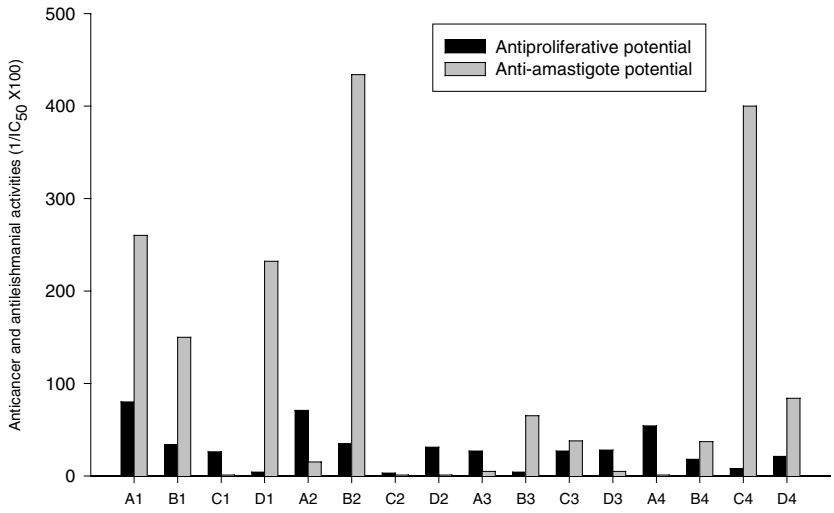


Fig. 2. Antiproliferative and antileishmanial potentials.

compounds (**A1** and **A2**) exerted a significant activity on the amastigote form of the parasite. This antileishmanial activity was associated with a weak specificity for the parasite (SI < 5), suggesting that the corresponding compounds did not react with *Leishmania*-specific targets.

Addition of a benzothiazole group on the parent molecule (compounds of the **B** series) decreased the cytotoxic properties of the compounds towards human cells and enhanced their toxicity against both the promastigote and the amastigote forms of the parasite, leading to interesting antileishma-

nial activities. Among these derivatives, 2-(benzothiazol-2-ylamino)-10H-acridin-9-one (**B2**), displayed a strong anti-amastigote activity, however, this toxicity was not specific of the parasite and led to a SI of 12.4.

The presence of a 6-nitro group on the benzothiazole ring (compounds **C1, C2** and **C3**), at the contrary, clearly decreased the toxicity of the compounds toward *Leishmania* promastigotes, leading in most cases in a weak global antileishmanial activity. However, compound **C4**, 4-(6-nitro-benzothiazol-2-ylamino)-10H-acridin-9-one, demonstrated a strong ability to specifically inhibit intracellular amastigote growth, with a SI = 49.8. In the same way, addition of a 6-amino group on the benzothiazole ring observed for compounds of the **D** series, resulted in a decrease of the anti-promastigote activity. Among these derivatives, compound **D1**, 1-(6-amino-benzothiazol-2-ylamino)-10H-acridin-9-one, inhibited the amastigote form of the parasite with a good efficiency and showed a promising SI of 51.9.

Results observed on the human immunodeficiency virus (data not shown) revealed that none of the compounds exerted significant antiviral activity.

5. Conclusion

Results observed in the present study clearly demonstrated that addition of a benzothiazole group on a parent amino-9-(10*H*)-acridinone ring could modulate the cytotoxic and antileishmanial activities of the compounds. However, they also revealed that the pharmacological properties of the derivatives greatly depended on both the nature and the position of the substituted benzothiazole groups, rendering difficult structure–activity relationships. Two derivatives, **D1** and **C4**, exhibited a strong selective antiparasitic activity, demonstrating that the presence of a 6-amino-benzothiazole group on position 2 amino chain or a 6-nitro-benzothiazole group on position 4 amino chain was essential for antileishmanial ability. On this basis, they confirmed the hypothesis that addition of a benzothiazole group on a parent amino-9-(10*H*)-acridinone ring could lead to interesting antileishmanial abilities. They also revealed that addition of a 6-nitro or a 6-amino group on the benzothiazole ring contributed to reduce cytotoxicity towards mammalian cells and to enhance antiparasitic properties. Complementary experiments should be performed in order to confirm these results on in vivo models and determine the possible targets in *Leishmania* amastigotes.

6. Experimental

6.1. Chemistry

Melting points (m.p.) were determined using a Bibby SMP3 apparatus. ^{1}H and ^{13}C-NMR spectra were recorded on a Brüker Avance DRX 300 spectrometer. All experiments were carried out in DMSO-d_6 and the ^{1}H and ^{13}C chemical shifts of the solvent were used as a secondary reference and referred to the TMS signal from the usual relationships; the values of the chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. The numbering of the carbons is arbitrary. All chemicals used were of reagent grade and progress of the reaction was monitored by TLC on silica gel plates (Merck Silica gel 60 F_{254}). Elemental analyses were performed on a ThermoFinnigan FlashEA 1112 elemental analyzer: results were within ±0.4% of the theoretical values. Yields referred to purified products and were not optimized. All compounds were dissolved in sterile dimethyl sulfoxide (analytical grade, Sigma, St. Louis, MO, USA) and stored frozen at –70 °C until used.

6.1.1. General procedure for the coupling of 2-chlorobenzothiazole and 2-chloro-6-nitrobenzothiazole with the different amino-acridones

Two millimols of amino-acridinone was solubilized in phenol (1 g) at 80 °C, and then 2.0 mmol of the corresponding 2-chloro-benzothiazole was added and the reaction mixture was stirred at the above temperature for 4 or 12 h. The mixture was cooled to r.t. and poured onto cold water (100 ml) to give a colored precipitate which was collected by filtration, dried and crystallized with acetone. Purification of each compound was done by flash column chromatography.

*6.1.1.1. 1-(Benzothiazol-2-ylamino)-10H-acridin-9-one (**B1**).* Following the general procedure, from **A1** and 2-chlorobenzothiazole, **B1** was obtained as a yellow solid. Yield 54%. M.p. 273 °C. Anal. Calc. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.99; H, 3.79; N, 12.19.

*6.1.1.2. 2-(Benzothiazol-2-ylamino)-10H-acridin-9-one (**B2**).* Following the general procedure, from **A2** and 2-chlorobenzothiazole, **B2** was obtained as a green solid. Yield 75%. M.p. 301 °C. Anal. Calc. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 70.01; H, 3.83; N, 12.26.

*6.1.1.3. 3-(Benzothiazol-2-ylamino)-10H-acridin-9-one (**B3**).* Following the general procedure, from **A3** and 2-chlorobenzothiazole, **B3** was obtained as a pale brown solid. Yield 80%. M.p. 338 °C. Anal. Calc. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.91; H, 3.78; N, 12.26.

*6.1.1.4. 4-(Benzothiazol-2-ylamino)-10H-acridin-9-one (**B4**).* Following the general procedure, from **A4** and 2-chlorobenzothiazole, **B4** was obtained as a grey solid. Yield <10%. M.p. >370 °C. Anal. Calc. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.99; H, 3.81; N, 12.28.

*6.1.1.5. 1-(6-Nitro-benzothiazol-2-ylamino)-10H-acridin-9-one (**C1**).* Following the general procedure, from **A1** and 2-chloro-6-nitro-benzothiazole, **C1** was obtained as a red solid. Yield 86%. M.p. >370 °C. Anal. Calc. for

$C_{20}H_{12}N_4O_3S$: C, 61.85; H, 3.11; N, 14.43. Found: C, 61.88; H, 3.14; N, 14.39.

*6.1.1.6. 2-(6-Nitro-benzothiazol-2-ylamino)-10H-acridin-9-one (**C2**).* Following the general procedure, from **A1** and 2-chloro-6-nitro-benzothiazole, **C2** was obtained as a brown solid. Yield 83%. M.p. >370 °C. Anal. Calc. for $C_{20}H_{12}N_4O_3S$: C, 61.85; H, 3.11; N, 14.43. Found: C, 61.78; H, 3.09; N, 14.38.

*6.1.1.7. 3-(6-Nitro-benzothiazol-2-ylamino)-10H-acridin-9-one (**C3**).* Following the general procedure, from **A1** and 2-chloro-6-nitro-benzothiazole, **C3** was obtained as an orange solid. Yield 79%. M.p. >370 °C. Anal. Calc. for $C_{20}H_{12}N_4O_3S$: C, 61.85; H, 3.11; N, 14.43. Found: C, 62.00; H, 3.12; N, 14.45.

*6.1.1.8. 4-(6-Nitro-benzothiazol-2-ylamino)-10H-acridin-9-one (**C4**).* Following the general procedure, from **A1** and 2-chloro-6-nitro-benzothiazole, **C4** was obtained as a pale green solid. Yield 72%. M.p. >370 °C. Anal. Calc. for $C_{20}H_{12}N_4O_3S$: C, 61.85; H, 3.11; N, 14.43. Found: C, 61.88; H, 3.12; N, 14.49.

6.1.2. General procedure for the reduction of the nitro group of the benzothiazole ring

One millimolar of the desired nitro compounds was solubilized in DMF (10 ml) with 10% weight of palladium/carbon catalyst. The solution was placed under hydrogen atmosphere under 40 psi at 60 °C and vigorously stirred for 5 h. The reaction was monitored by thin-layer chromatography. After complete consumption of starting materials, the resulting solution was filtered and the filtrate was thrown into water smoothly basic to obtain a colored precipitate of the desired compound.

*6.1.2.1. 1-(6-Amino-benzothiazol-2-ylamino)-10H-acridin-9-one (**D1**).* Prepared from **C1** with the above method **D1** was obtained as a green powder. Yield 80%. M.p. 256 °C. Anal. Calc. for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63. Found: C, 67.10; H, 3.99; N, 15.60.

*6.1.2.2. 2-(6-Amino-benzothiazol-2-ylamino)-10H-acridin-9-one (**D2**).* Prepared from **C2** with the above method **D2** was obtained as a green powder. Yield 89%. M.p. 332 °C. Anal. Calc. for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63. Found: C, 66.98; H, 3.98; N, 15.62.

*6.1.2.3. 3-(6-Amino-benzothiazol-2-ylamino)-10H-acridin-9-one (**D3**).* Prepared from **C3** with the above method **D3** was obtained as a green powder. Yield 58%. M.p. 297 °C. Anal. Calc. for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63. Found: C, 67.09; H, 3.91; N, 15.59.

*6.1.2.4. 4-(6-Amino-benzothiazol-2-ylamino)-10H-acridin-9-one (**D4**).* Prepared from **C3** with the above method **D4** was obtained as pale green powder. Yield 96%. M.p. 304 °C. Anal. Calc. for $C_{20}H_{14}N_4OS$: C, 67.02; H, 3.94; N, 15.63. Found: C, 67.03; H, 3.99; N, 15.65.

6.2. Pharmacology

6.2.1. Antileishmanial activity against promastigotes

Antileishmanial activity was assessed on the referenced strain *L. infantum* (MHOM/FR/78/LEM75). *L. infantum* promastigotes in late log-phase were incubated in RPMI medium supplemented with 12% fetal calf serum, at an average of 10^5 cells per ml and a range of acridine concentrations was aseptically incorporated into duplicate cultures (final DMSO concentration less than 5%). Following a 48 h incubation period at 25 °C, promastigote growth was estimated by counting parasites with an hemacytometer.

6.2.2. Antileishmanial activity against intracellular amastigotes

Intracellular amastigote cultures were performed in human monocyte-derived macrophages according to the methodology previously described by Ogunkolade et al. [19]. Maturation of monocytes into adherent macrophages was performed by treating exponentially-growing monocytes (10^5 cells per ml) with 1 μM phorbol myristate acetate (Sigma). After a 48 h incubation period at 37 °C (5% CO_2) in chamber-slides (Fisher, Paris, France), cells were rinsed with fresh medium and suspended in RPMI medium containing stationary-phase promastigotes (cells/promastigotes ratio = 1:10). After a 24 h incubation period at 37 °C (5% CO_2), promastigotes were removed by four successive watches with fresh medium. Adapted dilutions of chemical compounds were added in duplicate chambers and cultures were incubated for 96 h at 37 °C (5% CO_2). Negative controls treated by solvent (DMSO) and positive controls containing a range of amphotericin **B** (Sigma) concentrations were added to each set of experiments. At the end of the incubation period, cells were harvested with analytical grade methanol (Sigma) and stained with 10% Giemsa stain (Eurobio, Paris, France). The percentage of infected macrophages in each assay was determined microscopically at 1000 times magnification.

6.2.3. Antiproliferative activity towards human transformed monocytes

In vitro antiproliferative activity of acridine derivatives was assessed on human monocytes maintained in RPMI medium (Eurobio) supplemented with 10% fetal calf serum (Eurobio) at 37 °C in 5% CO_2 and replicated every 7 days. A range of concentrations was incorporated in late log-phase monocytes (10^5 cells per ml) and cultures were incubated at 37 °C with 5% CO_2. After a 72 h incubation period, cell growth was measured by counting monocytes in an hemacytometer.

6.2.4. Anti-HIV activity assays

The human immunodeficiency virus strain used was HIV-1 (III_B) [20]. Anti-HIV activity and cytotoxicity mea-

surements were carried out in parallel. They were based on the viability of MT-4 cells that had been infected with HIV and then exposed to various concentrations of the test compounds. After the MT-4 cells were allowed to proliferate for 5 days, the number of viable cells was quantified by a tetrazolium-based colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) procedure in 96-well microtrays [21]. In all of these assays, viral input (viral multiplicity of infection, MOI) was 0.01, or 100 times the 50% cell culture infective dose ($CCIDS_{50}$) defined as the compound concentration required to protect 50% of the virus-infected cells against viral cytopathicity. CC_{50} was defined as the compound concentration required to reduce the viability of mock-infected cells by 50%. The > symbol is used to indicate the highest concentration at which the compounds were tested and still found to be non-cytotoxic. The 50% antivirally effective concentration $IC_{50\ HIV}$ and the 50% cytotoxic concentration $CC_{50\ MT\text{-}4}$ values for several separate experiments are presented as defined above. As a rule, the individual values did not deviate by more than twofold up or down from the mean values indicated in the results.

References

[1] P. Alberti, J. Ren, M.P. Teulade-Fichou, L. Guittat, J.F. Riou, J. Chaires, C. Helene, J.P. Vigneron, J.M. Lehn, J.L. Mergny, J. Biomol. Struct. Dyn. 19 (2001) 505–513.
[2] L.R. Ferguson, W.A. Denny, Mutat. Res. 258 (1991) 123–160.
[3] M. Wainwright, J. Antimicrob. Chemother. 47 (2001) 1–13.
[4] M. Demeunynck, F. Charmantray, A. Martelli, Curr. Pharm. Des. 7 (2001) 1703–1724.
[5] I. Antonini, P. Polucci, A. Magnano, M. Sante, J. Med. Chem. 56 (2001) 3329–3333.
[6] S. Girault, P. Grellier, A. Berecibar, L. Maes, E. Mouray, P. Lemiere, M.A. Debreu, E. Davioud-Charvet, C. Sergheraert, J. Med. Chem. 43 (2000) 2646–2654.
[7] S. Girault, S. Delarue, P. Grellier, A. Berecibar, L. Maes, L. Quirijnen, P. Lemiere, M.A. Debreu-Fontaine, C. Sergheraert, J. Pharm. Pharmacol. 53 (2001) 935–938.
[8] S.A. Gamage, D.P. Figgit, S.J. Wojcik, R.K. Ralph, A. Ransijn, J. Mauel, V. Yardley, D. Snowdon, S.L. Croft, W. Denny, J. Med. Chem. 40 (1997) 2634–2642.
[9] K.A. Werbovetz, P.G. Spoors, R.D. Pearson, T.L. Macdonald, Mol. Biochem. Parasitol. 65 (1994) 1–10.
[10] C.M. Mesa-Valle, J. Castilla-Calvente, M. Sanchez-Moreno, V. Moraleda-Lindez, J. Barbe, A. Osuna, Antimicrob. Agents Chemother. 40 (1996) 684–690.
[11] C.T. Lowden, K.F. Bastow, Antiviral Res. 59 (2003) 143–154.
[12] C. Di Giorgio, F. Delmas, N. Filloux, M. Robin, L. Seferian, N. Azas, M. Gasquet, P. Timon-David, J.P. Galy, Antimicrob. Agents Chemother. 47 (2003) 174–180.
[13] F. Delmas, C. Di Giorgio, M. Robin, N. Azas, M. Gasquet, C. Detang, M. Costa, P. Timon-David, J.P. Galy, Antimicrob. Agents Chemother. 46 (2002) 2588–2594.
[14] N. Bsiri, C. Johnson, M. Kayirere, A.M. Galy, J.P. Galy, J. Barbe, A. Osuna, M.C. Mesa-Valle, J.J. Castilla-Calvente, M.N. Rodriguez-Cabezas, Ann. Pharm. 54 (1996) 27–33.
[15] J.P. Hanoun, J.P. Galy, A. Tenaglia, Synth. Commun. 25 (1995) 2443–2448.
[16] L. Katz, J. Chem. Soc. 75 (1953) 712–714.
[17] P. Bouchet, C. Coquelet, G. Joncheray, J. Elguero, Synth. Commun. 4 (1974) 57.
[18] A. Avellaneda, M. Robin, R. Faure, A. Périchaud, J.P. Galy, Magn. Reson. Chem. 40 (2002) 545–548.
[19] B.W. Ogunkolade, I. Colomb-Valet, L. Monjour, A. Rhodes-Feuillette, J.P. Abita, D. Frommel, Acta Trop. 47 (1990) 171–176.
[20] M. Popovic, M.G. Sarngadharan, E. Read, R.C. Gallo, Science 224 (1984) 497.
[21] R. Pauwels, J. Balzarini, M. Baba, R. Snoeck, D. Schols, J. Pherdewijn, J. Desmyter, E. De Clercq, J. Virol. Methods 20 (1988) 309.