Polyhedron 97 (2015) 30–38

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Effect of coordination to antimony(III) on the antifungal activity of 2-acetylpyridine- and 2-benzoylpyridine-derived hydrazones

Elisa D.L. Piló [a], Angel A. Recio-Despaigne [a,1], Jeferson G. Da Silva [b], Isabella P. Ferreira [a], Jaqueline A. Takahashi [a], Heloisa Beraldo [a,*]

[a] Departamento de Química, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, Minas Gerais, Brazil
[b] Departamento de Farmácia, Universidade Federal de Juiz de Fora, Campus Governador Valadares, 35010-177 Governador Valadares, Minas Gerais, Brazil

ARTICLE INFO

Article history:
Received 20 February 2015
Accepted 4 May 2015
Available online 9 May 2015

Keywords:
Hydrazones
Antimony(III) complexes
Crystal structures
Antifungal activity
Cell viability

ABSTRACT

Antimony(III) [$Sb(L)Cl_2$] complexes were obtained with 2-acetylpyridine-phenylhydrazone (H2AcPh), 2-acetylpyridine-*para*-chloro-phenylhydrazone (H2Ac*p*ClPh), 2-acetylpyridine-*para*-nitro-phenylhydrazone (H2Ac*p*NO_2Ph) and 2-acetylpyridine-*para*-hydroxy-phenylhydrazone (H2Ac*p*OHPh) along with the 2-benzoylpyridine-phenylhydrazone analogs H2BzPh, H2Bz*p*ClPh, H2Bz*p*NO_2Ph, H2Bz*p*OHPh (HL). [$Sb(2Bzp ClPh)Cl_2$], complex (**6**), (IC_{50} = 4.91 ± 1.20 μmol L^{-1}) was as active as nystatin (IC_{50} = 4.44 ± 0.76 μmol L^{-1}) and twofold more active than H2Bz*p*ClPh (IC_{50} = 10.05 ± 0.67 μmol L^{-1}) against *Candida dubliniensis*. While H2Bz*p*ClPh proved to be inactive against *Candida glabrata*, **6** (IC_{50} = 10.11 ± 0.64 μmol L^{-1}) was more active than miconazole nitrate (IC_{50} = 19.50 ± 4.53 μmol L^{-1}). Similarly, H2Bz*p*NO_2Ph revealed to be inactive against *Candida lusitaniae* whereas complex [$Sb(2Bzp NO_2Ph)Cl_2$] (**7**) (IC_{50} = 8.54 ± 2.21 μmol L^{-1}) proved to be as active as nystatin (IC_{50} = 5.31 ± 0.84 μmol L^{-1}).

1. Introduction

Antimony compounds have been employed in Medicine for centuries. The major clinical use of antimony compounds is as a treatment for Leishmaniasis, a group of infective tropical parasitic diseases, which are endemic in 98 countries, reaching up to 1.2 million new cases per year [1]. However, antimony compounds have also shown to possess antitumor properties [2]. In fact, antimony(III) complexes with a variety of organic ligands exhibit *in vitro* as well as *in vivo* cytotoxic activity against leukemia and solid tumor cells [2,3]. Antimony(V) complexes also demonstrated antitumor activity against several cancer cell lineages [2,3]. In addition, antimony(III) [4] and antimony(V) [5,6] complexes present antimicrobial activity.

Thiosemicarbazones [7] and hydrazones [8,9] are Schiff base-derivatives with a wide range of pharmacological applications. In previous works we demonstrated that antimony(III) complexes with 2-bezoylpyridine thiosemicarbazones present cytotoxic activity against human leukemia cell lines [10]. We also demonstrated that antimony(III) complexes with pyridine-derived thiosemicarbazones show significant antitrypanosomal activity [11,12]. Moreover, antimony(III) complexes with a family of *bis*(hydrazone) ligands revealed to be cytotoxic to HL60 (leukemia) and MCF-7 (breast tumor) cells [4].

2-acetylpyridine-phenyl hydrazones and 2-benzoylpyridine-phenyl hydrazones were previously investigated by us. The hydrazones and their gallium(III) complexes proved to be highly cytotoxic to glioma cells [13]. Coordination of the hydrazones to copper(II) revealed to be an effective strategy for antimicrobial activity improvement [14]. Hence in the present work antimony(III) complexes were obtained with 2-acetylpyridine-phenylhydrazone (H2AcPh), 2-acetylpyridine-*para*-chloro-phenylhydrazone (H2Ac*p*ClPh), 2-acetylpyridine-*para*-nitro-phenylhydrazone (H2Ac*p*NO_2Ph) and 2-acetylpyridine-*para*-hydroxy-phenylhydrazone (H2Ac*p*OHPh) along with the 2-benzoylpyridine-phenylhydrazone analogs (H2BzPh, H2Bz*p*ClPh, H2Bz*p*NO_2Ph, H2Bz*p*OHPh) (see Scheme 1). The effect of coordination to antimony(III) on the antifungal activity of the hydrazones was investigated.

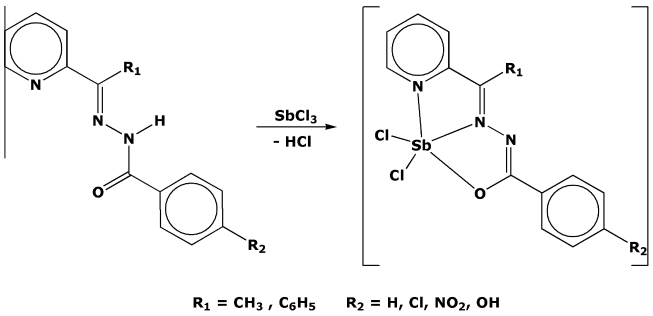
2. Experimental

2.1. Materials and measurements

All common chemicals were purchased from Aldrich and were used without further purification. Partial elemental analyses were

* Corresponding author. Tel.: +55 (31) 3409 5740.
E-mail address: hberaldo@ufmg.br (H. Beraldo).
[1] Present/permanent address: Departamento de Química, Universidade Federal de Viçosa, 36570–900 Viçosa, Minas Gerais, Brazil.

http://dx.doi.org/10.1016/j.poly.2015.05.004
0277-5387/



Scheme 1. Formation of antimony(III) complexes with 2-acetylpyridine- and 2-benzoylpyridine-derived hydrazones.

performed on a Perkin Elmer CHN 2400 analyzer. A Quimis model Q405 M conductivity bridge was employed for molar conductivity measurements. Infrared spectra were recorded on a Perkin Elmer FT-IR 1000 spectrometer using CsI discs (4000–200 cm^{-1}). NMR spectra were obtained with a Bruker DPX-400 Advance (400 MHz) spectrometer using DMSO-d_6 as the solvent and TMS as internal reference. Single crystal X-ray diffraction measurements were carried out on an Oxford-Diffraction GEMINI-Ultra diffractometer (LabCri-UFMG) using graphite-Enhance Source Mo Kα radiation (λ = 0.71073 Å) at 150(2) K. Data collection, cell refinements, and data reduction were performed using the CrysAlisPro software package [15]. An absorption correction based on multi-scan method was applied [15]. The structures were solved by direct methods using SHELXS-97 [16]. Full-matrix least-squares refinement procedure on F^2 with anisotropic thermal parameters was carried on using SHELXL-97 [17]. Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were placed geometrically and the positional parameters were refined using a riding model.

2.2. Chemistry

2.2.1. Syntheses of the hydrazones

The hydrazones were prepared as previously reported [18,19].

2.2.2. Syntheses of antimony(III) complexes (**1**–**8**)

The antimony(III) complexes were obtained by stirring under reflux a methanol solution (60 mL) of the desired hydrazone (2.0 mmol) with an equimolar amount of $SbCl_3$ for 4 h. The solids were washed with methanol followed by ethanol and diethyl ether and then dried *in vacuo*.

*2.2.2.1. [2-Acetylpyridine-phenylhydrazonato(dichloro)antimony(III)] [Sb(2AcPh)Cl$_2$] (**1**).* Yellow solid. *Anal.* Calc. ($C_{14}H_{12}Cl_2N_3OSb$): C, 39.02; H, 2.81; N, 9.75. Found: C, 38.90; H, 3.06; N, 9.70%. FW: 430.93 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1565s, ρ(py) 642w, ν(M–N) 463w, ν(M–O) 394w, ν(M–N_{py}) 290w, ν(M–Cl) 226s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 8.55–8.43 [m, 2H, H(3), H(4)], 8.09–7.98 [m, 1H, H(5)], 9.35 [d, 1H, H(6), 4.96], 7.60–7.57 [m, 2H, H(10), H(14)], 8.26 [d, 2H, H(11), H(13), 7.32], 7.66 [t, 1H, H(12), 7.24], 2.99 [s, 1H, C(15)H_3]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 170.12 [C(8)], 155.51 [C(7)], 146.25 [C(6)], 128.51 [C(5), C(11), C(13)], 128.82 [C(10), C(14)], 142.97 [C(4)], 126.76 [C(3)], 144.26 [C(2)], 15.28 [C(15)]. Λ_M 11.10 Ω^{-1} cm^2 mol^{-1} in DMF. Melting point: dec. 251.4 °C. Yield 69%.

*2.2.2.2. [2-Acetylpyridine-para-chloro-phenylhydrazonato(dichloro) antimony(III)] [Sb(2AcpClPh)Cl$_2$] (**2**).* Yellow solid. *Anal.* Calc. ($C_{14}H_{11}Cl_3N_3OSb$): C, 36.13; H, 2.38; N, 9.03. Found: C, 36.10; H, 2.60; N, 9.19%. FW: 465.37 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1577s, ρ(py) 644w, ν(M–N) 477w, ν(M–O) 401w, ν(M–N_{py}) 293w, ν(M–Cl) 226s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 8.55–8.45 [m, 2H, H(3), H(4)], 8.10–7.99 [m, 1H, H(5)], 9.36 [d, 1H, H(6), 5.0], 8.25 [d, 2H, H(10), H(14), 8.56], 7.65 [d, 2H, H(11), H(13), 8.56], 2.98 [s, 1H, C(15)H_3]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 169.26 [C(8)], 155.98 [C(7)], 146.31 [C(6)], 128.59 [C(5)], 143.00 [C(4)], 126.86 [C(3)], 144.22 [C(2)], 130.27 [C(10), C(14)], 129.02 [C(11), C(13)], 15.31 [C(15)]. Λ_M 10.59 Ω^{-1} cm^2 mol^{-1} in DMF. Melting point: dec. 238.1 °C. Yield: 68%.

*2.2.2.3. [2-Acetylpyridine-para-nitro-phenylhydrazonato(dichloro)-antimony(III)] [Sb(2AcpNO$_2$Ph)Cl$_2$] (**3**).* Yellow solid. *Anal.* Calc. ($C_{14}H_{11}Cl_2N_4O_3Sb$): C, 35.33; H, 2.33; N, 11.77. Found: C 35.37; H, 2.57, N, 11.95%. FW: 475.93 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1589s, ρ(py) 643w, ν(M–N) 417w, ν(M–O) 397w, ν(M–N_{py}) 271w, ν(M–Cl) 217s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 8.58–8.51 [m, 2H, H(3), H(4)], 8.11–8.03 [m, 1H, H(5)], 9.39 [d, 1H, H(6), 4.92], 8.40 [d, 2H, H(10), H(14), 8.84], 8.47 [d, 2H, H(11), H(13), 8.84] 3.02 [s, 1H, C(15)H_3]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 168.34 [C(8)], 157.63 [C(7)], 146.51 [C(6)], 128.85 [C(5)], 143.02 [C(4)], 127.17 [C(3)], 144.18 [C(2)], 123.98 [C(10), C(14)], 129.73 [C(11), C(13)], 15.45 [C(15)]. Λ_M 12.29 Ω^{-1} cm^2 mol^{-1} in DMF. Melting point: dec. 234.2 °C. Yield: 67%.

*2.2.2.4. [2-Acetylpyridine-para-hydroxy-phenylhydrazonato(dichloro)-antimony(III)] hemihydrate [Sb(2AcpOHPh)Cl$_2$]·$^1/_2$H$_2$O (**4**).* Yellow solid. *Anal.* Calc. ($C_{14}H_{12}Cl_2N_3O_2Sb\cdot{}^1/_2H_2O$): C, 36.88; H, 2.87; N, 9.22. Found: C, 37.46, H, 3.05, N, 9.43%. FW: 455.94 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1593s, ρ(py) 628w, ν(M–N) 448w, ν(M–O) 409w, ν(M–N_{py}) 282w, ν(M–Cl) 228s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 8.52–8.41 [m, 2H, H(3), H(4)], 8.04–7.97 [m, 1H, H(5)], 9.31 [d, 1H, H(6), 4.92], 8.11 [d, 2H, H(10), H(14), 8.68], 6.93 [d, 2H, H(11), H(13), 8.68], 2.94 [s, 1H, C(15)H_3], 10.36 [s, 1H, OH]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 170.30 [C(8)], 153.30 [C(7)], 146.02 [C(6)], 128.14 [C(5)], 142.94 [C(4)], 126.36 [C(3)], 144.37 [C(2)], 130.87 [C(10), C(14)], 115.61 [C(11), C(13)], 15.09 [C(15)]. Λ_M 11.11 Ω^{-1} cm^2 mol^{-1} in DMF. Melting point: dec. 263.9 °C. Yield: 81%.

*2.2.2.5. [2-Benzoylpyridine-phenylhydrazonato(dichloro)antimony (III)] hemihydrate [Sb(2BzPh)Cl$_2$]·$^1/_2$H$_2$O (**5**).* Yellow solid. *Anal.* Calc. ($C_{19}H_{14}Cl_2N_3OSb\cdot{}^1/_2H_2O$): C, 45.46; H, 3.01; N, 8.37. Found: C, 46.02; H, 3.13; N, 8.72%. FW: 502.01 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1596s, ρ(py) 647w, ν(M–N) 469w, ν(M–O) 403w, ν(M–N_{py}) 263w, ν(M–Cl) 229s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 8.07 [d, 1H, H(3), 7.88], 8.38 [t, 1H, H(4), 7.24], 8.09–8.02 [m, 1H, H(5)], 9.44 [d, 1H, H(6), 4.68], 8.00 [d, 2H, H(10), H(14), 7.32], 7.51 [t, 2H, H(11), H(13), 7.40]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 129.47 [C(15)], 131.13 [C(9)], 170.86 [C(8)], 153.07 [C(7)], 146.95 [C(6)], 128.29 [C(5), C(3)], 142.87 [C(4)], 144.33 [C(2)], 128.42 [C(10), C(14)], 128.70 [C(11), C(13)]. Λ_M 10.95 Ω^{-1} cm^2 mol^{-1} in DMF. Melting point: 269.9 °C–271.9 °C. Yield: 72%.

*2.2.2.6. [2-Benzoylpyridine-para-chloro-phenylhydrazonato(dichloro) antimony(III)] [Sb(2BzpClPh)Cl$_2$] (**6**).* Yellow solid. *Anal.* Calc. ($C_{19}H_{13}Cl_3N_3OSb$): C, 43.27; H, 2.48; N, 7.97. Found: C, 43.14; H, 2.73; N, 8.00%. FW: 527.44 g mol^{-1}. IR (CsI, cm^{-1}): ν(C=N) 1577s, ρ(py) 644w, ν(M–N) 420w, ν(M–O) 411w, ν(M–N_{py}) 291w, ν(M–Cl) 227s. ^{1}H NMR [400 MHz, DMSO-d_6, δ(ppm), J (Hz)]: 7.80 [d, 1H, H(3), 7.92], 8.38 [t, 1H, H(4), 7.64], 8.10–8.01 [m, 1H, H(5)], 9.45 [d, 1H, H(6), 4.64], 7.98 [d, 2H, H(10), H(14), 8.52], 7.60 [d, 2H, H(11), H(13), 8.52]. ^{13}C NMR [100 MHz, DMSO-d_6, δ(ppm), J