Late metal salicylaldimine complexes derived from 5-aminosalicylic acid — Molecular structure of a zwitterionic mono Schiff base zinc complex

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Abstract: Condensation of salicylaldehyde (2-$HOC_6H_4C(O)H$) with 5-aminosalicylic acid (5-$H_2NC_6H_3$-2-(OH)-CO_2H) afforded the Schiff base 2-$HOC_6H_4C(H)=NC_6H_3$-2-(OH)-5-CO_2H (**a**). Similar reactivity with 5-bromosalicylaldehyde was also observed to give 5-Br-2-$HOC_6H_3C(H)=NC_6H_3$-2-(OH)-5-CO_2H (**b**). Reaction of these salicylaldehydes with Pd(II), Cu(II), and Zn(II) salts gave the corresponding bis(*N*-arylsalicylaldiminato)metal complexes (M = Pd (**1**), Cu (**2**), Zn (**3**)). The molecular structure of the Schiff base compound **a** has been confirmed by an X-ray diffraction study. Crystals of **a** were monoclinic, space group *P*2(1)/*c*, *a* = 7.0164(7) Å, *b* = 11.0088(11) Å, *c* = 14.8980(15) Å, β = 102.917(2)°, *Z* = 4. The molecular structure of a novel zwitterionic conformer of **3a** was also characterized by an X-ray diffraction study. Crystals of **4** were monoclinic, space group *P*2(1)/*c*, *a* = 9.5284(5) Å, *b* = 19.5335(11) Å, *c* = 8.6508(5) Å, β = 90.596(1)°, *Z* = 4. All new compounds have been tested for their antifungal activity against *Aspergillus niger* and *Aspergillus flavus*.

Key words: 5-aminosalicylic acid (5-ASA), antifungal, copper, palladium, salicylaldimines, Schiff base, zinc.

Résumé : La condensation du salicylaldéhyde (2-$HOC_6H_4C(O)H$) avec l'acide 5-aminosalicylique (5-$H_2NC_6H_3$-2-(OH)-CO_2H) conduit à la formation de la base de Schiff 2-$HOC_6H_4C(H)=NC_6H_3$-2-(OH)-5-CO_2H (**a**). On a observé une réactivité semblable avec le 5-bromosalicylaldéhyde qui conduit à la formation de la 5-Br-2-$HOC_6H_3C(H)=NC_6H_3$-2-(OH)-5-CO_2H (**b**). La réaction de ces salicylaldéhydes avec des sels de Pd(II), Cu(II) et Zn(II) conduit aux complexes correspondants bis(*N*-arylsalicylaldiminato)métal (M = Pd (**1**), Cu (**2**), Zn (**3**)). La structure moléculaire de la base de Schiff **a** a été confirmée par une étude de diffraction des électrons. Les cristaux de **a** sont monocliniques, groupe d'espace *P*2(1)/*c*, avec *a* = 7,0164(7) Å, *b* = 11,0088(11) Å et *c* = 14,8980(15) Å, β = 102,917(2)° et *Z* = 4. Faisant appel à la diffraction des rayons X, on a aussi caractérisé la structure moléculaire d'un nouveau conformère zwitterionique du composé **3a**. Les cristaux de **4** sont monocliniques, groupe d'espace *P*2(1)/*c*, avec *a* = 9,5284(5) Å, *b* = 19,5335(11) Å et *c* = 8,6508(5) Å, β = 90,596(1)° et *Z* = 4. L'activité fongicide des tous les nouveaux composés a été vérifiée contre *Aspergillus niger* et *Aspergillus flavus*.

Mots clés : acide 5-aminosalicylique (5-AAS), fongicide, cuivre, palladium, salicylaldimines, base de Schiff, zinc.

[Traduit par la Rédaction]

Introduction

Inflammatory bowel disease (IBD) is a serious disorder of the lower gastrointestinal tract where tissue damage and inflammation can impair the use of the bowel (1–13). Ulcerative colitis involves inflammation of the lining of the colon while Crohn's disease affects all layers of the intestinal wall. Both disorders are chronic, progressive diseases whose etiopathogenesis is not well understood. Current therapies for treating these disorders include glucocorticoids and 5-aminosalicylic acid (5-ASA, Fig. 1*a*) derivatives. Despite the well-documented benefits of 5-ASA in the treatment of IBD, its efficacy is limited due to side effects and allergic reactions associated with its mode of delivery. For example, sulfasalazine (Fig. 1*b*) was introduced over 60 years ago and has become the most widely prescribed agent for IBD, where the pharmacological action of this compound has been attributed to 5-ASA (14). When ingested orally, 88%

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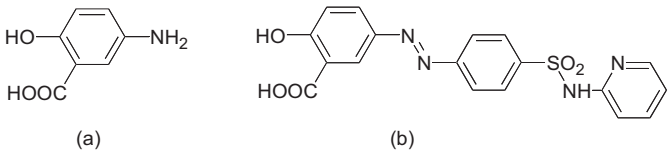
Fig. 1. (*a*) 5-ASA and (*b*) sulfasalazine.



of the sulfasalazine reaches the colon where it is degraded by azo reductases of the colonic microflora, into 5-ASA and sulfapyridine (8). All toxic effects associated with sulfasalazine are believed to arise from the sulfapyridine and, as a result, there has been a considerable amount of research focussed on designing new prodrugs of 5-ASA with less harmful side effects.

As part of our program designing metal complexes containing biologically active ligands, we have made Schiff base metal complexes derived from 5-ASA. As an initial screen of potential biological properties, we have examined all new complexes for their ability to act as antifungal agents.

Experimental

General

Reagents and solvents used were purchased from Aldrich Chemicals. $Pd(OAc)_2$ was purchased from Precious Metals Online Ltd. (Melbourne, Australia). NMR spectra were recorded on a JEOL JNM-GSX270 FT spectrometer or a Varian Mercury Plus 200 NMR spectrometer. ^{1}H NMR chemical shifts are reported in ppm and referenced to residual solvent protons in deuterated solvent at 270 and 200 MHz, respectively. ^{13}C NMR chemical shifts are referenced to solvent carbon resonances as internal standards at 68 and 50 MHz, respectively, and are reported in ppm. Multiplicities are reported as singlet (s), doublet (d), triplet (t), multiplet (m), broad (br), and overlapping (ov). IR spectra were obtained using a Mattson Genesis II FT-IR spectrometer. Melting points were determined using a Mel-Temp apparatus and are uncorrected. Microanalyses for C, H, and N were carried out at Guelph Chemical Laboratories, Guelph, Ontario.

5-{[(1*E*)-(2-Hydroxyphenyl)methylene]amino}-2-hydroxybenzoic acid (a)

To an EtOH (10 mL) solution of 5-aminosalicylic acid (0.50 g, 3.26 mmol) was added an EtOH (5 mL) solution of salicylaldehyde (0.44 g, 3.60 mmol). The mixture was heated at reflux for 2 h to ensure completion, at which point a yellow precipitate was collected by suction filtration and washed with EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The yellow solid was then dried to afford **a** (0.63 g, 75%); mp 258–260 °C. IR (Nujol, cm^{-1}) ν: 1610 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 13.07 (br s, 1H, -O*H*), 8.98 (s, 1H, C(*H*)=N), 7.84 (d, *J* = 3 Hz, 1H, Ar), 7.67–7.64 (ov m, 2H, Ar), 7.39 (d of d, *J* = 8, 3 Hz, 1H, Ar), 7.06–6.94 (ov m, 3H, Ar). ^{13}C{^{1}H} NMR δ: 172.2, 162.2, 160.8, 160.7, 139.7, 133.4, 133.0, 129.1, 123.1, 119.8, 119.5, 118.6, 117.0, 114.1.

5-{[(1*E*)-(5-Bromo-2-hydroxyphenyl)methylene]amino}-2-hydroxybenzoic acid (b)

To an EtOH (10 mL) solution of 5-aminosalicylic acid (0.50 g, 3.26 mmol) was added an EtOH (5 mL) solution of 5-bromosalicylaldehyde (0.72 g, 3.58 mmol). The mixture was heated at reflux for 2 h to ensure completion, at which point a yellow precipitate was collected by suction filtration and washed with EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried to afford **b** (0.93 g, 85%); mp 271 °C. IR (Nujol, cm^{-1}) ν: 1604 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 13.05 (br s, 1H, -O*H*), 8.94 (s, 1H, C(*H*)=N), 7.84–7.81 (ov m, 2H, Ar), 7.62 (d of d, *J* = 8, 3 Hz, 1H, Ar), 7.50 (d of d, *J* = 8, 3 Hz, 1H, Ar), 7.03 (d, *J* = 8 Hz, 1H, Ar), 6.90 (d, *J* = 8 Hz, 1H, Ar). ^{13}C{^{1}H} NMR δ: 172.2, 161.0, 160.9, 159.8, 139.8, 135.8, 134.6, 129.7, 123.3, 121.9, 119.6, 118.9, 114.2, 110.5.

Compound 1a

To an EtOH (50 mL) solution of palladium(II) acetate (0.20 g, 0.89 mmol) was added an EtOH (15 mL) solution of **a** (0.48 g, 1.87 mmol). The mixture was heated at reflux for 3 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried to afford complex **1a** (0.47 g, 85%); mp 305 to 306 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1608 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 8.11 (s, 2H, C(*H*)=N), 7.71 (d, *J* = 3 Hz, 2H, Ar), 7.47–7.43 (ov m, 4H, Ar), 7.17 (d of d, *J* = 8, 3 Hz, 2H, Ar), 6.99 (d, *J* = 8 Hz, 2H, Ar), 6.51 (t, *J* = 8 Hz, 2H, Ar), 6.03 (d, *J* = 8 Hz, 2H, Ar). ^{13}C{^{1}H} NMR δ: 172.1, 164.5, 164.4, 160.2, 140.8, 135.9, 135.7, 132.9, 126.2, 120.6, 120.1, 116.7, 115.4, 112.8. Anal. calcd. for $C_{28}H_{20}N_2O_8Pd$ (%): C 54.34, H 3.26, N 4.53; found: C 53.95, H 2.89, N 4.09.

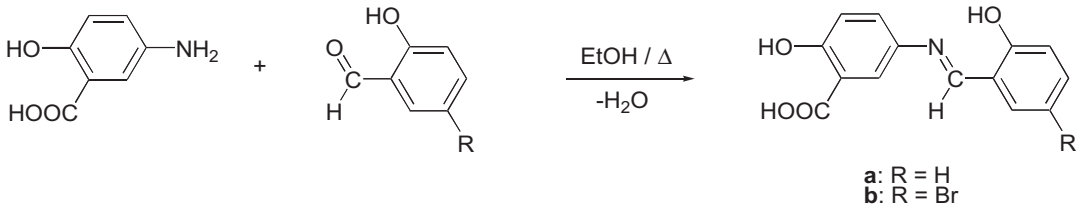
Compound 1b

To an EtOH (40 mL) solution of palladium(II) acetate (0.15 g, 0.67 mmol) was added an EtOH (10 mL) solution of **b** (0.47 g, 1.40 mmol). The mixture was heated at reflux for 2 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried to afford complex **1b** (0.47 g, 90%); mp 294 to 295 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1603 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 8.09 (s, 2H, C(*H*)=N), 7.67 (d of d, *J* = 8, 3 Hz, 4H, Ar), 7.48 (d of d, *J* = 8, 3 Hz, 2H, Ar), 7.25 (d of d, *J* = 8, 3 Hz, 2H, Ar), 6.97 (d, *J* = 8 Hz, 2H, Ar), 5.93 (d, *J* = 8 Hz, 2H, Ar). ^{13}C{^{1}H} NMR δ: 172.2, 164.1, 163.4, 160.3, 140.6, 138.1, 137.2, 133.1, 126.2, 122.5, 122.4, 117.0, 112.7, 105.6. Anal. calcd. for $C_{28}H_{18}N_2Br_2O_8Pd$ (%): C 43.30, H 2.34, N 3.61; found: C 43.62, H 2.32, N 3.27.

Compound 2a

To an EtOH (50 mL) solution of copper(II) acetate (0.20 g, 1.10 mmol) was added an EtOH (15 mL) solution of **a** (0.59 g, 2.29 mmol). The mixture was heated at reflux for 3 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried

Scheme 1. Synthesis of Schiff base compounds derived from 5-ASA.



to afford complex **2a** (0.60 g, 95%); mp 291 to 292 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1608 (C=N). Anal. calcd. for $C_{28}H_{20}N_2CuO_8$ (%): C 58.38, H 3.51, N 4.86; found: C 57.74, H 3.32, N 4.75.

Compound 2b

To an EtOH (50 mL) solution of copper(II) acetate (0.20 g, 1.10 mmol) was added an EtOH (15 mL) solution of **b** (0.78 g, 2.32 mmol). The mixture was heated at reflux for 3 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and $CHCl_3$ (3 × 10 mL). The pale yellow solid was then dried to afford complex **2b** (0.52 g, 64%); mp 318–320 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1610 (C=N). Anal. calcd. for $C_{28}H_{18}N_2Br_2CuO_8 \cdot 1.5CHCl_3$ (%): C 38.80, H 2.16, N 3.07; found: C 38.90, H 2.03, N 2.79.

Compound 3a

To an EtOH (50 mL) solution of zinc(II) acetate (0.20 g, 1.09 mmol) was added an EtOH (15 mL) solution of **a** (0.59 g, 2.29 mmol). The mixture was heated at reflux for 3 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried to afford complex **3a** (0.60 g, 95%); mp 332–334 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1608 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 13.36 (br s, 2H, -O*H*), 8.91 (s, 2H, C(*H*)=N), 7.79 (d, *J* = 3 Hz, 2H, Ar), 7.59 (d, *J* = 8 Hz, 2H, Ar), 7.44 (d of d, *J* = 8, 3 Hz, 2H, Ar), 7.33 (t, *J* = 8 Hz, 2H, Ar), 6.95–6.80 (ov m, 6H, Ar). ^{13}C{^{1}H} NMR δ: 173.6, 161.5, 161.1, 160.8, 139.1, 133.3, 133.0, 127.6, 123.7, 120.0, 119.6, 118.1, 117.6, 117.1. Anal. calcd. for $C_{28}H_{20}N_2O_8Zn$ (%): C 58.19, H 3.50, N 4.85; found: C 58.14, H 3.62, N 4.87.

Compound 3b

To an EtOH (50 mL) solution of zinc(II) acetate (0.20 g, 1.09 mmol) was added an EtOH (15 mL) solution of **b** (0.77 g, 2.29 mmol). The mixture was heated at reflux for 3 h at which point a yellow-green precipitate was collected by suction filtration and washed with cold EtOH (3 × 5 mL) and Et_2O (3 × 10 mL). The pale yellow solid was then dried to afford complex **3b** (0.64 g, 80%); mp 298–300 °C (decomposition). IR (Nujol, cm^{-1}) ν: 1601 (C=N). Spectroscopic NMR data (in DMSO-d_6): ^{1}H NMR δ: 13.33 (br s, 2H, -O*H*), 8.92 (s, 2H, C(*H*)=N), 7.81 (br m, 4H, Ar), 7.51–7.44 (ov m, 4H, Ar), 6.91–6.84 (ov m, 4H, Ar). ^{13}C{^{1}H} NMR δ: 173.1, 162.0, 159.9, 159.7, 138.4, 135.5, 134.5, 127.8, 123.6, 122.0, 119.6, 118.1, 118.0, 110.4. Anal. calcd. for $C_{28}H_{18}Br_2N_2O_8Zn$ (%): C 45.71, H 2.47, N 3.81; found: C 46.16, H 2.47, N 3.57.

X-ray crystallography

Crystals of **a** and **4** were grown from saturated EtOH and DMSO solutions, respectively, at 20 °C. Single crystals were coated with Paratone-N oil, mounted using a glass fibre, and frozen in the cold stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and θ scans with a scan width of 0.3° and exposure times of 40 (**a**) and 30 s (**4**). The detector distances were 5 cm. The data were reduced (15) and corrected for absorption (16). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 (17). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined using a riding model (**a**) or located in Fourier difference maps and refined isotropically (**4**).

Antifungal testing

Compounds were tested for antifungal activity against pure cultures of *Aspergillus niger* and *Aspergillus flavus* supplied by Ward's Natural Science Ltd. (St. Catharines, Ontario). Cultures were maintained on Sabouraud dextrose agar. Six agar plugs (10 mm diameter) were cut from a 5–8 day old colony and homogenized in distilled, sterilized water (3 mL). From this suspension, 0.5 mL was transferred aseptically to a petri plate with Sabouraud dextrose agar (15 mL) and spread evenly over the entire surface. Each plate was provided with four evenly spaced paper disks (6 mm Fisherbrand P8 filter paper) containing the compound (100 μg). Each compound was applied to the disks as a solution (5 mg of compound per 1 mL of THF), where control disks were treated with neat THF (20 μL). Amphotericin B acted as a standard (100 μg) prepared in THF. Test plates with fungal homogenates were incubated at 20 °C for 48 h. Four replicate plates were used for each test. Antifungal activity was taken by the diameter of the clear zone surrounding the disk.

Results and discussion

Salicylaldimines

Schiff bases are remarkable compounds that have been utilized extensively in organic syntheses (18–24). For instance, a recent report describes a highly diastereo- and enantioselective asymmetric aldol reaction of glycinate Schiff bases with aldehydes (24). In this study, we have found that salicylaldehyde derivatives add to 5-aminosalicylic acid to give compounds having spectroscopic data consistent with the Schiff bases **a** and **b** (Scheme 1). As expected, a shift for the aldehyde proton from 10 to 9 ppm is observed in the ^{1}H NMR spectra and a resonance at ca. 160 ppm in the ^{13}C NMR spectra corresponds to the N=CH methine carbon. Likewise, formation of these compounds can be monitored

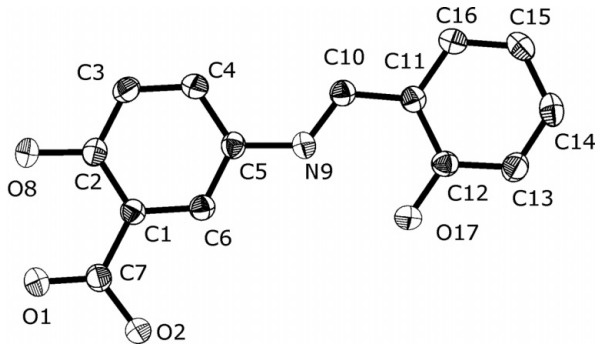
Table 1. Crystallographic data collection parameters for **a** and **4**.

Complex	**a**	**4**
Chemical formula	$C_{14}H_{11}NO_4$	$C_{16}H_{15}NO_5SZn$
Formula weight	257.26	398.72
Crystal dimensions (mm^3)	0.20 × 0.125 × 0.10	0.30 × 0.15 × 0.125
Crystal system	Monoclinic	Monoclinic
Space group	*P*2(1)/*c*	*P*2(1)/*c*
Z	4	4
a (Å)	7.016 4(7)	9.528 4(5)
b (Å)	11.008 8(11)	19.533 5(11)
c (Å)	14.898 0(15)	8.650 8(5)
β (°)	102.917(2)	90.596(1)
V ($Å^3$)	1121.63(19)	1 610.03(15)
$\rho_{calcd.}$ (Mg m^{-3})	1.517	1.645
Temperature (K)	198(1)	173(1)
Radiation	Mo Kα (λ = 0.710 73 Å)	Mo Kα (λ = 0.710 73 Å)
μ (mm^{-1})	0.113	1.681
Total reflections	7445	10 977
Total unique reflections	2484	3 617
Observed reflections ($F_o > 4\sigma(F_o)$)	2482	3 617
No. of variables	212	220
R_{int}	0.021 4	0.024 9
θ range (°)	2.32–27.48	2.09–27.48
S (GoF) on F^2	1.106	1.036
R_1 ($I > 2\sigma(I)$)[a]	0.047 9	0.031 2
wR_2 (all data)[b]	0.140 4	0.087 0
Largest diff. peak and hole (e $Å^{-3}$)	0.779 and –0.220	0.905 and –0.273

[a] $R_1 = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$.

[b] $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma w[F_o^4])^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0575 \cdot P)^2 + (0.2611 \cdot P)]$ (**a**) and $w = 1/[\sigma^2(F_o^2) + (0.0513 \cdot P)^2 + (0.7014 \cdot P)]$ (**4**), where $P = (\max(F_o^2, 0) + 2 \cdot F_c^2)/3$.

Fig. 2. Molecular structure of **a** with ellipsoids drawn at the 30% probability level. Hydrogen atoms omitted for clarity.



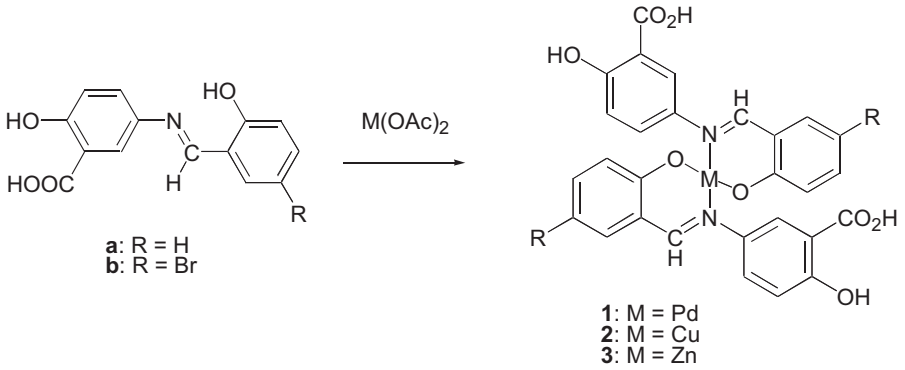
by the diagnostic C=N stretching band in the IR spectra at ca. 1620 cm^{-1} (20).

Compound **a** has also been characterized by a single crystal X-ray diffraction study, the molecular structure of which is shown in Fig. 2. Crystallographic data are provided in Table 1[3] and bond distances and angles are shown in Table 2. Structural features of **a** are similar to those reported recently for the hydroxy imide tautomer of sulfasalazine, 5-[4-[(2-pyridylideneamino)sulfonyl]phenyldiazenyl]salicylic acid (25). For instance, both molecules are almost planar as a result of extensive delocalization arising from an additional intramolecular interaction between the phenolic OH group on the 5-ASA fragment and the carboxylic acid C=O moiety (in **a**, O(8)-H(8)···O(1) = 1.622(2) Å). The imine C(10)—N(9) bond distance of 1.307(2) Å in **a** is comparable to bond lengths observed in other salicylaldimine derivatives (26). Although *N*-salicylaldimines are well-known to exist in tautomeric forms because of the intramolecular proton shift between the phenolic oxygen and the imine nitrogen (O-H···N ↔ O···H-N), no evidence for the other keto amine tautomer is present in the case of **a** (27).

Interestingly, lavendustin A, a structural derivative of compound **a**, has been reported to inhibit tyrosine kinase, an enzyme whose activity is often overexpressed in proliferative diseases (28). Compound **a** has also shown some inhibitory activity against tyrosine kinase (29). Likewise, the anti-inflammatory and antipyretic activities of Schiff bases derived from mesalazine and arylaldehydes have also been reported (30). These promising biological properties prompted

[3] Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 4009. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 261731 and 261732 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Scheme 2. Synthesis of metal Schiff base complexes **1**–**3**.



us to investigate the antifungal properties of late metal complexes containing these bioactive ligands.

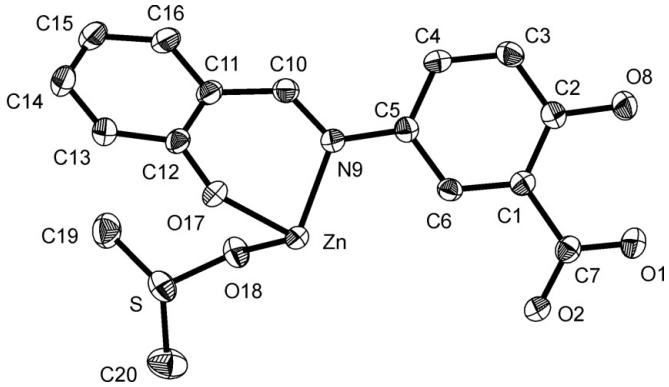
Metal complexes

Schiff bases are ubiquitous in coordination chemistry and several reviews have recently been published outlining the practical aspects and challenges associated with these complexes (31–33). As part of our investigation into designing new chelating agents from biologically active compounds, we decided to examine the synthesis, reactivity, and antifungal properties of Schiff base Pd(II), Cu(II), and Zn(II) complexes derived from 5-ASA. Related Schiff base Pd(II) complexes derived from *S*-alkyldithiocarbazates have recently shown considerable antimicrobial activity against a number of pathogenic bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus subtilis* (34). Copper and zinc Schiff base complexes have also shown considerable antibacterial and antifungal activity (35, 36).

We have found that addition of **a** and **b** to $M(OAc)_2$ (M = Pd, Cu, Zn) afforded bis(salicylaldiminato)metal(II) complexes (Scheme 2, **1**–**3**) in high to excellent yields (64%–95%). Complexes **1**–**3** have been characterized by a number of physical methods. For instance, elemental analyses for paramagnetic copper complexes **2** are consistent with bis-Schiff base formulation (37). The diagnostic C=N stretching band in the FT-IR spectra has shifted from ca. 1620 cm^{-1} to ca. 1595 cm^{-1} upon coordination to the metal centre (38). Multinuclear NMR spectroscopy was also used to characterize diamagnetic palladium and zinc complexes. For instance, a significant upfield shift in the ^1H NMR spectra is observed for the imine methine proton, from ca. 9 ppm to ca. 8 ppm, upon coordination of the ligand to the d^8 metal centre in complexes **1**. Coordination to the d^{10} zinc centres resulted in only minor shifts to ca. 8.9 ppm. More notable, however, is the absence of the broad OH stretch in the FT-IR spectra when the ligands are coordinated to the metals.

Interestingly, a zwitterionic conformer of complex **3a** has been characterized by an X-ray diffraction study, the molecular structure of which is shown in Fig. 3. Crystallographic data are given in Table 1, and bond distances and angles are listed in Table 3. Attempts to grow single crystals of **3a** in DMSO resulted in the loss of one Schiff base ligand, presumably via protonation by the carboxylic acid group of the 5-ASA moiety, to give the DMSO adduct **4** shown in Fig. 3. The solvent ligand is coordinated to the hard zinc via the oxygen atom of the DMSO. The remaining coordinated Schiff

Fig. 3. The molecular structure of **4** with ellipsoids drawn at the 30% probability level. Hydrogen atoms omitted for clarity.



base ligand must be behaving as a divalent anion to balance the Zn^{2+} cation. Indeed, the carboxylic carbon–oxygen bond lengths are roughly equivalent with C(7)—O(1) (1.254(3) Å) and C(7)—O(2) (1.261(3) Å), which is consistent with a deprotonated resonance structure (39). In comparison, the analogous distances in **a** are C(7)—O(1) (1.238(2) Å) and C(7)—O(2) (1.308(2) Å), where the single C(7)—O(2) bond is clearly defined as the benzylic oxygen. In related zinc 5-ASA complexes, coordination is believed to occur through the deprotonated carboxylate group (40).

Complex **4** exists as a self-assembled polymer consisting of dimeric units where two zinc atoms are connected asymmetrically by bridging Schiff base ligands via the phenolic oxygens (Fig. 4) (Zn—O(17) = 1.980(2) Å, Zn—O(17′) = 2.139(2) Å). The dimers form a 1D polymer via the carboxylic acid group (Zn—O(2) = 1.960(2) Å), and the distorted square pyramidal environment of Zn is completed by coordination of a DMSO molecule (Zn—O(18) = 2.130(2) Å) and the imine nitrogen (Zn—N(9) = 2.048(2) Å), the latter occupying the axial position.

Although zwitterionic zinc complexes are relatively well-known (41–48), Schiff base analogues are much less common. For instance, Zn(II) complexes of the type $ZnX_2(H_2salen)$ (X = Cl, Br, I, NO_3, SO_4) containing *N*,*N*′-ethylenebis(salicylideneimine) ligands have been reported previously (49). However, in these complexes the Schiff base ligand is bound to the metal centre through the negatively charged phenolic oxygens and not the nitrogen atoms. Related copper complexes containing only one tridentate Schiff base ligand have also been reported (50, 51). Complex **4** is

Table 2. Bond lengths (Å) and angles (°) for **a**.

Bond lengths (Å)	
C(1)—C(6)	1.388(2)
C(1)—C(2)	1.408(2)
C(1)—C(7)	1.477(2)
C(2)—O(8)	1.351(2)
C(2)—C(3)	1.391(3)
C(3)—C(4)	1.373(3)
C(4)—C(5)	1.400(2)
C(5)—C(6)	1.388(2)
C(5)—N(9)	1.417(2)
C(7)—O(1)	1.238(2)
C(7)—O(2)	1.308(2)
N(9)—C(10)	1.307(2)
C(10)—C(11)	1.414(2)
C(11)—C(16)	1.412(2)
C(11)—C(12)	1.430(2)
C(12)—O(17)	1.310(2)
C(12)—C(13)	1.404(3)
C(13)—C(14)	1.372(3)
C(14)—C(15)	1.396(3)
C(15)—C(16)	1.363(3)
Bond angles (°)	
C(6)-C(1)-C(2)	119.19(16)
C(6)-C(1)-C(7)	121.21(15)
C(2)-C(1)-C(7)	119.58(16)
O(8)-C(2)-C(3)	117.92(16)
O(8)-C(2)-C(1)	122.10(16)
C(3)-C(2)-C(1)	119.98(16)
C(4)-C(3)-C(2)	120.26(17)
C(2)-C(3)-H(3)	123.2(11)
C(3)-C(4)-C(5)	120.33(17)
C(6)-C(5)-C(4)	119.64(16)
C(6)-C(5)-N(9)	117.10(15)
C(4)-C(5)-N(9)	123.25(15)
C(5)-C(6)-C(1)	120.58(16)
O(1)-C(7)-O(2)	122.87(16)
O(1)-C(7)-C(1)	121.51(16)
O(2)-C(7)-C(1)	115.60(15)
C(10)-N(9)-C(5)	127.25(15)
N(9)-C(10)-C(11)	122.31(16)
C(16)-C(11)-C(10)	120.27(16)
C(16)-C(11)-C(12)	119.12(17)
C(10)-C(11)-C(12)	120.60(16)
O(17)-C(12)-C(13)	122.42(16)
O(17)-C(12)-C(11)	119.24(16)
C(13)-C(12)-C(11)	118.34(16)
C(14)-C(13)-C(12)	120.54(18)
C(13)-C(14)-C(15)	121.36(19)
C(16)-C(15)-C(14)	119.61(18)
C(15)-C(16)-C(11)	121.02(18)

unique, however, in that it contains only one zwitterionic bidentate Schiff base ligand where the third coordination site is occupied by a solvent molecule.

Antifungal activity

As mentioned previously, the ability of metal Schiff base complexes to inhibit fungal growth is well-documented (34–

Table 3. Selected bond lengths (Å) and angles (°) for **4**.

Bond lengths (Å)	
Zn—O(2)^a	1.9598(16)
Zn—O(17)	1.9796(15)
Zn—N(9)	2.0476(18)
Zn—O(18)	2.1296(17)
Zn—O(17)^b	2.1387(16)
Zn—Zn^b	3.1381(5)
C(2)—O(8)	1.352(3)
C(5)—N(9)	1.427(3)
C(7)—O(1)	1.254(3)
C(7)—O(2)	1.261(3)
O(2)—Zn^a	1.9597(16)
N(9)—C(10)	1.295(3)
C(12)—O(17)	1.341(3)
O(17)—Zn^b	2.1387(16)
O(18)—S	1.5149(17)
S—C(20)	1.785(3)
S—C(19)	1.786(3)
Bond angles (°)	
O(2)^a-Zn-O(17)	145.61(7)
O(2)^a-Zn-N(9)	121.03(7)
O(17)-Zn-N(9)	93.03(7)
O(2)^a-Zn-O(18)	91.32(7)
O(17)-Zn-O(18)	93.35(6)
N(9)-Zn-O(18)	90.18(7)
O(2)^a-Zn-O(17)^b	89.02(7)
O(17)-Zn-O(17)^b	80.79(7)
N(9)-Zn-O(17)^b	98.26(7)
O(18)-Zn-O(17)^b	169.93(6)
O(2)^a-Zn-Zn^b	120.59(5)
O(17)-Zn-Zn^b	42.28(5)
N(9)-Zn-Zn^b	97.54(5)
O(18)-Zn-Zn^b	135.07(4)
O(17)^b-Zn-Zn^b	38.51(4)
C(6)-C(5)-N(9)	117.79(19)
C(4)-C(5)-N(9)	123.54(19)
C(7)-O(2)-Zn^a	118.25(14)
C(10)-N(9)-C(5)	120.35(19)
C(10)-N(9)-Zn	117.84(15)
C(5)-N(9)-Zn	121.61(14)
N(9)-C(10)-C(11)	126.8(2)
N(9)-C(10)-H(10)	116.6
O(17)-C(12)-C(13)	119.2(2)
O(17)-C(12)-C(11)	122.94(19)
C(12)-O(17)-Zn	118.62(13)
C(12)-O(17)-Zn^b	125.57(14)
Zn-O(17)-Zn^b	99.21(6)
S-O(18)-Zn	119.87(10)
O(18)-S-C(20)	105.27(13)
O(18)-S-C(19)	104.83(12)
C(20)-S-C(19)	98.85(14)

[a]Symmetry transformations used to generate equivalent atoms: –x, –y + 1, –z + 1.
[b]Symmetry transformations used to generate equivalent atoms: –x, –y + 1, –z.

Fig. 4. View of compound **4**, showing the polymeric nature. Thermal ellipsoids are at the 50% probability level. Hydrogen atoms and DMSO molecules have been omitted for clarity.

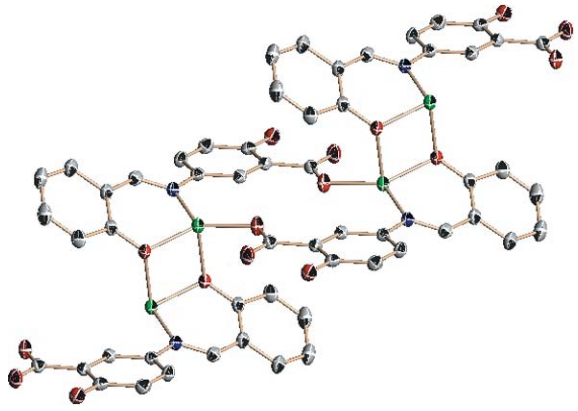


Table 4. Antifungal testing in THF at a dose of 100 μg/disk.

	Diameter of clear zone (mm)	
Compound	*Aspergillus niger*	*Aspergillus flavus*
1a	0	3
1b	3	5
2a	2	3
2b	7	8
3a	3	2
3b	6	11
Amphotericin B	18	12

36). As a result, we have carried out initial antifungal studies on all new metal 5-ASA complexes described above (52). Unfortunately, only compounds **2b** and **3b** showed any appreciable activity against both *A. niger* and *A. flavus* (Table 4). It is interesting to note that the brominated derivatives showed slightly increased activities as compared to the parent Schiff base complexes and that copper and zinc complexes were more active than the analogous palladium complexes. Further work is needed, however, to fully understand the structural activity relationships in these complexes in an effort to design a more powerful antifungal agent.

Conclusion

We have prepared salicylaldimine compounds from 5-ASA and examined their ability to chelate to metals. Pd(II), Cu(II), and Zn(II) bis(*N*-arylsalicylaldiminato) complexes have been prepared in good to excellent yields. A novel zinc complex has been structurally characterized as a mono Schiff base DMSO adduct that forms a self-assembled polymer unit. The brominated complexes all showed moderate antifungal activity against both *A. niger* and *A. flavus*.

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