Journal of Molecular Structure 1128 (2017) 162–173

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Efficient synthesis and evaluation of bis-pyridinium/bis-quinolinium metallosalophens as antibiotic and antitumor candidates

Reda F.M. Elshaarawy [a, c, *], Ibrahim M. Eldeen [b], Eman M. Hassan [a]

[a] Chemistry Department, Faculty of Science, Suez University, 43518 Suez, Egypt
[b] Department of Chemistry, Faculty of Science, Port Said University, Port Said, Egypt
[c] Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine Universität Düsseldorf, 40204 Düsseldorf, Germany

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
9 August 2016
Accepted 21 August 2016
Available online 26 August 2016

Keywords:
Salophens
Metallosalophens
Pyridinium
Antimicrobial
Anticancer

ABSTRACT

Inspired with the pharmacological diversity of salophens and in our endeavor to explore a new strategy which may conflict the invasion of drug resistance, we report herein efficient synthetic routes for the synthesis of new RO-salophen(Cl), pyridinium/quinolinium-based salophens (**3**a-e) and metallosalophens (**4**a-j). These new architectures have been structurally characterized by elemental and spectral analysis as well pharmacologically evaluated for their *in vitro* antimicrobial, against a common panel of pathogenic bacterial and fungal strains, and anticancer activities against human colon carcinoma (HCT-116) cell lines. Antimicrobial assay results revealed that all tested compounds exhibited moderate to superb broad-spectrum efficacy in comparison to the standard antibiotic with a preferential ability to perform as a fungicides than to act as bactericides. Noteworthy, VO(II)-salophens are more effective in reduction HCT-116 cell viability than Cu(II)-salophens. For example, VO(II)-salophen3 (**4**f) ($IC_{50} = 2.13$ μg/mL) was *ca.* 10-fold more efficient than Cu(II)-salophen3 (**4**e) ($IC_{50} = 20.30$ μg/mL).

1. Introduction

Recently, the relentless growth of multidrug-resistant (MDR) becomes a serious chemotherapeutic issue [1,2] due to a lack of patient response to the drug and the outbreak of the disease. Hence, there is urgent call to explore a novel strategy to negate this drug resistance. Among proposed strategies, development of new generation of pharmacological agents with innovative modes of action that able to nullify the current resistance mechanisms [3,4] are at the forefront of attention for many biomedical researchers.

Since the preparation of the *N-N'-bis* (salicylidene) ethylenediamine and its copper(II)/nickel(II) complexes [5] coupled with the discovery of new generation of chelating ligands, salen Schiff-bases, many chemists have endeavored to synthesize a wide range of salens and salophens ligands due to their ability to coordinate to a wide range of metal ions to form metallosalens/metallosalophens with various oxidation states [6] which have diverse applications in several fields including catalysis [7], antimicrobial [8,9], anticancer [10], sensors [11], magnetic [12] and non-linear optical (NLO) applications [13].

Among metal ions, much attention has been paid to copper(II) and oxovanadium(IV) ions because of their admirable structural and pharmacological features, in particular their complexes. Copper is an essential element for our life as it is played a critical role in diverse of Cu-dependent enzymatic process that are the keys features in many biological systems [14]. Moreover, copper(II) complexes have been found to exhibit multiple pharmacological activities such as antiulcer [15], anti-amoebic [16], anti-diabetic [17] anticonvulsant [18], anti-inflammatory [19], antimicrobial [20] and antitumor [21]. Notably, vanadyl complexes containing N-donor chelating ligands have shown very interesting biochemical and pharmacological efficacies such as insulin-mimetic profile [22], antiparasitic [23] and antitumor activities [24].

In the race of fabrication of new pharmaceutical drugs, ionic liquids (ILs) have attracted a considerable attention due to their amphiphilic nature which may realizes considerable enhancements in controlling the aqueous solubility, pharmacokinetic properties, stability, polymorphism of drug, delivery options, or even customized pharmaceutical cocktails [25].

* Corresponding author. Permanent address: Chemistry Department, Faculty of Science, Suez University, 43518 Suez, Egypt. Current address: Institut für Anorganische Chemie und Strukturchemie, Heinriche-Heine-Universität Düsseldorf, D-40225 Düsseldorf, Germany

E-mail addresses: reda_elshaarawi@science.suez.edu.eg, Reda.El-Shaarawy@uni-duesseldorf.de (R.F.M. Elshaarawy).

http://dx.doi.org/10.1016/j.molstruc.2016.08.059
0022-2860/

Interestingly, antimicrobial assessments of pyridinium and quinolinium ionic liquid (IL)-based architectures revealed significant broad-spectrum biocidal activities [26]. Moreover, many ionic liquids display biocidal efficacy against Gram-positive/-negative bacteria, fungi and algae [27,28].

In resumption our ongoing programs directed toward the development of novel potent and therapeutic agents [28,29] we report herein a synthetic strategy and *in vitro* biological (antimicrobial and anticancer) evaluation of new pyridinium and quinolinium-based salophen-type ligands and their metal complexes (Scheme 1) which may allow us to develop novel therapeutic strategy to combat antibiotic resistance and offer potent anticancer agents.

Intersetingly, the possible structural and geometrical features of our metallosalophen complexes could be identified by comparing with the spectral studies of the related salen and salophen complexes isolated in the former work [30,31]. As the crystallographic data collected from X-ray diffraction analysis for Cu(II) salophen- and salen-type ligands [30] reveal that the central Cu(II) ion was situated in a slightly distorted square-planar environment with CuN_2O_2 coordination core. On other hand, X-ray crystallography obtained from VO(II)-salophens demonstrate that the tetradentate (ONNO) salophen ligand coordinates the vanadium(IV) ion in four equatorial sites while the terminal O atom of vanadyl ion occupies the axial position to form a distorted square pyramidal geometry [31].

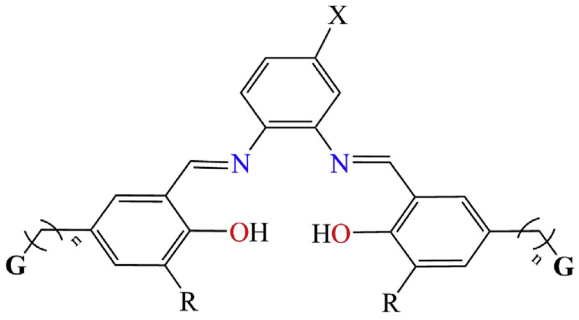
2. Experimental

2.1. Materials

Chemicals were obtained from the following suppliers and used without further purification: salicylaldehyde (Sal), quinoline (Qn), 2-methylpyridine (2-picoline, 2-MePy) (Sigma–Aldrich), paraformaldehyde ($(CH_2O)_n$) (Roth), 4-Chloro-*o*-phenylenediamine (4-Cl-Phen) and isoquinoline (*iso*-Qn) (Alfa Aesar), anhydrous zinc chloride ($ZnCl_2$) (Grüssing GmbH), *o*-phenylenediamine (Phen) and copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$), (ADWIC) and vanadyl sulfate pentahydrate ($VOSO_4 \cdot 5H_2O$) (VWR). 5-chloromethyl-salicylaldehyde (**1**) was synthesized as described in the literature [28] and obtained as white needles (73.0% Yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 11.12 (s, 1H, Ar–O**H**) 9.93 (s, 1H, Ar–**H**C=O), 7.57 (m, 2H, 2 x Ar–**H**), 7.00 (d, 1H, J_{HH} = 8.34 Hz, Ar–**H**), 4.58 (s, 2H, C**H$_2$**–Ar).

2.2. Instrumentation

Elemental analyses C, H, N, were performed with a Perkin–Elmer 263 elemental analyzer. FT-IR spectra were recorded on a BRUKER Tensor-37 FT-IR spectrophotometer in the range 400–4000 cm^{-1} as KBr disc in the 4000–550 cm^{-1} region with 2 cm^{-1} resolution. For signal intensities the following abbreviations were used: br (broad), sh (sharp), w (weak), m (medium), s (strong), vs (very strong). UV/Vis spectra were measured at 25 °C in DMSO (10^{-3} mol/L) on a Shimadzu UV-2450 spectrophotometer using quartz cuvettes (1 cm). NMR-spectra were obtained with a Bruker Avance DRX200 (200 MHz for ^{1}H) or Bruker Avance DRX500 (125 MHz for ^{13}C) spectrometer with calibration to the residual proton solvent signal in DMSO-d_6 (^{1}H NMR: 2.52 ppm, ^{13}C NMR: 39.5 ppm), $CDCl_3$ (^{1}H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm) against TMS (δ = 0.00 ppm) for ^{1}H and ^{13}C NMR. Multiplicities of the signals were specified s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). The mass spectra were acquired in the linear mode for positive ions on a UHR-QTOF maXis 4G (Bruker Daltonics) and Bruker Ultraflex MALDI-TOF instrument equipped with a 337 nm nitrogen laser pulsing at a repetition rate of 10 Hz. The 2 + charge assignment of ions in ESI-MS was confirmed by the m/z = 0.5 difference between the isotope peaks (x, x+1, x+2). The molar conductances of 10^{-3} mol/L solution of various compounds have been measured at ambient temperature with a digital conductivity meter (S30 SevenEasy™ conductivity, Mettler-Toledo Electronics, LLC, Polaris Parkway, Columbus). The overall accuracy of the conductance measurements was found to be ±0.2%.



R	X	n	G
OMe	Cl	0	H
OEt	Cl	0	H
H	H	1	2-MePy$^+$Cl$^-$
H	H	1	Qn$^+$Cl$^-$
H	H	1	*iso*-Qn$^+$Cl$^-$

Scheme 1. Proposed salophen-type Schiff bases that used in this work.

2.3. Synthesis of salicylaldehyde ionic liquids (Sal-ILs, **2***a-c*)

To a vigorously stirred solution of *N*-heterocyclic derivatives (19.50 mmol) in dry toluene (25 mL) at room temperature was added a solution of 5-chloromethyle salicylaldehyde **1** (4.15 g, 19.50 mmol) in dry toluene (50 mL), drop-wise over 30 min, under nitrogen atmosphere. The resulting solution was stirred under nitrogen atmosphere at 60 °C for 24 h. After cooling, the isolated products were washed intensively with 5 × 5 mL dry toluene, several with ether (5 × 10 mL), to remove the unreacted materials, and dried under vacuum to give the desired products which used for the following preparations without further purification. Samples of the isolated products were characterized as follows;

2.3.1. 3-(3-Formyl-4-hydroxybenzyl)-2-methylpyridinium chloride (**2***a*)

Obtained as pale yellow solid in 91% yield. FTIR (KBr, cm^{-1}): 3385 (m, br, $\nu_{(O-H)}$), 2959 (m, sh, $\nu_{asym(C-H)}$, CH_3), 2884 (m, sh, ν_{CH2}), 1661 (vs, sh, $\nu_{(C=O)}$), 1573, 1485, 1455 (s, sh, $\nu_{(C=CAr\ +\ C-H\text{-}bend)}$), 1149 (s, sh, $\nu_{(H-C=C\ +\ H-C=N)bend}$, Py). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 10.83 (s, 1H, Ar–O**H**) 10.30 (s, 1H, Ar–**H**C=O), 9.15 (d, J = 2.10 Hz, 1H, Py–**H**), 8.68 (m, 2H, 2 x Py–**H**), 7.84 (d, 1H, J = 1.39 Hz, Py–**H**), 7.75 (d, J_{HH} = 1.41 Hz, 1H, Ar–**H**), 7.38 (m, 2H, 2 x Ar–**H**), 5.45 (s, 2H,–C**H$_2$**–Ar), 2.73 (s, 3H, C**H$_3$**). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.88, 160.76, 151.06, 142.28, 136.95, 135.54, 133.24, 131.19, 129.58, 127.86, 123.77, 64.61 and 25.29. ESI MS: In positive mode peaks at m/z 228.10 (100%, $[C_{14}H_{14}NO_2]^+$, M–Cl) a.m.u.

2.3.2. 3-(3-Formyl-4-hydroxybenzyl)-quinolinium chloride (**2***b*)

Obtained as dark yellow solid in 86% yield. FTIR (KBr, cm^{-1}): 3369 (m, br, $\nu_{(O-H)}$), 1666 (vs, sh, $\nu_{(C=O)}$), 1574, 1487, 1453 (s, sh,