HETEROCYCLES, Vol. 81, No. 3, 2010, pp. 585 - 600. © The Japan Institute of Heterocyclic Chemistry
Received, 24th October, 2009, Accepted, 25th December, 2009, Published online, 29th December, 2009
DOI: 10.3987/COM-09-11862

SYNTHESIS OF METAL COMPLEXES WITH 1-SUBSTITUTED 3-HYDROXY-2(1*H*)-PYRIDINETHIONES AND THEIR INSULIN-MIMETIC ACTIVITIES

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Abstract – Eight kinds of 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones were synthesized from a commercially available 3-methoxy-2(1*H*)-pyridinone via 3 steps. Zn(II) and vanadyl complexes were synthesized by treatment with $Zn(OAc)_2$ or $ZnSO_4$, and $VOSO_4$, respectively. Vanadyl complexes were found to exist in $VO(S_2O_2)$ coordination mode by means of ESR spectroscopy. From *in vitro* evaluation of the inhibitory effect on FFA release from rat adipocytes treated with epinephrine, it was found that IC_{50} values of Zn(II) complexes with 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones, regardless of the methylene-chain length at N-1 position, were in micromolar levels. In other words, these Zn(II) complexes showed higher insulin-mimetic activities than those synthesized previously. On the other hand, the insulin-mimetic activity of vanadyl complexes unfortunately could not be measured owing to their insolubility in KRB buffer which is used *in vitro* assay.

INTRODUCTION

One of the most widespread lifestyle-related diseases in the 21st century is thought to be diabetes mellitus (DM). The number of patients that suffer from DM in the world has been projected to rise approximately 366 million by 2030 from 171 million in 2000.[1] DM develops many secondary

complications such as atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormalities, diabetic retinopathy, and other ocular disorders.

DM is generally classified into type 1 and type 2 DM. Type 1 DM is caused by destruction of pancreatic β-cells, and so it is characterized by a lack of insulin production. Type 2 DM is caused by aging, obesity, spiritual stress or other environmental factors including high cholesterol and high blood pressure, and so it is characterized by insulin resistance and abnormality of insulin-secretion.[2] Type 1 DM can be only treated by daily hypodermic injections of insulin, and type 2 DM is treated by dietary measures, exercise and several types of synthetic therapeutic medicines. Both treatments have some defects that several insulin injections in a day have pain and stress for patients, and synthetic therapeutic medicines have severe side effects. Therefore, the development of orally active compounds in place of physically and mentally painful insulin injections for type 1 DM and of compounds without severe side effects for type 2 DM is still required not only to treat DM but also to improve the quality of life (QOL) in DM patients.

Several metal ions have been reported to show insulin-mimetic activity *in vitro*.[3,4] Hg^{2+}, Se^{4+}, and Cd^{2+} strongly inhibited free fatty acid (FFA)-release, but these metal ions are highly toxic. Following these ions, V^{3+}, V^{4+} (VO^{2+}), Zn^{2+} and Mn^{2+} also inhibited FFA-release. Since V^{3+} is readily oxidized to V^{4+} and V^{5+} states at physiological pH and V^{4+} is less toxic than V^{5+}, we exclusively used V^{4+} in our study. In addition to V^{4+}, we extended our work to Zn^{2+}.

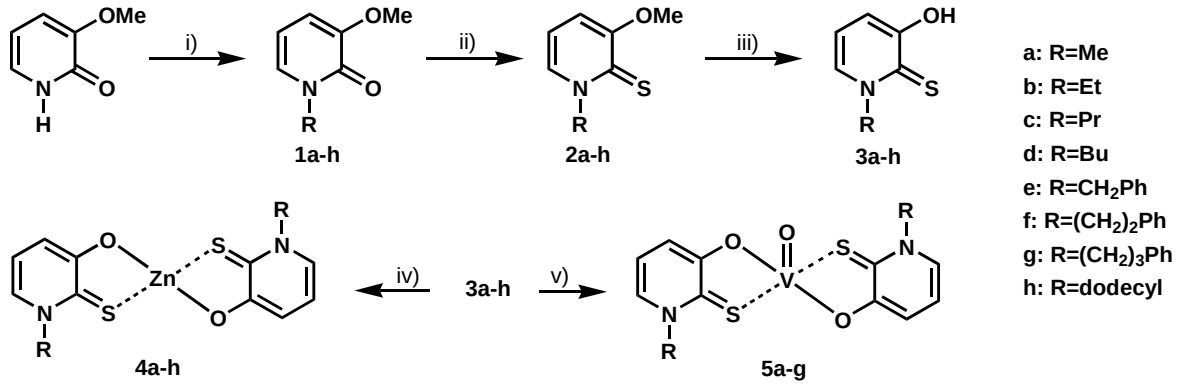
Both metals in the form of inorganic salts such as $VOSO_4$,[5] $ZnCl_2$, and $ZnSO_4$[6-8] could decrease and normalize the blood glucose level in diabetic animals even by an oral dosage, but they are generally poorly absorbed from lipid bilayer cell membrane. High dosage is required to lower the blood glucose level, and it is responsible for emerging some undesirable side-effects. To overcome defects with respect to absorption and dosage, many researchers have focused on the design and synthesis of metal complexes with low-molecular-weight organic bidentate ligands. Zn(II) complexes such as O_4,[9-12] N_4,[13] N_2O_2,[14,15] S_2O_2,[16-18] and vanadyl complexes such as O_4,[9,19-23] N_4,[24,25] N_2O_2,[26-29] S_2O_2[17,18,20,30] coordination modes have been reported to exhibit insulin-mimetic activities both *in vitro* and *in vivo*. Further it has been revealed that without exception, complexes with S_2O_2 coordination mode showed higher insulin-mimetic activities than those with O_4 coordination mode.[31]

As an extensive studies on chemistry and biochemistry[32] of insulin-mimetic vanadium and zinc complexes and with the objective of providing a new family of insulin-mimetic complexes with $M(S_2O_2)$ (M=VO and Zn) coordination modes, we describe here synthesis of novel vanadyl and Zn(II) complexes with 3-hydroxy-2(1*H*)-pyridinethiones and their insulin-mimetic activities.

RESULTS AND DISCUSSION

Synthesis of metal complexes with 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones

A synthetic procedure for metal complexes with 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones is depicted in Scheme 1.



Reagents and conditions: i) RI or RBr/KOH in MeOH; ii) Lawessson's reagent in toluene; iii) 1M BBr_3 in CH_2Cl_2 iv) $Zn(OAc)_2$ in EtOH/H_2O for 3a-d and $ZnSO_4$/LiOH in MeOH/H_2O for 3e-h; v) $VOSO_4$ in H_2O at pH 10.

Scheme 1

A commercially available 3-methoxy-2(1*H*)-pyridinone was treated with alkyl halides in dry MeOH in the presence of KOH to give 1-alkyl-3-methoxy-2(1*H*)-pyridinones **1a-h**.[33] The conversion of the carbonyl into the corresponding thiocarbonyl was carried out using Lawesson's reagent to give the corresponding 1-alkyl-3-methoxy-2(1*H*)-pyridinethiones **2a-h**. Compounds **2a-h** were allowed to react with an equimolar amount of BBr_3 to give 1-alkyl-3-hydroxy-2(1*H*)- pyridinethiones **3a-h**.

Bidentate ligands **3a-d** were treated with a 0.5 equimolar amount of $Zn(OAc)_2$[12,34] in H_2O:EtOH (1:1) mixture at room temperature to give Zn(II) complexes **4a-d**. On the other hand, compounds **3e-h** which have a long alkyl chain and a phenyl group were sparingly soluble in organic solvents, and thus the $ZnSO_4$-LiOH method[17] was employed. Bidentate ligands **3e-h** were treated with $ZnSO_4 \cdot 7H_2O$ in the presence of LiOH in H_2O:MeOH (1:1) mixture at room temperature to afford Zn(II) complexes **4e-h**. The structural assignment of compounds **4a-h** was carried out by ^{1}H-NMR, IR and MALDI-TOF MS spectroscopies, and the combustion analysis. Each MALDI-TOF MS spectrum exhibited the peak related to the molecular ion ($[M+H]^+$), strongly indicating the formation of the desired Zn(II) complex. Bidentate ligands **3a-g** were treated with a 0.5 equimolar amount of $VOSO_4 \cdot H_2O$[18,19] in H_2O at pH 10 at room temperature for compounds **3a-c** and with refluxing overnight for compounds **3d-g** to give vanadyl complexes **5a-g**. The structural assignment of compounds **5a-g** was carried out by IR, UV-vis and MALDI-TOF MS spectroscopies, and the combustion analysis. On IR spectra, characteristic absorption bands owing to V=O stretching vibrations were observed around 970 cm^{-1}. Each MALDI-TOF MS spectrum exhibited the peak related to the molecular ion ($[M]^+$), strongly indicating the formation of the desired vanadyl complex.

Structural characteristics of ligands and metal complexes

The p*Ka* value of compound **3b** was measured in aqueous solution by the conventional pH titration

method and was calculated to be 9.4. The p*Ka* value of 3-hydroxy-2(1*H*)-pyridinethione **3b** was larger than that of 3-hydroxy-2(1*H*)-pyridinone (p*Ka* = 8.8[35]). Considering the resonance effect, the contribution of $–N^{+}=C–S^{-}$ in resonance hybrid should be larger than that of $–N^{+}=C–O^{-}$. In addition, higher p*Ka* value may be attributable to an intramolecular hydrogen bonding between $–O\text{-}H\cdots{}^{-}S–C=N^{+}–$. It is recognized that the biological activity is affected by the degree of the hydrophobicity of compound. In fact, the partition coefficient is one of the most important factors on oral administration of drugs. Therefore, the partition coefficients of compounds **3a-h** and Zn(II) complexes **4a-h** were measured using two phases of an aqueous solution buffered at pH 7.4 and 1-octanol. The partition coefficients, $\log P_{ow} = \log(C_{octanol}/C_{buffer})$, are summarized in Table 1.

Table 1 The Partition coefficients of bidentate ligands 3a-h

Ligand	3a	3b	3c	3d	3e	3f	3g	3h
log P_{ow}	0.3	1.2	1.3	1.4	1.7	∞	∞	∞

Among a series of 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones **3a-e**, an increase in the alkyl chain length and introduction of phenyl group at N-1 position result in an increase of the solubility in 1-octanol. Unfortunately, the partition coefficients of compounds **3f-h** could not be measured because of insolubility in KRB buffer. The partition coefficient of Zn(II) complexes **4a-g** also could not be measured, because they were practically insoluble in both solutions.

UV-vis spectra of vanadyl complexes **5a-g** were measured in DMSO solution, and the results are summarized in Table 2. On the basis of small molar extinction coefficients (ε), the absorption bands of vanadyl complexes **5a-g** around 540 nm can be attributed to d-d transition.

Table 2 UV-vis spectral data for vanadyl complexes 5a-g

VO complex*	5a	5b	5c	5d	5e	5f	5g
λmax nm(ε)	544(65)	541(87)	535(82)	540(91)	535(79)	540(76)	537(62)

* [VO complex]=1.0 mM in DMSO

Vanadyl ion has an unpaired electron. ESR spectrum is useful tool for investigation of electronic structure of vanadyl complexes. ESR spectra of vanadyl complexes **5a-g** were measured. When vanadyl is VO^{2+} state, the nuclear spin quantum number (*I*) of vanadium (IV) is 7/2. The number (n) of hyperfine signal of vanadium(IV) becomes eight according to the following equation; $n = 2I + 1$. Eight

resonance line signals characteristic to VO^{2+} state were detected in DMSO at room and liquid nitrogen temperatures. ESR parameters such as universal constants (g-values) and hyperfine coupling constants (A-values) were calculated. (see Experimental section) The calculated $g_{//}$ and $A_{//}$ values are consistent with those of vanadyl complexes with S_2O_2 coordination mode[36] reported previously.

Evaluation of insulin-mimetic activities of metal complexes

Previously, Sakurai and co-workers have demonstrated that the FFA release from rat adipocytes is a good *in vitro* evaluation system to find a compound exhibiting an insulin-mimetic action.[5,37] The results on Zn(II) complexes are compiled in Figure 1, together with $ZnSO_4$ as the positive control. As seen in Figure 1, all Zn(II) complexes **4a-h** inhibited FFA release in a dose-dependent manner from the epinephrine-stimulated rat adipocytes.

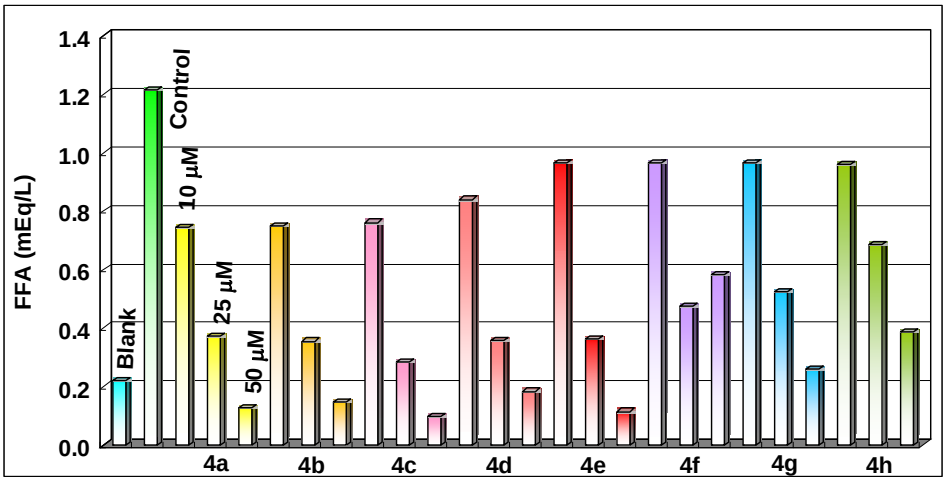


Figure 1. The inhibitory effects of Zn(II) complexes 4a-h on epinephrine-stimulated FFA release from rat adipocytes.

IC_{50} values which are 50% inhibition concentrations of the FFA release level stimulated by epinephrine were estimated from these graphic data, and the results are summarized in Table 3. All Zn(II) complexes **4a-h** showed the insulin-mimetic activity 15 times as much as $ZnSO_4$ as the positive control.

Table 3 The IC_{50} values of Zn(II) complexes 4a-h.

Complex	$ZnSO_4$	4a	4b	4c	4d
IC_{50} value (μM)	292±31	18.4±0.9	18.4±1.5	17.6±1.2	21.3±1.5
Complex	4e	4f	4g	4h	
IC_{50} value (μM)	21.5±0.7*	36.1±2.0*	24.1±2.7*#	44.6±5.8	

Each value is expressed as the mean±SD for 3 experiments.
Significance; * $p > 0.05$ vs. 4a, # $p > 0.05$ vs. 4e.

Previously, it was found that the balance of the hydrophilicity/hydrophobicity is one of the most important factors exhibiting the insulin-mimetic activity.[10] However, such balance was not observed in this experiment. In the case of vanadyl complexes **5a-g** no activity was observed. It may be mainly responsible for the insolubility of vanadyl complexes in the KRB buffer.

In conclusion, Zn(II) and vanadyl complexes with eight kinds of 1-alkyl-3-hydroxy-2(1*H*)-pyridine-thiones were synthesized. On the basis of *in vitro* results, Zn(II) complexes **4a-h** are expected to become potent insulinomimetic complexes for treating type 2 DM in animals.

EXPERIMENTAL

Melting points were measured on a MELTING POINT APPARATUS SMP3 in open capillaries and are uncorrected. IR and UV-vis spectra were recorded on a JASCO FT/IR-470 infrared and on a JASCO Ubest V-550 spectrophotometers. ^{1}H-NMR spectra were obtained on a JEOL JIM-LA400D NMR spectrometer in an appropriate solvent. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane (TMS). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} with 0.2 mm thickness. Column chromatography was carried out with Merck Silica Gel 60 (63-210 mesh). The combustion analysis was performed on a PERKIN-ELMER 2400 CHNS/O analyzer series II. MALDI-TOF MS was performed on a AXIMA-LNR/-CFR/-CFR Plus (S/W Version 2.4).

General synthetic procedure for 1-alkyl-3-methoxy-2(1*H*)-pyridinones

A typical example: 3-methoxy- 1-methyl-2(1*H*)-pyridinone (1a). 3-Methoxy-2(1*H*)-pyridinone (2.5 g, 20 mmol) and KOH (1.5 g, 27 mmol) were dissolved in dry MeOH (125 mL) under Ar atmosphere. To the mixture was slowly added MeI (5.7 g; 2.5 mL, 40 mmol), and then the reaction mixture was refluxed for 24 h. After evaporation of the solvent, the residue was dissolved in H_2O (50 mL), and extracted with $CHCl_3$ (50 mL). The aqueous layer was further extracted with $CHCl_3$ (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$:MeOH (10:1) mixture as an eluant to give the product **1a** as an orange oil. Yield: 3.12 g (quant.); IR (neat): 3074, 2938, 1654, 1599, 1557, 1457, 1375, 1254, 1034, 750 and 661 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.58 (3H, s), 3.82 (3H, s), 6.10 (1H, dd, *J*=6.9 and 7.3 Hz), 6.62 (1H, dd, *J*=1.5 and 7.3 Hz), and 6.91 ppm (1H, dd, *J*=1.5 and 6.9 Hz). *Anal*. Calcd for $C_7H_9NO_2 \cdot 1.2H_2O$: C, 52.30; H, 7.15; N, 8.71%. Found: C, 52.12; H, 6.97; N, 8.59%.

3-Methoxy-1-ethyl-2(1*H*)-pyridinone (1b): as a yellow oil; yield: 62%; IR (neat): 3063, 2976, 1651, 1596, 1558, 1460, 1236, 1050, 752 and 706 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.35 (3H, t, *J*=7.3 Hz), 3.82 (3H, s), 4.25 (2H, q, *J*=7.3 Hz), 6.11 (1H, dd, *J*=7.1 and 7.3 Hz), 6.59 (1H, dd, *J*=1.7 and 7.3 Hz), and 6.90 ppm (1H, dd, *J*=1.7 and 7.1 Hz). *Anal*. Calcd for $C_8H_{11}NO_2 \cdot 0.7H_2O$: C, 57.96; H, 7.54; N,

8.45%. Found: C, 58.04; H, 7.64; N, 8.13%.

3-Methoxy-1-propyl-2(1*H*)-pyridinone (1c): as an orange oil; yield: 76%; IR (neat): 3065, 2964, 1652, 1600, 1460, 1229, 1059, 751 and 702 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.95 (3H, t, *J*=7.5 Hz), 1.78 (2H, sext, *J*=7.3 Hz), 3.81 (3H, s), 3.94 (2H, t, *J*=7.3 Hz), 6.08 (1H, dd, *J*=6.8 and 7.3 Hz), 6.59 (1H, dd, *J*=1.7 and 7.3 Hz), and 6.87 ppm (1H, dd, *J*=1.7 and 6.8 Hz). *Anal*. Calcd for $C_9H_{13}NO_2 \cdot 0.5H_2O$: C, 61.34; H, 8.01; N, 7.95%. Found: C, 61.30; H, 8.17; N, 7.85%.

3-Methoxy-1-butyl-2(1*H*)-pyridinone (1d): as an orange oil; yield: 69%; IR (neat): 2958, 2870, 1650, 1595, 1461, 1253, 1060, 751 and 700 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.94 (3H, t, *J*=7.3 Hz), 1.36 (2H, sext, *J*=7.6 Hz), 1.73 (2H, quint, *J*=7.6 Hz), 3.80 (3H, s), 3.97 (2H, t, *J*=7.3 Hz), 6.08 (1H, dd, *J*=6.9 and 7.4 Hz), 6.59 (1H, dd, *J*=1.5 and 7.4 Hz), and 6.87 ppm (1H, dd, *J*=1.5 and 6.9 Hz). *Anal.* Calcd for $C_{10}H_{15}NO_2 \cdot 0.3H_2O$: C, 64.35; H, 8.42; N, 7.50%. Found: C, 64.21; H, 8.68; N, 7.44%.

3-Methoxy-1-benzyl-2(1*H*)-pyridinone (1e): as a yellow oil; yield: 81%; IR (neat): 3062, 2937, 1653, 1602, 1455, 1226, 1062, 747 and 699 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.80 (3H, s), 5.91 (2H, s), 6.08 (1H, dd, *J*=6.8 and 7.3 Hz), 6.59 (1H, dd, *J*=1.7 and 7.3 Hz), 6.89 (1H, dd, *J*=1.7 and 6.8 Hz), and 7.27-7.33 ppm (5H, m). *Anal.* Calcd for $C_{13}H_{13}NO_2 \cdot 0.4H_2O$: C, 70.19; H, 6.25; N, 6.30%. Found: C, 70.20; H, 6.22; N, 6.17%.

3-Methoxy-1-phenethyl-2(1*H*)-pyridinone (1f): as an orange oil; yield: 85%; IR (neat): 3060, 2940, 1653, 1601, 1455, 1251, 1065, 749 and 701 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.06 (2H, t, *J*=7.2 Hz), 3.82 (3H, s), 4.18 (2H, t, *J*=7.2 Hz), 5.95 (1H, t, *J*=7.2 Hz), 6.55 (1H, dd, *J*=1.6 and 7.2 Hz), 6.58 (1H, dd, *J*=1.6 and 7.2 Hz), and 7.15-7.30 ppm (5H, m). *Anal.* Calcd for $C_{14}H_{15}NO_2 \cdot 0.4H_2O$: C, 71.11; H, 6.73; N, 5.92%. Found: C, 70.92; H, 6.87; N, 5.98%.

3-Methoxy-1-phenylpropyl-2(1*H*)-pyridinone (1g): as an orange oil; yield: 75%; IR (neat): 3062, 2938, 1652, 1601, 1456, 1252, 1068, 748 and 700 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 2.10 (2H, quint, *J*=7.6 Hz), 2.68 (2H, t, *J*=7.8 Hz), 3.81 (3H, s), 3.99 (2H, t, *J*=7.3 Hz), 6.08 (1H, t, *J*=7.2 Hz), 6.59 (1H, dd, *J*=1.6 and 7.2 Hz), 6.82 (1H, dd, *J*=1.6 and 7.2 Hz), and 7.17-7.30 ppm (5H, m). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%. Found: C, 73.76; H, 7.19; N, 5.64%.

3-Methoxy-1-dodecyl-2(1*H*)-pyridinone (1h): as an orange oil; yield: 64%; IR (neat): 3056, 2938, 1650, 1610, 1542, 1445, 1260, 1057, 783 and 718 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz):0.88 (3H, t, *J*=7.3 Hz), 1.25 (20H, m), 3.81 (3H, s), 3.95 (3H, t, *J*=7.3 Hz), 6.09 (1H, dd, *J*=7.1 and 7.6 Hz), 6.58 (1H, dd, *J*=1.6 and 7.6 Hz), and 6.87 ppm (1H, dd, *J*=1.6 and 7.1 Hz). *Anal.* Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77%. Found: C, 73.66; H, 10.96; N, 4.91%.

General synthetic procedure for 1-alkyl-3-methoxy-2(1*H*)-pyridinethiones

A typical example: 3-methoxy-1-methyl-2(1*H*)-pyridinethione (2a). A solution of compound **1a**

(1.40 g, 10.1 mmol) and Lawesson's reagent (2.24 g, 5.54 mmol) in toluene (100 mL) was refluxed for 5.5 h. After cooling to rt, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with $CHCl_3$:acetone:EtOH (100:5:1) mixture as an eluant to give the product **2a** as yellow solids. Yield: 1.42 g (91%); mp 127.2-130.2 °C; IR (KBr): 3069, 2934, 1617, 1502, 1468, 1393, 1260 and 1057, 1137, 769 and 710 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.93 (3H, s), 4.07 (3H, s), 6.61 (1H, dd, *J*= 6.5 and 7.8 Hz), 6.71 (1H, dd, *J*=1.3 and 7.8 Hz), and 7.43 ppm (1H, dd, *J*=1.3 and 6.5 Hz). *Anal*. Calcd for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02%. Found: C, 54.10; H, 5.63; N, 8.72%.

3-Methoxy-1-ethyl-2(1*H*)-pyridinethione (2b): as yellow solids; yield: 68%; mp 140.0-141.2 °C; IR (KBr): 3016, 2969, 1616, 1539, 1444, 1188, 1045, 1135, 773 and 717 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.48 (3H, t, *J*=7.3 Hz), 3.92 (3H, s), 4.70 (2H, q, *J*=7.1 Hz), 6.63 (1H, dd, *J*=6.4 and 7.6 Hz), 6.68 (1H, dd, *J*=1.1 and 7.6 Hz), and 7.39 ppm (1H, dd, *J*=1.1 and 6.4 Hz). *Anal*. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28%. Found: C, 56.50; H, 6.73; N, 8.14%.

3-Methoxy-1-propyl-2(1*H*)-pyridinethione (2c): as yellow solids; yield: 78%; mp 75.4-76.1 °C; IR (KBr): 3017, 2955, 1617, 1537, 1461, 1051, 1139, 781 and 718 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.00 (3H, t, *J*=7.3 Hz), 1.96 (2H, sext, *J*=7.6 Hz), 3.92 (3H, s), 4.58 (2H, t, *J*= 7.7 Hz), 6.60 (1H, dd, *J*=6.3 and 7.5 Hz), 6.68 (1H, dd, *J*=1.0 and 7.5 Hz), and 7.37 ppm (1H, dd, *J*=1.3 and 6.3 Hz). *Anal.* Calcd for $C_9H_{13}NOS$: C, 58.98; H, 7.51; N, 7.64%. Found: C, 58.96; H, 7.22; N, 7.56%.

3-Methoxy-1-butyl-2(1*H*)-pyridinethione (2d): as a brown oil; yield: 98%; IR (neat): 3052, 2956, 1617, 1540, 1451, 1181, 1052, 1135, 770 and 714 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.98 (3H, t, *J*=7.3 Hz), 1.42 (2H, sext, *J*=7.6 Hz), 1.90 (2H, quint, *J*=7.7 Hz), 3.92 (3H, s), 4.62 (2H, t, *J*=7.7 Hz), 6.60 (1H, dd, *J*=6.6 and 7.8 Hz), 6.67 (1H, dd, *J*=1.1 and 7.8 Hz), and 7.37 ppm (1H, dd, *J*=1.1 and 6.6 Hz). *Anal*. Calcd for $C_{10}H_{15}NOS \cdot 0.5H_2O$: C, 58.22; H, 7.82; N, 6.79%. Found: C, 58.08; H, 7.85; N, 6.64%.

3-Methoxy-1-benzyl-2(1*H*)-pyridinethione (2e): as yellow solids; yield: 86%; mp 123.4-124.3 °C; IR (KBr): 3060, 2973, 1617, 1539, 1452, 1131, 1062, 770 and 695 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.94 (3H, s), 5.94 (2H, s), 6.58 (1H, dd, *J*=6.8 and 7.6 Hz), 6.68 (1H, dd, *J*= 1.0 and 7.6 Hz), 7.30-7.37 (5H, m), and 7.35 ppm (1H, dd, *J*=1.0 and 6.8 Hz). *Ana*l. Calcd for $C_{13}H_{13}NOS \cdot 0.1H_2O$: C, 66.98; H, 5.71; N, 6.01%. Found: C, 66.73; H, 5.57; N, 6.02%.

3-Methoxy-1-phenethyl-2(1*H*)-pyridinethione (2f): as yellow solids; yield 81%; mp 125 °C (decomp.); IR (KBr): 3073, 2993, 1617, 1539, 1450, 1134, 1048, 769 and 700 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.25 (2H, t, *J*=7.3 Hz), 3.94 (3H, s), 4.84 (2H, t, *J*=7.3 Hz), 6.49 (1H, t, *J*=7.0 Hz), 6.69 (1H, d, *J*=7.0 Hz), 7.08 (1H, d, *J*=7.0 Hz), and 7.20-7.31 ppm (5H, m). *Anal*. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71%. Found: C, 68.66; H, 6.33; N, 5.68%.

3-Methoxy-1-phenylpropyl-2(1*H*)-pyridinethione (2g): as yellow solids; yield: 88%; mp 92.9-94.4 °C; IR (KBr): 3065, 2945, 1617, 1537, 1445, 1125, 1054, 786 and 698 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 2.27 (2H, quint, *J*=7.6 Hz), 2.74 (2H, t, *J*=7.6 Hz), 3.92 (3H, s), 4.63 (2H, t, *J*=7.6 Hz), 6.58 (1H, dd, *J*=6.6 and 7.8 Hz), 6.68 (1H, dd, *J*=1.0 and 7.8 Hz), and 7.19-7.32 ppm (6H, m). *Anal*. Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40%. Found: C, 69.63; H, 6.76; N, 5.37%.

Synthesis of 3-methoxy-1-dodecyl-2(1*H*)-pyridinethione (2h): as yellow amorphous solids; yield: 60%; IR (KBr): 3058, 2956, 1619, 1541, 1444, 1262, 1058, 1136, 777 and 717 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz):0.88 (3H, t, *J*=7.3 Hz), 1.25 (20H, m), 3.92 (3H, s), 4.60 (3H, t, *J*=7.3 Hz), 6.60 (1H, dd, *J*=7.1 and 7.6 Hz), 6.67 (1H, dd, *J*=1.6 and 7.6 Hz), and 7.36 ppm (1H, dd, *J*=1.6 and 7.1 Hz). *Anal*. Calcd for $C_{18}H_{31}NOS$: C, 69.85; H, 10.10; N, 4.53%. Found: C, 70.10; H, 10.25; N, 4.70%.

General synthetic procedure for 1-alkyl-3-hydroxy-2(1*H*)-pyridinethiones

A typical example: 3-hydroxy-1-methyl-2(1*H*)-pyridinethione (3a). To a solution of compound **2a** (1.47 g, 9.47 mmol) in dry CH_2Cl_2 (115 mL) was slowly added 1M BBr_3 in dry CH_2Cl_2 (9.5 mL) at -30 °C under Ar atmosphere. The reaction mixture was stirred for 48 h at rt. The mixture was again cooled to -30 °C, and then MeOH (38 mL) was slowly added to the mixture. After evaporation of the solvent, the residue was adjusted to pH 7 with 1M NaOH, and then extracted with $CHCl_3$ (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (20 g) with $CHCl_3$:acetone:EtOH (100:5:1) mixture as an eluant to give the product **3a** as yellow solids. Yield: 1.10 g (82%); mp 117-119 °C; IR (KBr): 3113, 1623, 1550, 1472, 1351, 1420, 1283, 1132, 773 and 710 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 4.07 (3H, s), 6.65 (1H, dd, *J*=6.6 and 7.2 Hz), 7.00 (1H, dd, *J*=1.3 and 7.2 Hz), 7.37 (1H, dd, *J*=1.3 and 6.6 Hz), and 8.51 ppm (1H, s, D_2O exchangeable). *Anal*. Calcd for C_6H_7NOS: C, 51.04; H, 5.00; N, 9.92%. Found: C, 51.28; H, 5.05; N, 9.81%.

3-Hydroxy-1-ethyl-2(1*H*)-pyridinethione (3b): as yellow solids; yield: 98%; mp 50.0-51.2 °C; IR (KBr): 3449, 3046, 2975, 1626, 1546, 1470, 1425, 1272, 1132, 770 and 713 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.52 (3H, t, *J*=7.1 Hz), 4.61 (2H, q, *J*=7.3 Hz), 6.68 (1H, dd, *J*=6.6 and 7.6 Hz), 6.98 (1H, dd, *J*=1.0 and 7.6 Hz), 7.35 (1H, dd, *J*=1.0 and 6.6 Hz), and 8.60 ppm (1H, s). *Anal*. Calcd for C_7H_9NOS: C, 54.17; H, 5.84; N, 9.02%. Found: C, 54.10; H, 5.64; N, 8.72%.

3-Hydroxy-1-propyl-2(1*H*)-pyridinethione (3c): as a yellow oil; yield: 93%; IR (neat): 3073, 2965, 2874, 1628, 1546, 1472, 1429, 1283, 1137, 770 and 713 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.02 (3H, t, *J*=7.4 Hz), 1.97 (2H, sext, *J*=7.6 Hz), 4.49 (2H, t, *J*=7.6 Hz), 6.65 (1H, dd, *J*=6.6 and 7.8 Hz), 6.98 (1H, dd, *J*=1.2 and 7.8 Hz), 7.32 (1H, dd, *J*=1.2 and 6.6 Hz), and 8.61 ppm (1H, s). *Anal.* Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28%. Found: C, 56.76; H, 6.78; N, 8.23%.

3-Hydroxy-1-butyl-2(1*H*)-pyridinethione (3d): as a brown oil; yield: 91%; IR (neat): 3073, 2958, 2932, 1628, 1545, 1472, 1429, 1283, 1138, 769 and 713 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.99 (3H, t, *J*=7.4 Hz), 1.43 (2H, sext, *J*=7.4 Hz), 1.92 (2H, quint, *J*=7.7 Hz), 4.53 (2H, t, *J*=7.7 Hz), 6.65 (1H, dd, *J*=6.6 and 7.6 Hz), 6.98 (1H, dd, *J*=1.4 and 7.6 Hz), 7.32 (1H, dd, *J*=1.4 and 6.6 Hz), and 8.62 ppm (1H, s). *Anal.* Calcd for $C_9H_{13}NOS \cdot 0.1H_2O$: C, 58.41; H, 7.19; N, 7.57%. Found: C, 58.19; H, 7.19; N, 7.53%.

3-Hydroxy-1-benzyl-2(1*H*)-pyridinethione (3e): as yellow solids; yield: 92%; mp 90.8-92.0 °C; IR (KBr): 3463, 3049, 2960, 1622, 1544, 1468, 1431, 1287, 1121, 765 and 695 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 5.81 (2H, s), 6.64 (1H, t, *J*=7.3 Hz), 6.98 (1H, d, *J*=7.3 Hz), 7.31-7.40 (6H, m), and 8.58 ppm (1H, s). *Anal*. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45%. Found: C, 66.23; H, 4.95; N, 6.32%.

3-Hydroxy-1-phenethyl-2(1*H*)-pyridinethione (3f): as yellow solids; yield: 93%; mp 104.8-106.1 °C; IR (KBr): 3639, 3076, 3024, 1628, 1599, 1475, 1432, 1283, 1122, 768 and 700 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.26 (2H, t, *J*=7.3 Hz), 4.74 (2H, t, *J*=7.3 Hz), 6.51 (1H, t, *J*=6.7 Hz), 6.99 (1H, d, *J*=6.7 Hz), 7.17-7.32 (5H, m), and 8.62 ppm (1H, s). *Anal*. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06%. Found: C, 67.56; H, 5.47; N, 5.90%.

3-Hydroxy-1-phenylpropyl-2(1*H*)-pyridinethione (3g): as yellow solids; yield: 75%; mp 56.5-57.3 °C; IR (KBr): 3461, 3056, 2944, 1623, 1547, 1463, 1420, 1282, 1116, 790 and 701 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 2.29 (2H, quint, *J*=7.6 Hz), 2.75 (2H, t, *J*=7.6 Hz), 4.54 (2H, t, *J*=7.6 Hz), 6.64 (1H, t, *J*=5.6 Hz), 6.97 (1H, d, *J*=5.6 Hz), 7.21-7.33 (6H, m), and 8.59 ppm (1H, s). *Anal.* Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71%. Found: C, 68.43; H, 6.19; N, 5.71%.

3-Hydroxy-1-dodecyl-2(1*H*)-pyridinethione (3h): as a yellow oil; yield: 72%; IR (neat): 3052, 2923, 2853, 1629, 1524, 1470, 1429, 1284, 1118, 767 and 736 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.88 (3H, t, *J* = 7.3 Hz), 1.25 (20H, m), 4.51 (3H, t, *J*=7.3 Hz,), 6.65 (1H, dd, *J*=7.1 and 7.6 Hz), 6.97 (1H, dd, *J*=1.6 and 7.6 Hz), 7.32 (1H, dd, *J*=1.6 and 7.1 Hz), and 8.60 ppm (1H, s). *Anal*. Calcd for $C_{17}H_{29}NOS$: C, 69.10; H, 9.89; N, 4.74%. Found: C, 69.21; H, 10.08; N, 4.86%.

General synthetic procedure for zinc(II) Complexes

A typical example: bis(1,2-dihydro-1-methyl-2-thioxo-3-pyridinolato)zinc(II) complex (4a). A solution of $Zn(OAc)_2$ (155 mg, 0.708 mmol) in H_2O/EtOH (1:1) mixture (7.2 mL) was added to a solution of **3a** (200 mg, 1.41 mmol) in H_2O/EtOH (1:2) mixture (20 mL). The reaction mixture was stirred for 5 h at rt, and then the precipitate was filtrated off. Drying *in vacuo* over anhydrous P_2O_5 gave the product **4a** as white solids. Yield: 240 mg (83%); mp 355 °C (decomp.); IR (KBr): 3100, 3044, 1591, 1547, 1457, 1396, 1123, 760 and 705 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 4.13 (3H, s), 6.84 (1H, dd, *J*=6.1

and 8.0 Hz), 7.06 (1H, dd, *J*=0.7 and 8.0 Hz), and 7.22 ppm (1H, dd, *J*=0.7 and 6.1 Hz). *Anal.* Calcd for $C_{12}H_{12}N_2O_2S_2Zn \cdot 0.8H_2O$: C, 40.02; H, 3.81; N, 7.78%. Found: C, 39.91; H, 3.92; N, 7.61%. MALDI-TOF MS (*m/z*): 344.96 $[M+H]^+$.

Bis(1,2-dihydro-1-ethyl-2-thioxo-3-pyridinolato)zinc(II) complex (4b): as pale yellow solids; yield: quant.; mp 205 °C (decomp.); IR (KBr): 3089, 2974, 1590, 1536, 1437, 1127, 769 and 715 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.58 (3H, t, *J*=7.2 Hz), 4.61 (2H, q, *J*=7.2 Hz), 6.86 (1H, dd, *J*=6.1 and 8.3 Hz), 7.06 (1H, dd, *J*=1.2 and 8.3 Hz), and 7.21 ppm (1H, dd, *J*=1.2 and 6.1 Hz). *Anal*. Calcd for $C_{14}H_{16}N_2O_2S_2Zn \cdot 0.8H_2O$: C, 43.31; H, 4.57; N, 7.22%. Found: C, 43.18; H, 4.61; N, 7.12%. MALDI-TOF MS (*m/z*): 373.81 $[M+H]^+$.

Bis(1,2-dihydro-1-propyl-2-thioxo-3-pyridinolato)zinc(II) complex (4c): as white solids; yield: 98%; mp 243°C (decomp.); IR (KBr): 3046, 2872, 1590, 1542, 1437, 1135, 781 and 716 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 1.02 (3H, t, *J*=7.4 Hz), 2.06 (2H, sext, *J*=7.6 Hz), 4.50 (2H, t, *J*=7.6 Hz), 6.84 (1H, dd, *J*=6.1 and 8.2 Hz), 7.06 (1H, dd, *J*=1.2 and 8.2 Hz), and 7.18 ppm (1H, dd, *J*=1.2 and 6.1 Hz). *Anal*. Calcd for $C_{16}H_{20}N_2O_2S_2Zn \cdot 0.5H_2O$: C, 46.77; H, 5.15; N, 6.82%. Found: C, 46.78; H, 4.97; N, 6.84%. MALDI-TOF MS (*m/z*): 401.07 $[M+H]^+$.

Bis(1,2-dihydro-1-butyl-2-thioxo-3-pyridinolato)zinc(II) complex (4d): as white solids; yield: 92%; mp 106 °C (decomp.); IR (KBr): 3073, 2958, 2932, 1628, 1545, 1472, 1429, 1283, 1138, 769 and 713 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.99 (3H, t, *J*=7.3 Hz), 1.43 (2H, sext, *J*=7.3 Hz), 1.99 (2H, quint, *J*=7.3 Hz), 4.53 (2H, t, *J*=7.6 Hz), 6.84 (1H, dd, *J*=6.2 and 8.2 Hz), 7.04 (1H, dd, *J*=1.2 and 8.2 Hz), and 7.17 ppm (1H, dd, *J*=1.2 and 6.2 Hz). *Anal*. Calcd for $C_{18}H_{24}N_2O_2S_2Zn \cdot 0.5H_2O$: C, 49.26; H, 5.74; N, 6.38%. Found: C, 49.29; H, 5.82; N, 6.32%. MALDI-TOF MS (*m/z*): 428.98 $[M+H]^+$.

Bis(1,2-dihydro-1-benzyl-2-thioxo-3-pyridinolato)zinc(II) complex (4e): as white solids; yield: 98%; mp 232 °C (decomp.); IR (KBr): 3072, 3032, 1590, 1544, 1438, 1116, 767 and 697 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 5.79 (2H, s), 6.85 (1H, dd, *J*=6.0 and 8.2 Hz), 7.07 (1H, dd, *J*=1.2 and 8.2 Hz), 7.21 (1H, dd, *J*=1.2 and 6.0 Hz), and 7.27-7.39 ppm (5H, m). *Anal.* Calcd for $C_{24}H_{20}N_2O_2S_2Zn$: C, 57.89; H, 4.05; N, 5.63%. Found: C, 57.86; H, 3.90; N, 5.60%. MALDI-TOF MS (*m/z*): 497.09 $[M+H]^+$.

Bis(1,2-dihydro-1-phenethyl-2-thioxo-3-pyridinolato)zinc(II) complex (4f): as white solids; yield: 97%; mp 247 °C (decomp.); IR (KBr): 3096, 3024, 1592, 1537, 1492, 1113, 773 and 702 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 3.33 (2H, t, *J*=7.4 Hz), 4.75 (2H, t, *J*=7.4 Hz), 6.73 (1H, dd, *J*=6.1 and 8.3 Hz), 6.89 (1H, dd, *J*=0.96 and 6.1 Hz), 7.08 (1H, dd, *J*=0.96 and 8.3 Hz), and 7.17-7.32 ppm (5H, m). *Anal*. Calcd for $C_{26}H_{24}N_2O_2S_2Zn$: C, 59.37; H, 4.60; N, 5.33%. Found: C, 59.41; H, 4.35; N, 5.30%. MALDI-TOF MS (*m/z*): 525.18 $[M+H]^+$.

Bis(1,2-dihydro-1-phenylpropyl-2-thioxo-3-pyridinolato)zinc(II) complex (4g): as white solids; yield: 88%; mp 80 °C (decomp.); IR (KBr): 3024, 2926, 1589, 1539, 1494, 1115, 750 and 700 cm^{-1}; ^{1}H-NMR (δ,

$CDCl_3$, 400 MHz): 2.36 (2H, quint, *J*=7.5 Hz), 2.76 (2H, t, *J*=7.5 Hz), 4.53 (2H, t, *J*=7.6 Hz), 6.83 (1H, dd, *J*=6.3 and 7.5 Hz), 7.05 (1H, dd, *J*=1.0 and 7.5 Hz), 7.11 (1H, dd, *J*=1.0 and 6.3 Hz), and 7.22-7.33 ppm (6H, m). *Anal*. Calcd for $C_{28}H_{28}N_2O_2S_2Zn \cdot 0.5H_2O$: C; 59.73, H; 5.19, N; 4.98%. Found: C; 59.78, H; 5.09, N; 4.96%. MALDI-TOF MS (*m/z*): 553.09 $[M+H]^+$.

Bis(1,2-dihydro-1-dodecyl-2-thioxo-3-pyridinolato)zinc(II) complex (4h): as pale yellow solids; yield: 93%; IR (KBr): 3090, 2923, 1590, 1537, 1436, 1123, 769 and 710 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, 400 MHz): 0.88 (3H, t, *J*=7.3 Hz), 1.25 (20H, m), 4.51 (3H, t, *J*=7.3 Hz), 6.83 (1H, dd, *J*=7.1 and 7.6 Hz), 7.04 (1H, dd, *J*=1.6 and 7.6 Hz), and 7.17 ppm (1H, dd, *J*=1.6 and 7.1 Hz). *Anal*. Calcd for $C_{34}H_{56}N_2O_2S_2Zn \cdot 2.5H_2O$: C, 58.39; H, 8.79; N, 4.01%. Found: C, 58.24; H, 8.63; N, 4.12%. MALDI-TOF MS (*m/z*): 651.66 $[M]^+$.

General synthetic procedure for vanadyl complexes

A typical example: bis(1,2-dihydro-1-methyl-2-thioxo-3-pyridinolato)oxovanadium(IV) complex (5a). A solution of **3a** (252 mg, 1.78 mmol) in H_2O (10 mL) was dissolved by adding 10M KOH. Then a solution of $VOSO_4 \cdot 3H_2O$ (194 mg, 0.89 mmol) in H_2O (2 mL) was added to the solution. The mixture was adjusted to pH 10 with 6M HCl, and then the reaction mixture was stirred for 48 h at rt. The resulting precipitate was collected by filtration, washed with H_2O, and dried over anhydrous P_2O_5 *in vacuo* to give the product **5a** as brown solids. Yield: 144 mg (47%); IR (KBr): 3092, 1594, 1541, 1456, 1413, 1128, 967, 778 and 671 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.975, $g_{//}$=1.959, $g_{\perp}$=1.983, A_0=85 x 10^{-4} cm^{-1}, $A_{//}$=160 x 10^{-4} cm^{-1}, $A_{\perp}$=48 x 10^{-4} cm^{-1}. *Anal*. Calcd for $C_{12}H_{12}N_2O_3S_2V$: C, 41.50; H, 3.48; N, 8.07%. Found: C, 41.67; H, 3.35; N, 8.07%. MALDI- TOF MS (*m/z*): 346.92 $[M]^+$.

Bis(1,2-dihydro-1-ethyl-2-thioxo-3-pyridinolato)oxovanadium(IV) complex (5b): as brown solids; yield: 53%; IR (KBr): 3093, 1594, 1542, 1427, 1119, 973, 772 and 670 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.977, $g_{//}$=1.959, $g_{\perp}$=1.986, A_0=83 x 10^{-4} cm^{-1}, $A_{//}$=155 x 10^{-4} cm^{-1}, $A_{\perp}$=47 x 10^{-4} cm^{-1}. *Anal*. Calcd for $C_{14}H_{16}N_2O_3S_2V \cdot 0.2H_2O$: C, 44.37; H, 4.36; N, 7.39%. Found: C, 44.29; H, 4.31; N, 7.40%. MALDI- TOF MS (*m/z*): 374.93 $[M]^+$.

Bis(1,2-dihydro-1-propyl-2-thioxo-3-pyridinolato)oxovanadium(IV) complex (5c): as brown solids; yield: 43%; IR (KBr): 3092, 1592, 1544, 1424, 1112, 971, 791 and 680 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.979, $g_{//}$=1.913, $g_{\perp}$=2.001, A_0=80 x 10^{-4} cm^{-1}, $A_{//}$=83 x 10^{-4} cm^{-1}, $A_{\perp}$=79 x 10^{-4} cm^{-1}. *Anal*. Calcd for $C_{16}H_{20}N_2O_3S_2V$: C, 47.64; H, 5.00; N, 6.94 %. Found: C, 47.81; H, 5.06; N, 6.92 %. MALDI-TOF MS (*m/z*): 403.00 $[M]^+$.

Bis(1,2-dihydro-1-buthyl-2-thioxo-3-pyridinolato)oxovanadium(IV) complex (5d): as brown solids; yield: 73%; IR (KBr): 2955, 2930, 1592, 1543, 1436, 1115, 970, 792 and 720 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.977, $g_{//}$=1.936, $g_{\perp}$=1.997, A_0=80 x 10^{-4} cm^{-1}, $A_{//}$=102 x 10^{-4} cm^{-1}, $A_{\perp}$=69 x 10^{-4} cm^{-1}.

Anal. Calcd for $C_{18}H_{24}N_2O_3S_2V$: C, 50.11; H, 5.61; N, 6.49%. Found: C, 50.21; H, 5.53; N, 6.43%. MALDI-TOF MS (*m/z*): 431.00 $[M]^+$.

Bis(1,2-dihydro-1-benzyl-2-thioxo-3-pyridinolato)oxovanadium(IV) complex (5e): as brown solids; yield: 82%; IR (KBr): 3026, 2939, 1591, 1542, 1456, 1119, 975, 776, 720 and 679 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.989, $g_{//}$=1.958, $g_{\perp}$=2.004, A_0=83 x 10^{-4} cm^{-1}, $A_{//}$=162 x 10^{-4} cm^{-1}, $A_{\perp}$=44 x 10^{-4} cm^{-1}. *Anal*. Calcd for $C_{24}H_{20}N_2O_3S_2V$: C, 57.71; H, 4.04; N, 5.61%. Found: C, 58.05; H, 3.97; N, 5.71%. MALDI- TOF MS (*m/z*): 498.51 $[M]^+$.

Bis(1,2-dihydro-1-phenethyl-2-thioxo-3-pyridinolato)oxovanadium (IV) complex (5f): as brown solids; yield: 60%; IR (KBr): 3093, 3028, 1595, 1541, 1435, 1117, 974, 750 and 700 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.985, $g_{//}$=1.963, $g_{\perp}$=1.997, A_0=83 x 10^{-4} cm^{-1}, $A_{//}$=155 x 10^{-4} cm^{-1}, $A_{\perp}$=47 x 10^{-4} cm^{-1}. *Anal.* Calcd for $C_{26}H_{24}N_2O_3S_2V$: C; 59.19, H; 4.59, N; 5.31%. Found: C; 59.45, H; 4.48, N; 5.31%. MALDI- TOF MS (*m/z*): 526.94 $[M]^+$.

Bis(1,2-dihydro-1-phenylpropyl-2-thioxo-3-pyridinolato)oxovanadium (IV) complex (5g): as brown solids; yield: 92%; IR (KBr): 3022, 2943, 1593, 1542, 1424, 1118, 970, 773 and 699 cm^{-1}. ESR parameters in DMSO at 77K: g_0=1.985, $g_{//}$=1.958, $g_{\perp}$=1.999, A_0=78 x 10^{-4} cm^{-1}, $A_{//}$=159 x 10^{-4} cm^{-1}, $A_{\perp}$=37 x 10^{-4} cm^{-1}. *Anal*. Calcd for $C_{28}H_{28}N_2O_3S_2V$: C; 60.53, H; 5.08, N; 5.04%. Found: C; 60.80, H; 5.14, N; 5.02%. MALDI- TOF MS (*m/z*): 555.12 $[M]^+$.

The p*Ka* measurement of compound 3b

A solution of compound **3b** (30 mg, 0.19 mmol) in H_2O (25mL) was titrated with 25 mM-NaOH solution at rt under Ar atmosphere. The p*Ka* was calculated to be 9.4 from the pH at midpoint of neutralization.

Measurement of the partition coefficient

To a solution of sample (5 mL) in KRB buffer solution (120 mM NaCl, 1.27 mM $CaCl_2$, 1.2 mM $MgSO_4$, 4.75 mM KCl, 1.2 mM KH_2PO_4, 24 mM $NaHCO_3$ and 5 mM glucose: pH 7.4) was added octanol (5 mL). The mixture was stirred at 600 rpm for 4 h with a magnetic stirrer, and then centrifuged at 4000 rpm for 20 min with a centrifugal separator. The concentrations of two phases were calculated using UV-vis spectral data. The partition coefficient was calculated from the following equation; $\log P_{ow} = \log(C_{octanol}/C_{buffer})$.

Evaluation of the inhibitory effect of the metal complexes on FFA release from rat adipocytes

Male Wistar rats, whose the age is 7 weeks, were killed by decapitation under anesthesia with Et_2O, and adipocytes were isolated from epididymal fat pads. Fat tissues were incubated for 1 h at 37ºC in KRB buffer (120 mM NaCl, 1.27 mM $CaCl_2 \cdot 2H_2O$, 1.20 mM $MgSO_4$, 4.75 mM KCl, 1.20 mM KH_2PO_4, and 24 mM $NaHCO_3$: pH 7.4) containing collagenase and 2% bovine serm albumin (BSA). Adipocytes were then separated by filtration through mesh, washed three times with the above buffer, and prepared

for 240 μL (2.5 x 10^6 cells/mL). Isolated adipocyte solutions were preincubated at 37ºC for 0.5 h with various concentrations of the metal complexes in DMSO containing 5 mM glucose. Then 10 μM epinephrine was added to the reaction mixtures and the resulting solutions were incubated at 37ºC for 3 h. The reactions were stopped by soaking in ice water and the mixtures were centrifuged at 3000 rpm at 4ºC for 10 min. For the outer solution of the cells, FFA levels were determined with an NEFA C-test Wako (Wako Pure Chemicals, Osaka, Japan).

ACKNOWLEDGEMENTS

This work was partially supported by Grants-in-Aid for Scientific Research C (No. 21550068) from the Japan Society for the Promotion of Science.

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