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ARTICLE

Novels Anti-Diabetic and Luminescence Coordination Compounds based on Vanadium

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Belén Fernández,[a,*] Alejandro Gómez-Vílchez,[a,b] Cristina Sánchez González,[b,*] Jakelhyne Bayón,[a,b] Eider San Sebastián,[c] Santiago Gómez-Ruiz,[d] Carlos López Chaves,[b] Pilar Aranda,[b] Juan Llopis [b] and Antonio Rodríguez-Diéguez [a,*]

We have designed and synthesized two novel vanadium coordination compounds using 1H-benzimidazole-2-carboxylic acid and 5-aminopyridine-2-carboxylic acid. These two materials exhibit a mononuclear structure with crystallization water molecules in the network. Both compounds exhibit intense photoluminescence emission at room temperature in the solid state and show in vivo antidiabetic activities together with low in vitro cell toxicities. Luminescence theoretical studies have been performed.

INTRODUCTION

Several pharmacological treatments are currently used for diabetes treatment, but there is a growing interest by the scientific community in the development of new drugs that improve treatment efficacy, mainly, showing minor adverse reactions and using different administration routes. Each class of drug has different mechanisms of action. Given that commonly used drugs are associated with several adverse effects, it is of great interest to search for new drugs that can fight this disease effectively with minimal side effects.[1] Recent studies aim to develop new drugs that can be administered orally for the treatment of diabetes.[2] Recently, we have shown that it is possible to synthesize new coordination compounds, with fascinating structures and interesting physical and antiparasital properties, by combining transition metal ions with the 1,2,4-triazolo[1,5-a] pyrimidine ligand (tp) and several pseudohalide auxiliary spacers.[3] More concretely, we have designed Zn based compounds with potential interest in the treatment of diabetes, pathology where Zn compounds have shown promising hypoglycemic properties.[4-11] Moreover, it´s interesting combining insulinmimetic and luminescence properties and synthesizing multifunctional materials. Other materials based on different metal ions as vanadium compounds have shown substantial promise as hypoglycemic agents for the pharmacotherapy of diabetes.[5] Diabetes mellitus is a chronic disease occurring when the pancreas does not produce enough insulin (type I) or when the body cannot effectively use the insulin it produces (type II). Hyperglycemia, is a common effect of uncontrolled diabetes and over time leads to serious damage of several body systems.[6] Some metal ions have shown insulin-like effects by supporting the signal transduction of insulin and by reducing the production of cytokines, triggering a cascade of events leading to beta-cell death during the pancreatic inflammatory process in the course of the disease. Antibodies against this zinc transporter have been detected in type I diabetic patients.[7] Coordination compounds have demonstrated to inhibit the protein-tyrosine phosphatase 1B (PTP1B), enzyme that plays a major role in modulating both insulin sensitivity and fuel metabolism.[8] The design of these novel materials based on metal ions could be an excellent tool to improve the distribution, and therefore, the effectiveness of metals as oral antidiabetic agent in the treatment of diabetes mellitus, showing as an alternative (or synergistic agent) to traditional parenteral insulin therapy. For these reasons, the milestone that we propose in this paper is to synthesize novel vanadium mononuclear coordination compounds with potential antidiabetic activity and, at the same time, exhibiting less side effects. A really relevant advantage of these compounds, is that could show luminescent properties that would allow monitoring drug levels in samples of diabetic patients. Here, we present two novel coordination compounds $[VO(HBIC)_2(H_2O)](H_2O)_4$ (**1**) and $[VO(AMPICA)_2(H_2O)]$ $(H_2O)_4$ (**2**) (H_2BIC = 1H-benzimidazole-2-carboxylic acid and *HAMPICA* = 5-aminopyridine-2-carboxylic acid) synthesized using derivative nitrogen ligands that possesses one carboxylate group and

[a] Departamento de Química Inorgánica, Universidad de Granada, Avda. Fuentenueva s/n, 18071, Granada, Spain. email: belenfernandez@ugr.es and antonio5@ugr.es
[b] Instituto de Nutrición y Tecnología de los Alimentos y Departamento de Fisiología, Campus Cartuja, Universidad de Granada, 18071, Granada, Spain. email:crissg@ugr.es
[c] Departamento de Química Aplicada, Facultad de Químicas de San Sebastián, Euskal HerrikoUnibertsitatea UPV/EHU, Paseo Manuel de Lardizabal 3, 20018, San Sebastián, Spain.
[d] Departamento de Biología y Geología, física y Química Inorgánica, E.S.C.E.T., Universidad Rey Juan Carlos, c/ Tulipán s/n, 28933 Móstoles, Spain.
Electronic Supplementary Information (ESI) available: [CCDC 1431965 and 1431966contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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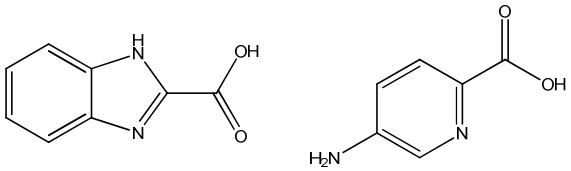
vanadium sulphate to enhance hydrogen bonding interactions in the structure, and in this form, the compounds are soluble in water. These compounds exhibit an intense photoluminescence emissions at room temperature in the solid state. *In vitro* results indicate the absence of toxicity of both compounds and *in vivo* experiments show clear antidiabetic effects, especially in compound **1**, reducing the peaks of hyperglycemia of diabetic rats.



Scheme 1. Ligands used in the formation of coordination compounds. Left, 1H-benzimidazole-2-carboxylic acid. Right, 5-aminopyridine-2-carboxylic acid.

RESULTS AND DISCUSSION

Convectional reaction of vanadium sulphate (1 mmol) with 1H-benzimidazole-2-carboxylic acid (2 mmol) and 5-aminopyridine-2-carboxylic acid in water (20 ml) at room temperature for 36 h produced prismatic grey-blue crystals of **1** and **2**, respectively in 65% and 45% yields. The crystal structures were determined using single crystal X-ray crystallography. These coordination compounds **1** and **2** show a hexa-coordinated cis-octahedral geometry, similar to other compounds reported in the literature based on picolinic, 5-carbomethoxypicolinic, 5-carboisopropoxypicolinic and imidizole-4-carboxylic acid.[9,20]

Description of the structures.

Compound **1** crystallizes in the triclinic space group *P-1*. The asymmetric unit consisting of one vanadium, two *HBIC*$^{-1}$ ligands, one *oxo* group, one water coordination molecule and four crystallization coordination molecules. Vanadium ion exhibits distorted octahedral VN_2O_4 geometry (Figure 1) with the N1A and N1B nitrogen atoms belonging to aromatic groups of two different anionic ligands in *cis* positions, and four oxygen atoms pertaining to two different carboxylate groups, one *oxo* and one water molecule. V-N distances have values of 2.0852(11) and 2.0957(10) Å, whereas V-O distances are in the range 2.0219(9)-2.24004(9) Å, highlighting the short distance 1.5926(9) Å between the vanadium atom and the *oxo* group. *Cis* and *trans* bond angles of metal environment are in the range of 74.57(4)-108.21(4) º and 154.28(4)-169.12(4) º, respectively. Each *bimca*$^{-1}$ ligand connects with the metal ion through O1 and N1 in a quelate coordination mode, resulting in the formation of mononuclear units in which entities are connected by a very complex hydrogen bond network. These hydrogen bonds involve all nitrogen and oxygen atoms present in the structure. The H-bond distances are in the range 2.576(1)-3.029(1) Å, highlighting the strong hydrogen interaction between the water molecules O1W and O2W with a value of 2.576(1) Å.

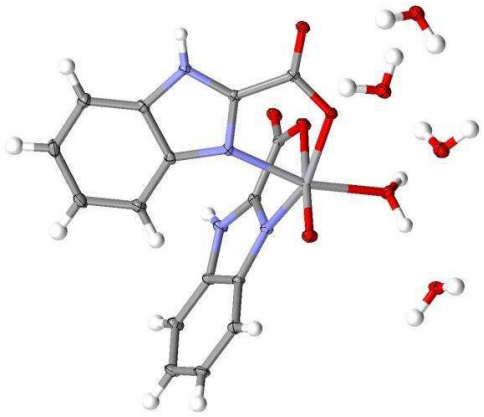


Figure 1. Perspective view of the mononuclear entity of compound **1**. Thermal ellipsoids are drawn at the 50% probability level. Color code: N = blue, O = red, C = grey, V = grey-blue.

Compound **2** crystallizes in the monoclinic space group *P21/c*. The asymmetric unit consisting of one vanadium, two *ampyca*$^{-1}$ ligands, one *oxo* group, one water coordination molecule and four crystallization coordination molecules. In this case, again vanadium ion exhibits distorted octahedral VN_2O_4 geometry (Figure 2) with the N1A and N1B nitrogen atoms belonging to pyridine groups of two different ligands in *cis* positions, and four oxygen atoms pertaining to two different carboxylate groups, one *oxo* and one water molecule. V-N distances have values of 2.1068(13) and 2.1350(13) Å, whereas V-O distances are in the range 1.9887(11)-2.1571(11) Å, highlighting the short distance 1.6019(11) Å between the vanadium atom and the *oxo* group. *Cis* and *trans* bond angles of metal environment are in the range of 74.51(5)-105.85(5) º and 159.65(5)-165.57(5) º, respectively. Each *ampyca*$^{-1}$ ligand connects with the metal ion through O1 and N1 in a quelate coordination mode, resulting in the formation of mononuclear units in which entities are united by a very complex hydrogen bond network. These hydrogen bonds involve all nitrogen and oxygen atoms present in the structure. The H-bond distances are in the range 2.623(2)-3.024(2) Å.

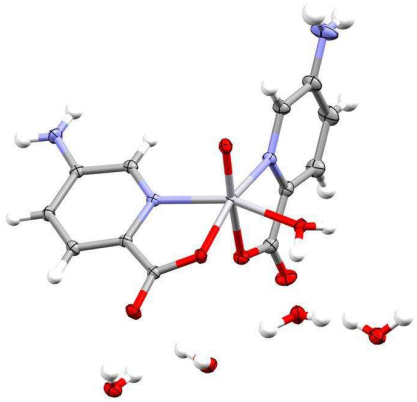


Figure 2. Perspective view of the mononuclear entity of compound **2**. Thermal ellipsoids are drawn at the 50% probability level. Color code: N = blue, O = red, C = grey, V = grey-blue.

Luminescence Studies.

The extended aromaticity of these anionic ligands coordinated with the vanadium centers suggests the existence of enhanced emissive properties in **1** and **2**. Complexes based on metals ions with aromatic ligands can show excellent luminescent properties, and therefore have received great attention for chemical sensing, photochemistry and electroluminescence applications.[10] Figure 3 shows the emission spectra of compound **1** and **2** in solid state at room temperature upon excitation at 322 nm. **1** exhibits a broad intense emission bands centered at 358 and 380 nm, respectively. On the other hand, **2** exhibits one unique intense emission band at 486 nm.

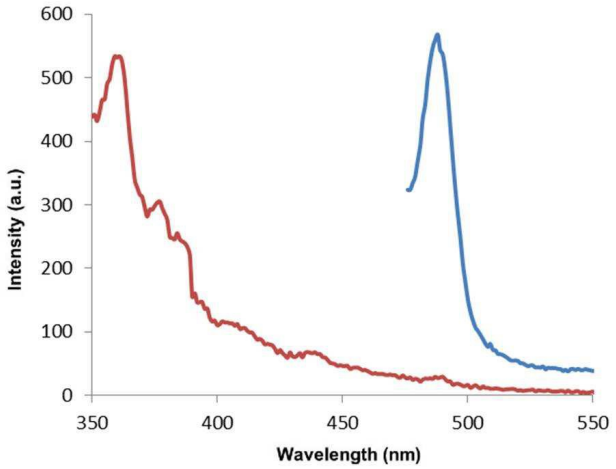


Figure 3. Emission spectra of compound **1** (blue line) and **2** (red line) at room temperature in the solid state.

The H_2BIC ligand has been studied by *Xia et al.* previously.[11] The emission in compounds can be tentatively assigned to a metal to ligand charge transfer (MLCT) and/or to a ligand to ligand charge transfer (LLCT). The emission of **1** is significantly shifted compared to that of the isolated ligand. This fact may be due to V having higher d* energy levels, which is consistent with similar bathochromic shifts that have been observed in other compounds.[12]

Theoretical absorption and emission spectra of free $HBIC^{-1}$ and $AMPICA^{-1}$ ligands (see ESI table S1, Figure S1 and Figure S2), as well as of complexes **1** and **2,** under covered the nature of the transitions responsible for the luminescence observed in the latter. The calculated emission spectra of $HBIC^{-1}$ and $AMPICA^{-1}$ show a maxima each at 419 and 424 nm, respectively (see Table 1 and Figure S3). The former maxima arises from two main transitions occurring in the free $HBIC^{-1}$ ligand at 415 and 438 nm, respectively, where photons are emitted when electrons relax from π* molecular orbitals delocalized over the entire ligand, to low lying molecular orbitals localized over the carboxylate moiety (see Figure S3, left). The maxima at 424 nm observed in the emission spectrum of the free $AMPICA^{-1}$ ligand, results from three main types of transitions occurring at 414, 421 and 431 nm, respectively, where the nature of the molecular orbitals involved is equivalent to the previously mentioned ones (see Figure S3, right). The calculated data describing the emissive properties of the free $AMPICA^{-1}$ ligand are in very good agreement with the experimental results obtained in the present study.

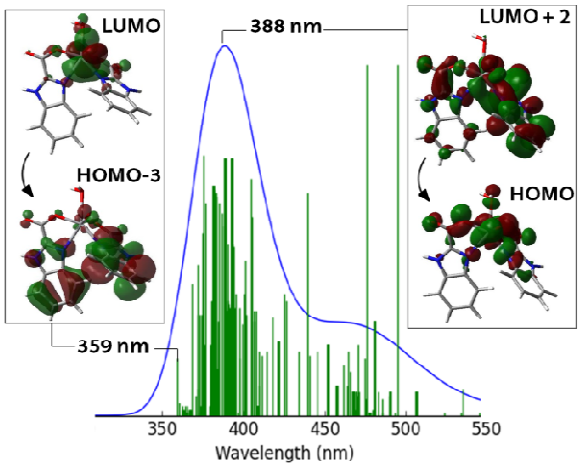


Figure 4. Normalized calculated emission spectra of complex **1**.

The theoretical emission spectrum of complex **1** shows a maximum at 388 nm (Figure 4), arising from electron relaxations from ligand-centered (LUMO+2) to metal centered (HOMO) molecular orbitals, in excellent agreement with the maximum observed experimentally at 380 nm. The relatively more significant maximum observed experimentally at 358 nm is under estimated by our theoretical calculations, which, are nevertheless able to identify a relatively significant transition (oscillator strength: 0,0017) happening at 359 nm, resulting from electron relaxations from metal centered (LUMO) to ligand-centered (HOMO-3) molecular orbitals. In summary, emission properties of complex **1** are derived from MLCT and LMCT charge transfer reactions.

Table 1. Calculated emission bands and involved electronic transitions in Ligands $HBIC^{-1}$ and $AMPICA^{-1}$, and complexes **1** and **2**.

	Emis. Max. λ (nm)	Transitions	Osc. Strength
$HBIC^{-1}$	415	H→ L+3	0.0086
	438	H-1→ L	0.0085
$AMPICA^{-1}$	421	H-1→ L	0.0053
	431	H-1→ L+1	0.009
Complex 1	388	H→ L+2	0.0076
Complex 2	484	H→ L+3	0.0148

The theoretical emission spectrum of complex **2** shows a maximum at 473 nm (Figure 5), arising from distinct electron relaxations occurring in the 400-500 nm range. The most intense transition occurs at 484 nm, and is assigned to electron relaxations from a molecular orbital delocalized all over the complex (LUMO+3), to a molecular orbital delocalized over one of the ligand copies. It is interesting to note that the optimization of the excited states yielded a completely octahedral geometry in the case of complex **1** but not complex **2**, where the axial water molecule adopts a semi equatorial position yielding a distorted octahedral geometry.

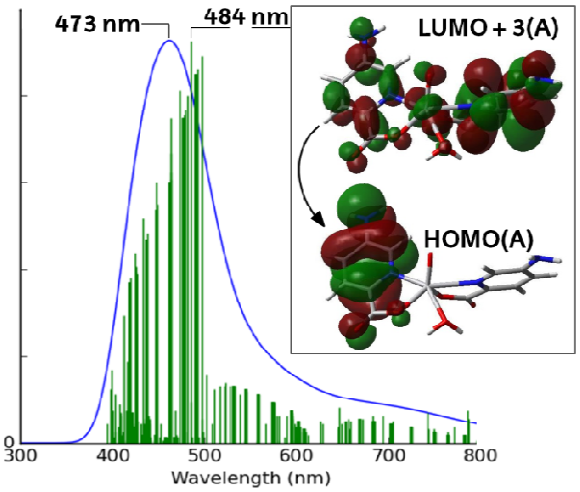


Figure 5. Normalized calculated emission spectra of complex **2**.

Cytotoxicity Studies.

In the current study, the effect of compound **1** and **2** on HEK293 cell viability was determined by using MTS assay (Figure 6). MTS test was used to measure the reduction mitochondrial metabolism, rate of the tetrazolium salt compound MTS (3-(4,5-dimethylthiazol-2- yl)- 5- (3- carboxymethoxy- phenyl)-2-(4-sulfophenyl)-2H tetrazolium) to formazan, correlating with the numbers of living cells. We found that in the presence of the highest concentrations of tested compound **1** (50 and 100 µM), cell proliferation of HEK293 was decreased to 70- 65%, and 60% at 48 and 72h, respectively, compared with the control cells ($P < 0.05$). On the other hand, the compound **2** followed the same tendency that compound **1** but with highest toxicity at 72h. Concretely, the cell proliferation of compound **2** at 72h was decreased to 50 and 40% at the concentration of 50 and 100µM, respectively. At 24h we do not find any significant variation on the cell viability measurements in both compounds tested, **1** and **2**.

Importantly, we demonstrated that compounds **1** and **2** have a significantly low cytotoxicity, thereby providing a rationale clinical use these kind of compounds as promising antidiabetic agents.

Our results on toxicity support those obtained *in vitro* by Rehder and co-workers in a study of many V(IV) compounds, who demonstrated that no toxicity is usually observed for concentration lower than 1 mM.[13] Moreover, our research team observed *in vivo*, the presence of gastrointestinal disorders at the dose of 5 mgV/Kg b.w./day.[14]

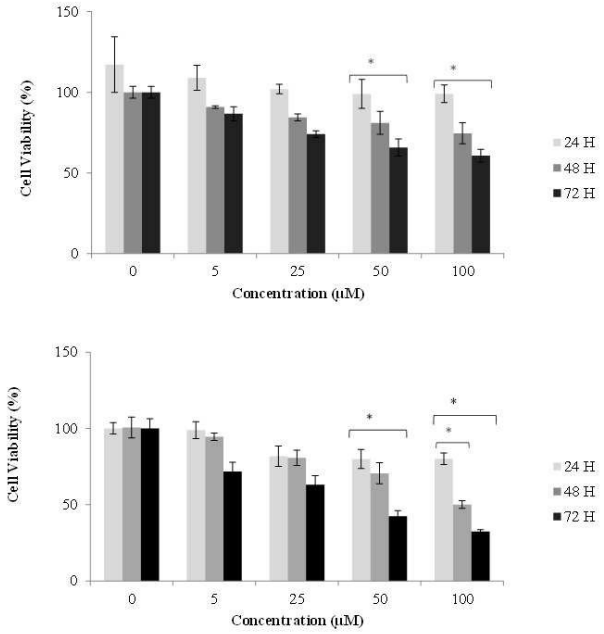


Figure 6. In vitro cytotoxicity of human embryonic kidney cell line HEK293 exposed to various concentrations of compound **1** (up) and **2** (bottom) for 24, 48 and 72 h. Data are means ± S.E.M. (n = 3; *p b 0.05; paired Student's t-test).

***In vivo* studies.**

Since the inorganic V(IV) salts are relatively toxic, a major advance in the use of vanadium pharmaceuticals as insulin-mimetic drugs has been the development of a variety of vanadium V(IV) complexes.[5] The main advantage of such species over direct insulin treatments is that they can be administrated orally and absorbed in the gastrointestinal tract.[15] Additionally, it has been known that the V complex, bis(maltolato)oxidovanadium (IV) (BMOV), is more effective as a glucose-lowering agent and less toxic than inorganic V.[16] In order to study the postprandial effect of the compounds 1 and 2 (mimicking the same administration pattern than the insulin), the oral glucose tolerance test (OGTT) was performed 1h after a single oral dose of the compound **1** or **2** (or the equivalent volume of water in cases of untreated groups of rats). The results obtained in the oral glucose tolerance test OGTT (Figure 7) showed that compound **1** caused a significant decrease in fasting blood glucose level after 30 minutes, despite the high fasting glucose levels presenting the diabetic rats under study. Moreover, 120 min after oral glucose load, compound **1** restored blood glucose levels to those found in basal conditions. These results are similar to those obtained after the administration of bis(allixinato)oxidovanadium(IV).[17] With this last compound, blood glucose level was also restored 2h after oral glucose load. However, according with this reasoning, the

compounds vanadylacetylacetonate, vanadyl 3-athylacetylacetonate, bis(maltolato) oxidovanadium and vanadyl sulphate showed worse effects, as failed to restore the baseline glycemia until 3 hours after the oral glucose load.[18] This effect shown by the compound **1**, subject of the present study, is beneficial in controlling diabetic patient, as it would reduce the undesirable effects of hyperglycemia and the formation of AGE (advanced glucose end products). However, the results obtained in the OGTT (Figure 7) for compound **2**, shown that this compound only caused a slight and not significant drop in blood glucose levels. The magnitude of this effect does not justify its use as a therapeutic agent in the diabetic patient. However, as previous publications have suggested that compound based on both ligands and vanadium itself possesses antineoplastic effects,[19] further experiments will be conducted by our team in the near future.

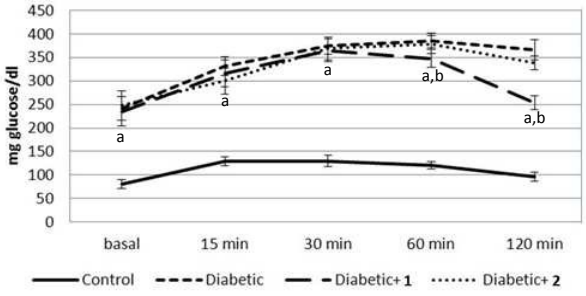


Figure 7. Oral glucose tolerance test for control, diabetic and diabetic rats treated with compound 1 or 2 after 10 days of treatment. Data are mean ± SD. a: different from Control; b: different from Diabetic. c: different from Diabetic+1. $p<0.05$.

The results obtained on the insulin mimetic properties of compounds **1** and **2** in this paper, are in concordance with those obtained in vitro (on fibroblasts and adipocytes) by Rehder and co-workers[19] and in vivo (in STZ-diabetic rats) by Sakurai and co-workers[20] Both groups deepened in the study of the pharmacological effects of various picolinic acid derivates complexes of vanadium (IV), finding very interesting insulin mimetic properties relating to the metabolism not only of the glucose but also of the lipids.[20,21,22]

It should be noted that certain biological or chemical changes may occur once the V compounds enter biological systems. Changes may occur in both the gut and the internal environment. Thus, the pharmacological activity would be attributable to the species generated and not the original molecule orally administered. Several authors have explored this topic, conducting studies of speciation. Particularly relevant are the studies *in vitro* performed by Santos et al, 2014; Kolesa-Dobravc et al, 2014 Jakusch et al, 2009 and *in vivo* by Gonzalez-Iglesias et al, 2012. Pessoa and co-workers determined the interaction of [VO(picolinato)2(H2O)] with lysozyme and showed that an Asp residue replaces the water molecule in the equatorial position[23]. Also F. Perdih and co-workers studied the interaction of picolinate derivatives with transferrin and albumin and showed that under physiological conditions these species can undergo speciation processes.[24] Jakusch and co-workers evaluated the ex vivo interactions of the V(IV)O complexes formed with maltol, picolinic acid and 1,2-dimethyl-3-hydroxy-4(1H)-pyridinonewith serum protein standards and also with human serum samples. The speciation studies were performed by means of HPLC-ICP-MS. All the studied V(IV)O compounds displayed similar chromatographic profiles, associated almost exclusively with apotransferrin as predicted by the modeling calculations. Under physiological conditions, the interactions with HSA of all of the species under study were negligible. Therefore transferrin seems to be the main V(IV)O transporter in the serum under in vitro conditions, and this association is practically independent of the chemical form in which V(IV)O is administered.[2d] Meanwhile, Iglesias-Gonzalez et al confirmed *in vivo* the above *in vitro* findings. Following the administration of BMOV, and by mean of speciation studies conducted by HPLC-ICP-MS, it was found that orally administered V binds to transferrin as single transport protein in serum.[2a]

CONCLUSIONS

In summary, we have designed and synthesized two novel vanadium coordination compounds. These coordination compounds exhibit mononuclear structures with intense photoluminescence emission at room temperature in the solid state. Theoretical studies revealed that emission properties of complexes are derived from MLCT and LMCT charge transfer reactions. The vanadium compounds designed in these studies exhibited *in vivo* antidiabetic postprandial activity together with low *in vitro* cell toxicity. With the above, the combination of the luminescence response and potential anti-diabetic activity of the compounds could signify their utility as multi-functional materials in biomedical applications.

MATERIALS AND METHODS

Materials and physical measurements

All reagents were obtained from commercial sources and used as received. Thermal stability of **1** was determined by simultaneous thermogravimetry and derivative thermogravimetry analyses (TGA/DTG under a nitrogen atmosphere with an N2 flow of 100 mL min−1at a heating rate of 5 °C min−1up to 900 °C, using a TA Instruments TGA 2950 apparatus. Elemental (C, H, and N) analyses were performed on a Leco CHNS-932 microanalyzer. IR spectra were recorded in the region 400–4000 cm−1 on a Nicolet 6700 FTIR spectrophotometer with samples as KBr disks.

Synthesis of compound $[VO(HBIC)_2(H_2O)](H_2O)_4$ (1).

An aqueous solution of vanadium sulphate (1 mmol) was slowly added to a solution of 1H-benzimidazole-2-carboxylic acid (2 mmol) in water (30 ml) with continuous stirring. The resulting blue solution was kept at room temperature for three days and provided well-developed blue crystals of **1**, which were filtered off and air dried; yield 35% based on V. Elemental Analysis of $C_{16}H_{20}N_4O_{10}V$, calcd: C, 40.09; N, 11.69; H, 4.21; found: C, 39.87; N, 11.71; H, 4.03.

Synthesis of compound $[VO(AMPICA)_2(H_2O)](H_2O)_4$ (2)

Compound **2** was prepared using the same procedure as for **1**, but with 5-aminopyridine-2-carboxylic acid (2 mmol) giving a resulting brown solution was kept at room temperature for two days and provided well-developed brown crystals of **2**, which were filtered off and air dried; yield 59% based on V. Elemental Analysis of $C_{12}H_{20}N_4O_{10}V$, calcd: C 33.42, H 4.67, N 12.99; found: C 32.91, H 4.57, N 13.09.

Luminescence measurements and calculations.

A Varian Cary-Eclipse fluorescence spectrofluorometer was used to obtain the fluorescence spectra. The spectrofluorometer was equipped with a xenon discharge lamp (peak power equivalent to 75 kW), Czerny–Turner monochromators, and a R-928 photomultiplier tube which is red sensitive (even 900 nm) with manual or automatic voltage controlled using Cary Eclipse software for Windows 95/98/NT system. The photomultiplier detector voltage was 700 V and the instrument excitation and emission slits were set at 5 and 5 nm, respectively.

To understand the origin of the observed emissions, TD-DFT theoretical calculations were performed using the Gaussian 09 package[5] at the B3LYP/6-311++G** level[6], on the isolated anionic $HBIC^{-1}$ and $AMPICA^{-1}$ ligands (see Table 1, and Table S1 and Figure S1 in ESI) as well as complexes **1** and **2** as found on the corresponding x-ray structures (crystallization water molecules were omitted).

Crystallographic refinement and structure solution.

Prismatic crystals for **1** and **2** were mounted on a glass fibre and used for data collection on a Bruker D8 Venture with Photon detector equipped with graphite monochromated *MoKα* radiation (λ=0.71073 Å). The data reduction was performed with the APEX2[25] software and corrected for absorption using SADABS.[26] Crystal structures were solved by direct methods using the SIR97 program[27] and refined by full-matrix least-squares on F^2 including all reflections using anisotropic displacement parameters by means of the WinGX crystallographic package.[28] Generally, anisotropic temperature factors were assigned to all atoms except for hydrogen atoms, which are riding their parent atoms with an isotropic temperature factor arbitrarily chosen as 1.2 times that of the respective parent. Final *R(F)*, $wR(F^2)$ and goodness of fit agreement factors, details on the data collection and analysis can be found in Table 1. CCDC 1431965 and 1431966 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Crystallographic Data for compounds **1** and **2**

Compound	**1**	**2**
chemical formula	$C_{16}H_{20}N_4O_{10}V$	$C_{12}H_{20}N_4O_{10}V$
M/gmol^{-1}	479.30	431.26
T (K)	100	100
λ/Å	0.71073	0.71073
cryst syst	triclinic	monoclinic
space group	*P-1*	*P21/c*
a/ Å	6.7527(2)	9.1728(7)
b/ Å	12.1817(4)	23.781(2)
c/ Å	13.4598(5)	8.3034(7)
α/ °	70.6580(10)	90
β/ °	76.2030(10)	93.4410(10)
σ/ °	86.5320(10)	90
V/ Å^3	1014.35(6)	1808.0(3)
Z	2	4
ρ(g cm-3)	1.569	1.584
μ(mm-1)	0.552	0.609
Unique reflections	20246	11545
R(*int*)	0.023	0.032
GOF on F^2	1.052	1.068
R1 [I > 2*σ*(*I*)] [a]	0.028	0.034
wR2 [I > 2*σ*(*I*)] [a]	0.069	0.089

[a] $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$; $wR(F^2) = [\sum w(F_o^2 - F_c^2)^2/\sum wF^4]^{1/2}$

Cytotoxicity studies.

HEK293 cells (derived from human embryonic kidney) were obtained from Scientific Instrumentation Centre of the University of Granada. HEK293 cells were grown in DMEM medium supplemented with 10% heat inactivated FBS and 50 units penicillin/streptomycin per ml (all from Invitrogen, Basel, Switzerland), at 37°C and 5% CO2 in a fully humidified incubator. HEK293 cells were seeded in 96-well plates (1×103 cells/well) and treated with different concentration of compound **1** (0, 5, 20, 50 and 100 μM) at 24, 48 and 72h. The viability of cells was examined by the use of the MTS [3- (4, 5-dimethylthiazol 2 - yl) - 5 - (3 - carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium] tetrazolium assay according to the manufacturers recommendations (Cell Titer96 Aqueous, Promega, Dübendorf, Switzerland).

***In vivo* studies.**

In vivo experiments were carried out using male Wistar rats weighing 200-250 g (Charles River Laboratories, L'Arbresle,

France) randomly divided into 4 groups of 8 rats: Control group (healthy rats); Untreated diabetic group; Treated diabetic group+1 (received compound 1); Treated diabetic group+2 (received compound 2). The treated diabetic groups received the respective V compound at the dose of 3 mg V/day extemporary prepared in water, administered using oral gavages.

The diabetes was induced in both groups by mean of the intraperitoneal administration of streptozotocin (STZ) as diabetogenic agent at the dose of 55 mg/kg body weight. One week after the STZ administration, animals with a glucose concentration (random glycemia) >200 mg/dl and with symptoms of polyuria, polydipsia, and hyperphagia were considered diabetic. All rats fed a standard diet for rats manufactured by Harlan (Madison, USA) and received distilled drinking water ad libitum.

All the animals were housed from day 0 of the experiment in individual metabolism cages. The cages were located in a well- ventilated, temperature-controlled room (21 ± 2 °C) with relative humidity ranging from 40 to 60%, and a light–dark period of 12h.

The oral glucose tolerance test (OGTT) was performed. For this purpose, D-glucose was dissolved in 0.9% saline solution. After a fasting period of 12h, each rat received an oral load of 1 g D-glucose/kg b.w. through oral gavage. Blood glucose concentration were measured just before (0min) and at 15, 30, 60 and 120 min after the glucose administration. For the determination of the glucose levels, peripheral blood was obtained from the tail vein of the rat. The blood glucose levels were analyzed by the use of a glucometer (Accucheck Aviva, Roche).

All the experiments were carried out in accordance with Directional Guides Related to Animal Housing and Care (European Council Community, 1986) and all procedures were approved by the Animal Experimentation Ethics Committee of the University of Granada.

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Novels Anti-Diabetic and Luminescence Coordination Compounds based on Vanadium

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Novel vanadium coordination compounds have been synthesized. Both compounds exhibit intense photoluminescence emissions and show in vivo antidiabetic activities.