CHEMISTRY
A European Journal

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201902441

Link to VoR: http://dx.doi.org/10.1002/chem.201902441

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Fast, facile and solvent-free dry melt synthesis of oxovanadium(IV) complexes: Simple design with high potency towards cancerous cells

Markus Zegke,[†] Hannah L. M. Spencer and Rianne M. Lord*

Abstract: A range of oxobis(phenyl-1,3-butanedione) vanadium(IV) complexes have been successfully synthesized from cheap starting materials and a simple and solvent-free one-pot dry-melt reaction. This direct, straightforward, fast and alternative approach to inorganic synthesis has the potential for a wide range of applications. Analytical studies confirm their successful synthesis, purity and solid-state coordination, and we report the complexes' uses as potential drug candidates for the treatment of cancer. After a 24-hour incubation of A549 lung carcinoma cells with the compounds, they reveal cytotoxicity values 11-fold greater than cisplatin, and remain non-toxic towards normal cell types. Additionally, the complexes are stable over a range of physiological pH values and show the potential for interactions with BSA.

Solvent-free syntheses have become increasingly important as resource efficient alternatives towards classic synthetic approaches. Such synthetic pathways are highly sought after in the field of drug development as they can eliminate the use of toxic or expensive solvents, minimize waste production and the use of chemical auxiliaries, and can provide cheaper, more efficient and high yielding reaction protocols.[1] The use of solvent-free syntheses has propelled in recent years, and more recently researchers have embarked on mechanochemical techniques for the synthesis of materials,[2–4] MOFs,[5–7] and pharmaceuticals.[8,9] These methods can give quantitative conversions which are analytically pure, with no by-products.[10] However, even when solvent-free reaction conditions are used, the use of solvents in the purification and isolation of the products remains an issue.[11] "Green" alternatives to standard procedures have recently seen high impact[12–14] and we have herein applied these principles of green chemistry towards new drug candidates.[15] Interestingly, dry melt conditions have been used widely in molten salt inorganic syntheses in the preparation of ceramics, semiconductors and carbon nanostructures at high temperatures between 200 and 1000 °C,[16–18] which has further branched out into syntheses in ionic liquids.[19–21] However, this method has only rarely been applied in the field or organic or coordination chemistry,[22–26] where the melt is not ionic, but a low-melting (< 200 °C) covalent ligand. Solvent-free complexation reactions more frequently use mechanochemical methods,[27] and though hot spots of up to 111 °C can be achieved due to deformational heating in mechanochemistry,[28] the overall temperatures of the reactions are relatively low (< 100 °C). In 2006, a melt approach was used for the successful synthesis of catena-phosphorous di-cations $[P_6Ph_4R_4]^{2+}$ (R = Ph, Me) at temperatures between 70 and 125 °C,[29] yet to the best of our knowledge no approach has been undertaken to investigate dry-melt reactions in coordination chemistry for pharmaceutical applications.

Drug design and development has over the past decade been heavily aimed at late transition metals, in particular the platinum group metals, Ru,[30–36] Os,[33,37] Rh[38] and Ir.[34,38,39] The early transition metal compounds are less developed, especially early transition metal coordination compounds, as they have reported issues with isomers and poor formulation.[40] However, studies inspired by vanadium haloperoxidases found in seaweeds and fungi have shown a great potential of vanadium compounds for both biomimetic and non-biomimetic reactivity.[41] It has been shown that vanadium compounds may activate tumor suppressor genes, and arrest the cell-cycle or damage DNA.[42–46] Moreover, vanadium is, with respect to drug design, a metal with high potential as it offers a variety of oxidations states, with V^{3+} (reductive),[47,48] VO^{2+} (stable on air)[49–51] and VO_2^+ (oxidizing)[52] being the three most important oxidation states which can be easily used as potential redox-active prodrugs.[53,54] It is a cheap and abundant metal,[55,56] it has been reported to be present in humans though its role is poorly understood,[57,58] it is not classified as carcinogenic,[59] and has only mild toxicity that can be modulated with an appropriate ligand environment. A drawback of vanadium is the lack of aqueous stability, with the complexes often undergoing rapid hydrolysis and forming a mixture of products.[60] Tshuva *et al.* have recently synthesized vanadium complexes incorporating phenolato ligands which show slow and/or defined hydrolysis to give a single product, with good anticancer properties.[61–63] In 2018, the same research group also highlighted vanadium complexes with nanomolar activities, however, the free ligands were as active as the complexes.[64] More recently, work by Ni et al.[65] and Kowalski et al.[66] has shown new oxidovanadium(IV) complexes which are cytotoxic towards a range of cancerous cell lines, yet have lower potency against normal cell types, which highlights their potential for cancer cell selectivity. All of the complexes suppressed cell proliferation by causing cell cycle arrest either the S- or G_2/M-phase, which gives indications as to the potential mechanistic pathways of the vanadium(IV) species.

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Supporting information for this article is given via a link at the end of the document and contains the experimental details, X-ray crystallographic analysis and data for chemosensitivity assays and stability studies.

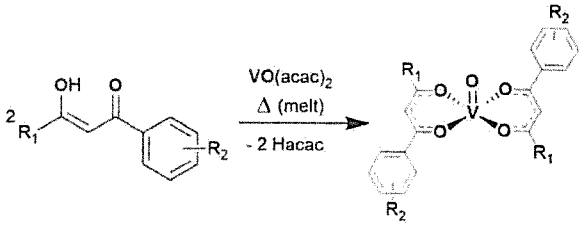
The best known early transition metal drug candidate is Budotitane, $[Ti(bzac)_2(OEt)_2]$ (where bzac = phenyl-1,3-butanedione) which was discovered by Keppler *et al.* The *in vivo* results were promising against a range of transplantable tumors, with no known evidence of mutagenicity, although Phase trials were halted due to formulation issues.[67–69] We have previously functionalized the bzac ligands and the corresponding group IV metal complexes, with promising cytotoxicity against a range of cell lines.[70,71] We report herein the synthesis of vanadium compounds incorporating the functionalized bzac ligands, and describe the first dry-melt method of synthesizing vanadium drug candidates.[11] The reactions do not require expensive equipment and a simple magnetic stirrer-hotplate can be used to complete all reactions in < 5 minutes. Importantly, these compounds require minimal work-up, and are elementally pure after simply heating the dry mixtures and washing with hexane. The compounds were screened against a range of cell lines, and show an increased cytotoxicity when using a simple and symmetrical functionalized diphenyl-1,3-butanedione ligand. After a 24-hour incubation and 72 hour recovery period with human lung carcinoma, A549, the complexes are up to 11-fold more cytotoxic than cisplatin, and remain non-toxic towards normal cell types. Additionally, the compounds are stable over physiological pH range and their compositions remain the same in 0.1% DMSO and 99.9% phosphate buffer solution (PBS), allowing us to confidently determine the nature of the *in vitro* active species. The interactions with bovine serum albumin (BSA) have been studied using UV-vis spectroscopy and indicate a potential interaction with BSA.

Results

Synthesis and characterization of oxobis(phenyl-1,3-butanedione) vanadium(IV)

Complexes **1-9**, $[VO(L)_2]$ (**L** = a functionalized bzac), were synthesized in moderate to high yields, by using a straightforward, rapid and environmentally friendly "green" dry melt synthesis as described in **Scheme 1**. Successful synthesis was achieved by mixing one equivalent of oxobis(acetylacetone) vanadium(IV), $[VO(acac)_2]$, with two equivalents of functionalized bzac ligand (**L**) and heating the mixture to the melt, whilst stirring for ~3-5 minutes. The driving force is the elimination of volatile acetylacetone from the vanadyl precursor, allowing for the straightforward isolation of the products. To ensure complexes were free from any remains of Hacac or potential decomposition products, the compounds were washed with a small amount of hexane and dried overnight prior to cell testing (**Table S1**). Complexes **9** have been previously reported and has been synthesized herein in order to gain structure activity relationships.[72]

Recrystallization of the material by slow evaporation of a hot concentrated DMSO solution yielded single crystals of the DMSO adduct complexes **1-DMSO**, **3-DMSO**, **5-DMSO**, **6-DMSO** and **7-DMSO**, and the DMSO adduct-free complexes **8** and **9**, which were all suitable for X-ray crystallographic analysis (**Table S2** and **S3**). Complex **9** was confirmed to be the same crystal space group as the published literature structure by Schilde et al. and Mohamadi et al.[72,73]



R_1 = CH_3	R_2 = H		**1 (56%)**
CH_3	3-Br		**2 (71%)**
CH_3	3-CF_3		**3 (66%)**
CH_3	4-F		**4 (64%)**
CH_3	4-Cl		**5 (84%)**
CH_3	4-Br		**6 (78%)**
CH_3	4-I		**7 (62%)**
CH_3	4-CF_3		**8 (91%)**
ph	H		**9 (81%)**

Scheme 1 Preparation of functionalised oxobis(phenyl-1,3-butanedione) vanadium(IV) complexes **1-9** by dry melt conditions

Due to a large amount of disorder, the molecular structure for **3-DMSO** is discussed in the *Supporting Information* only (**Figure S1**). Complexes **1-DMSO**, **5-DMSO** and **7-DMSO** show DMSO coordination, in which the DMSO molecule is crystallographically disordered over the two axial sites, resulting in an octahedral V atom, with V···O distances of 1.887(5) Å (**1-DMSO**), 1.896(3) Å (**5-DMSO**) and 1.666(12)/2.136(12) Å (**7-DMSO**) (disorder part A and B, **Table 1**). The inherent crystallographic disorder results in a rectangular coordination environment around the central atom with the equatorial *cis* bond angles similar to those of the axial to equatorial angles, all of which are in the range 86.5(6)° – 93.5(6)° (**Table S4**). Complex **6-DMSO** shows both axial oxygens, however, these are also disordered, and this coupled with the DMSO in the 6th coordinate position gives a lengthened V=O bond distance of 1.645(5) Å (**Table 1**). The structure is a disordered octahedron, with *cis* equatorial and axial to equatorial bond angles ranging from 83.8(2)° – 97.3(3)° (**Table S5**). Complex **8**, is the only structure to show the "classic" V=O motif, with a short bond distances of 1.587(4) Å (**Table 1**), and adopts a distorted square-pyramidal geometry due to the lack of DMSO in the 6th coordinate position. The *cis* equatorial bond angles range from 84.48(14)° – 87.39(14)°, whilst due to the strength of the V=O, the axial to equatorial angles range from 104.87(18)° – 106.28(17)° (**Table S6**). Though the details of complex **3-DMSO** cannot be described meaningfully due to crystallographic disorder, it is interesting to note that this is the only structure in which the bzac ligands are oriented with the functionalized phenyl in a *cis* configuration, while all other complexes have this moiety in a *trans* arrangement (**Figure S1** and **Table S5-6**). Further confirmation of the integrity of the material has been obtained by the characteristic V=O stretching frequencies, which are within the expected range and compare well to literature values of 997 cm^{-1} for $[VO(acac)_2]$ (**Table S1**).[74,75] Due to the DMSO in the 6th coordinate position of the structures, the vibration frequency of V=O stretching decreases due to a weakening and lengthening of the vanadyl bond.

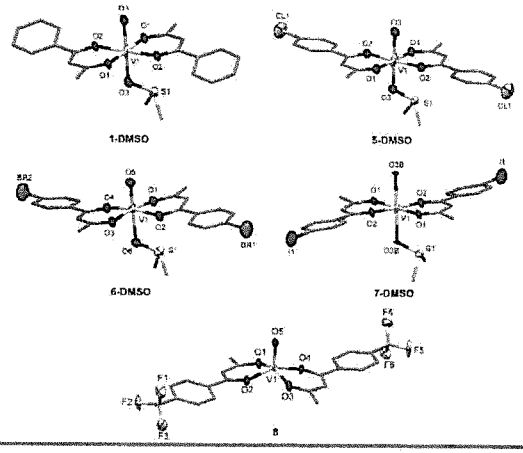


Figure 1 Molecular structures of oxobis(phenyl-1,3-butanedione) vanadium(IV) complexes **1-DMSO**, **5-DMSO**, **6-DMSO**, **7-DMSO** and **8**. Hydrogen atoms, solvent molecules and disordered atoms have been omitted for clarity. Displacement ellipsoids are at the 50% probability level.

Table 1 Bond lengths (Å) for complexes **1-DMSO**, **5-DMSO**, **6-DMSO**, **7-DMSO** and **8**, with s.u.s shown in parentheses

Bonds	1-DMSO	5-DMSO	6-DMSO	7-DMSO	8
V1-O1/ V1-O11	1.983(4)	1.987(3)	1.988(5)	1.973(6)/ 1.973(6)	1.977(4)
V1-O2/ V1-O21	1.990(4)	1.982(3)	1.981(6)	1.957(6)/ 1.957(6)	1.970(3)
V1-O3	--	--	2.001(5)	--	1.982)
V1-O4	--	--	1.993(6)	--	1.961(3)
V1--O	1.887(5)	1.896(3)	1.645(5)/ 2.175(6)	1.696(13) A/ 2.098(12) B/ 2.098 (12)B1	1.587(4)
S1--O	1.695(6)	1.645(4)	1.550(6)	1.490(18) B	--

*A and B represents the crystallographic disorder over the two axial sites

Chemosensitivity studies

Complexes **1-9**, $[VO(acac)_2]$ and cisplatin were all tested for their cytotoxicity against human colon colorectal carcinomas (HCT116 *p53*$^{+/+}$ (*p53* wild-type) and HCT116 *p53*$^{-/-}$ (*p53* null)), human breast adenocarcinoma (MCF-7), human lung carcinoma (A549), human pancreas carcinoma (MIA PaCa-2) and normal human adult retinal epithelial cells (ARPE-19). All ligands were screened for their cytotoxicity, and in line with our previously published work,[30,70,71] the IC_{50} values are > 100 μM. An ANOVA t-test has been conducted on all the values, where the probability $p < 0.05$ is considered significantly different, these values are shown in **Table S7** and **Table S8**.

96-h incubation + 0 h recovery period. The IC_{50} values were obtained after a 96 h incubation period and the results are stated in **Table 2** (**Figure S2**). When comparing the *para* substituted halogens (complexes **4-7**), the 4- bromo compound (**6**) is the most cytotoxic, with the lowest IC_{50} value observed against A549 (5.2 ± 0.9 μM), which is comparable to that of cisplatin (3.0 ± 0.1 μM, $p < 0.05$). This cytotoxicity may potentially be attributed to the effect of σ-hole binding towards cellular proteins[76–78] and/or a decreased metabolism of the drug due to the large bromine atom.[79,80] The compounds show a high cytotoxicity and selectivity towards colorectal cancer *p53*-null (HCT116 *p53*$^{-/-}$), and are > 7-fold more cytotoxic than cisplatin ($p < 0.05$). We have previously shown with the group IV metals, that the symmetric phenyl-1,3-butanedione complexes have an increased cytotoxicity when compared to the asymmetric complexes.[70] In line with these findings, the most promising results observed are those for complex **9**, which contains a simple symmetrical phenyl-1,3-butanedione ligand. This complex has increased cytotoxicity when compared to that of cisplatin ($p < 0.05$), with IC_{50} values of 1.1 ± 0.1 μM against HCT116 *p53*$^{+/+}$ (cisplatin = 3.5 ± 1.5 μM) and 1.4 ± 0.1 μM against MIA PaCa-2 (cisplatin = 3.6 ± 0.7 μM). The complex also remains relatively non-toxic towards normal APRE-19 cell line (IC_{50} = 68 ± 3 μM) when compared to cisplatin (IC_{50} = 6 ± 1 μM). Importantly, this complex is more selective towards cancerous cells, with selectivity indices (SI) > 60 (HCT116 *p53*$^{+/+}$), > 25 (MCF-7) and > 50 (MIA PaCa-2), compared to cisplatin which has SI ranging from 0.7-4.0 (**Table 2** and **Figure S2**, $p < 0.05$). The cytotoxicity of complex **9** has previously been reported against MCF-7, HPG-2 and HT-29 cell lines in a 24 h MTT assay,[72] and shows a slightly lower cytotoxicity value against the MCF-7 cell line, when compared to this work. This is due to the shorter incubation time (IC_{50} = 2.6 ± 0.2 μM versus 7.8 μM), and we would need to repeat our results at 24 h incubations in order to compare these results. The report suggests the complex is less active against HPG-2 (13.5 μM) and HT-29 (16.1 μM), although the complex remains significantly more active than the ligand alone.

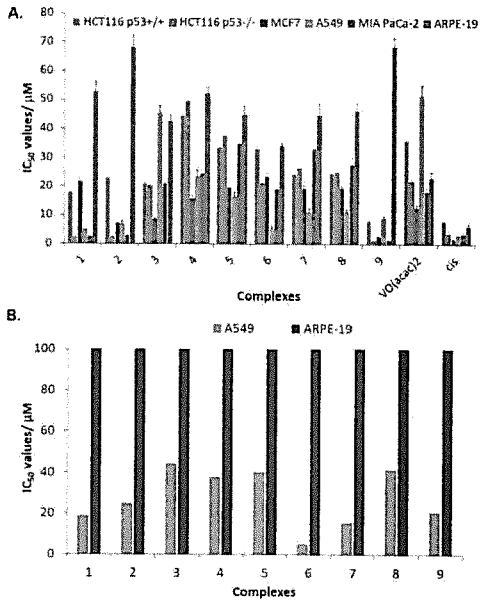


Figure 2. IC_{50} values of complexes **1-9**, $[VO(acac)_2]$ and cisplatin after **A.** a 96 h incubation (+ 0 h recovery) with HCT116 *p53*$^{+/+}$ (*p53* wildtype), HCT116 *p53*$^{-/-}$ (*p53* null), MCF-7, A549, MIA PaCa-2 and ARPE-19 cell lines; **B.** a 24 h incubation (0 h recovery) against A549 cell line..

Table 2. IC_{50} values (μM) ± SD for cisplatin, [VO(acac)$_2$] and complexes **1-9** after a 96 h incubation with HCT116 *p53*$^{+/+}$, HCT116 *p53*$^{-/-}$, MCF-7, A549, MIA PaCa-2 and ARPE-19, and IC_{50} values (μM) ± SD for cisplatin, [VO(acac)$_2$] and complexes **1-9** after a 24 h incubation (+ 72 h recovery period) with A549. Results are the average of triplicate repeats and the selectivity indices are states in parenthesis after each IC_{50} value.

Complex	IC_{50} values (μM) ± SD, 96 h						IC_{50} values (μM) ± SD, 24 h + 72 h recovery	
	HCT116 *p53*$^{+/+}$	HCT116 *p53*$^{-/-}$	MCF-7	A549	MIA PaCa-2	ARPE-19	A549	ARPE-19
cisplatin	3.5 ± 1.5[81] (1.7)	8.1 ± 1.8[81] (0.7)	1.5 ± 0.2 (4.0)	3.0 ± 0.1 (2.0)	3.6 ± 0.7 (1.7)	6 ± 1	59 ± 1 (0.7)	41 ± 1
VO(acac)$_2$	36 ± 2 (0.6)	± 1 (6.5)	12 ± 1 (1.8)	52 ± 4 (0.4)	18 ± 1 (1.3)	23 ± 2	47 ± 6 (2.1)	> 100
1	18 ± 1 (2.9)	2.4 ± 0.1 (22.2)	22 ± 1 (2.4)	4.95 ± 0.06 (10.6)	2.3 ± 0.3 (22.4)	68 ± 3	19 ± 1 (5.3)	> 100
2	22.7 ± 0.3 (3.0)	2.2 ± 0.4 (31.3)	7.0 ± 0.2 (9.7)	7 ± 1 (9.9)	2.7 ± 0.3 (25.7)	68 ± 4	25 ± 2 (4.0)	> 100
3	21 ± 1 (2.0)	20 ± 1 (2.1)	8.5 ± 0.6 (5.0)	45 ± 3 (0.9)	21 ± 2 (2.0)	42 ± 2	44 ± 2 (2.3)	> 100
4	44 ± 3 (1.2)	49 ± 3 (1.1)	16 ± 1 (3.3)	23 ± 3 (2.2)	24 ± 1 (2.1)	52 ± 2	38 ± 2 (2.7)	> 100
5	33 ± 2 (1.3)	27 ± 2 (1.2)	20 ± 1 (2.3)	16 ± 1 (2.7)	35 ± 3 (1.3)	45 ± 3	40 ± 3 (2.5)	> 100
6	33 ± 2 (1.0)	21 ± 2 (1.6)	23 ± 2 (1.5)	5.2 ± 0.9 (6.6)	19 ± 2 (1.8)	35.9 ± 0.2	5.1 ± 0.9 (19.3)	> 100
7	24 ± 2 (1.8)	26 ± 3 (1.7)	19 ± 1 (2.3)	11 ± 1 (4.1)	33 ± 3 (1.3)	45 ± 4	16 ± 2 (6.4)	> 100
8	24 ± 2 (1.9)	25 ± 1 (1.9)	19.4 ± 0.6 (2.4)	11.1 ± 0.8 (4.1)	27 ± 3 (1.7)	46 ± 3	41 ± 4 (2.4)	> 100
9	8.0 ± 0.7 (8.5)	1.1 ± 0.1 (60.4)	2.6 ± 0.2 (25.9)	8.9 ± 0.9 (8.9)	1.4 ± 0.1 (50.2)	68 ± 3	21 ± 1 (4.8)	> 100

24-h incubation + 72 h recovery period. Due to the low IC_{50} values obtained against the human lung carcinoma cells (A549), the complex **1-9**, [VO(acac)$_2$] and cisplatin were all screened against A549 and ARPE-19 using a 24-hour incubation period, followed by a 72-hour recovery period. The results are stated in **Table 2** and **Figure 2**, showing all complexes remain relatively active towards lung cancer after just 24 hours exposure. In particular, compound **6** is 11.5-fold more cytotoxic (5.2 ± 0.9 μM) when compared to cisplatin (59 ± 1 μM). Importantly, these vanadyl(IV) complexes are non-toxic towards the normal ARPE-19 cells with all IC_{50} values >100 μM. The selectivity indices have been calculated and complex **6** has significant selectivity towards the A549 cell line, with an SI >19 (**Figure S3**). Though these compounds are promising, no structure activity relationships can be determined at this stage, and further work is being conducted to determine their cytotoxic nature.

Oxidovanadium(IV) complexes containing phenanthroline and bipyridine based ligands have previously been screened for their potency against human hepatoma cell lines; HepG2 and SMMC-7721.[65] Although the complexes had increased cytotoxicity compared to the ligands alone, the cytotoxicity results were only moderate and remain less cytotoxic that the complexed reported herein. Recent results by Kowalski et al. on oxidovanadium(IV) complexes containing 2-methylnitrilotriacetate ligands, show selective cytotoxic effects against pancreatic carcinomas; PANC-1 = 10–25 μM; MIA PaCa-2 = 25 μM.[66] These results are comparable with most of our complexes, which have IC_{50} values in the range of 19-35 mM against MIA PaCa-2. However, three of our complexes (**1**, **2** and **9**) have increased cytotoxicity when compared to these results. The IC_{50} values herein are in the range of 1.4-2.7 μM (~9-fold increase), when compared to literature values.

Stability under acidic and basic conditions

Due to the ability of these complexes to form DMSO adducts, the UV-vis analysis of the adduct-free complexes **1-9** have been obtained in both $CHCl_3$ and DMSO at room temperature (**Figure S4**) and the spectra show no changes in chemical structure over time. Therefore, we believe that the addition of DMSO *trans* to the vanadyl oxygen atom is due to energetics, and the driving force for crystallization is only obtained in hot DMSO solution. Additionally, we tested the stability of the adduct-free complexes in DMSO over 3 weeks (**Figure S5**). The resulting UV-vis spectra show no changes over time, and we can confirm that the adduct-free complexes are the active species. In order to understand the complexes' structure and stability in biological conditions, UV-vis data has also been analyzed for complexes **3** and **6** in PBS and 0.1% DMSO, to mimic the *in vitro* conditions. The complexes were tested using the adduct-free compounds

under both acidic (**Figures S6-7**) and basic conditions (**Figure S8-S9**), and show that the compounds remain stable in acidic conditions, with only a hypochromic shift observed (**Figure 3**). However, in basic conditions changes were observed which suggest that the ligand dissociates from the complex at pH values >7.9, forming possible oxovanadate species and hydrolyzed ligand (**Figure 4**).[82] However, these results indicate that the vanadyl(IV) complexes are intact under physiological conditions, and during the duration of cell testing.

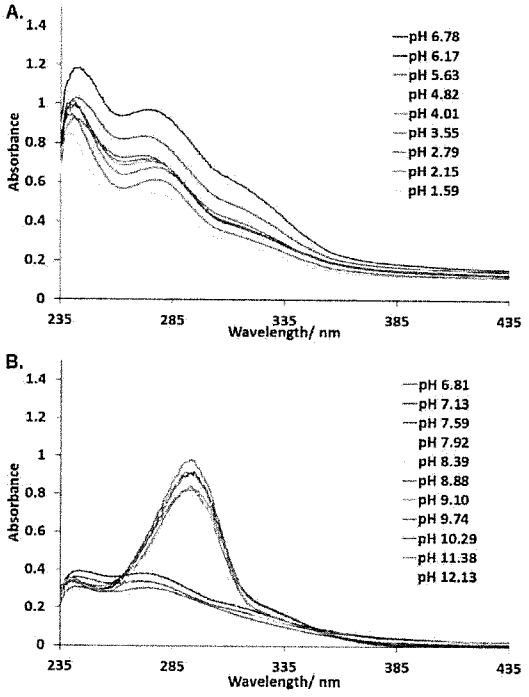


Figure 3. UVvis spectra of **A.** complex **3** at an initial pH of 6.65 and the spectrum obtained by decreasing the pH with 0.01-0.1 M HCl and **B.** complex **3** at an initial pH of 6.59 and the spectrum obtained by increasing the pH with 0.01-0.1 M NaOH.

Stability in bovine serum albumin

The binding to BSA is potentially important for complexes to be able to be transported through the blood stream, therefore, the interactions may affect the suitability of the drug.[83,84] The absorbance of BSA at 278 nm is responsible for the aromatic acid residues, such as Trp, Tyr and Phe, therefore any changes in this region can be attributed to interactions with these hydrophobic residues. Complex **9** was reported to increase the peak at 278 nm and is blue shifted by ~4 nm, suggestive of an interaction between BSA and the V(IV) complex.[72] Additionally, docking experiments showed that complex **9** binds the domain II pocket of BSA and shows the hydrophobic contacts between BSA and the vanadium complex. Therefore, absorption titration experiments have been performed at a constant BSA concentration of 50 μM, and varying concentrations of complexes **3** and **6**, ranging from 25 – 1.56 μM. UV-vis spectra were recorded for each addition of the complex after allowing to equilibrate for 10 minutes. As our complexes need to be dissolved in DMSO, it poses some issues with the quality of the BSA, in which the solvent has been shown to strongly reduce the initial helical content of BSA.[85] UV-vis spectra for BSA and complexes **3** (**Figure S10A**) and **6** (**Figure S10B**), show no significant changes, only the increase of vanadium peaks (~330 nm) were observed when the titration concentrations were increased, and a bathochromic shift of ~5 nm (at 278 nm) with BSA and complex **3**. The previous work by Mohamadi et al. highlights a 4 nm change as a potential interaction with vanadium and BSA; therefore, further work will be conducted in this area to determine any interactions with our complexes and BSA.

Conclusions

We have successfully synthesized a series of oxobis(phenyl-1,3-butanedione) vanadium(IV) complexes through a facile and straightforward solid state synthesis, with moderate to high yields. The compounds show a high cytotoxicity and selectivity towards cancer cells, with IC_{50} values >7-fold more cytotoxic than cisplatin. Additionally, after just 24 hours incubation periods the compounds are non-toxic towards normal cells, but remain moderately cytotoxic towards lung carcinoma (A549), with IC_{50} values up to 11.5-fold more cytotoxic than cisplatin. The most promising results are from complex **9**, which incorporates simple symmetrical ligands. More importantly, this complex is 2.5-7 times more cytotoxic than cisplatin, and it is selective towards cancerous cell lines over heathy ell lines, with selectivity indices (SI) > 60 (HCT116 $p53^{+/+}$), > 25 (MCF-7) and > 50 (MIA PaCa-2). The complexes are also stable under physiological conditions, however, they possibly convert to hydroxy or oxovanadate species at pH values > 7.9. Additionally, our UV-vis studies do only show small changes when titrated with BSA, however, literature have shown such complexes binding to the domain II of BSA. Overall, we envisage this synthesis to be of great potential for large scale applications, as using solvent-free methods are fast, efficient and eliminate the use of toxic solvents, which are important aspects in pharmaceutical drug synthesis.

Acknowledgements

The authors acknowledge the University of Bradford's Analytical Centre for support, in particular Andrew Healey for conducting mass spectrometry experiments. They also wish to acknowledge both Amy Scholes and Humairaa Parvaz who joined the group as part of the Nuffield Foundation summer project. Thank you to Dr Gary S. Nichol (University of Edinburgh) for crystallographic advice and Stephen Boyer (London Metropolitan University) for conducting elemental analysis. A special thank you to both Professor Roger Phillips and Dr Simon Allison (University of Huddersfield) for the in-kind donation of the MIA PaCa-2 and ARPE-19 cell lines, and the Institute of Cancer Therapeutics (Bradford) for providing access to the Cat. II laboratories. The University of Bradford Research Development Fund provided part of the costs for this project.

Keywords: bioinorganic chemistry • cancer • coordination compounds • solid-state synthesis • vanadium

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10.1002/chem.201902441

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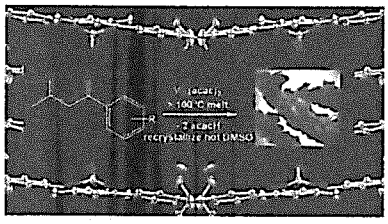
The use of a straight-forward, fast, facile and solvent-free reaction by dry melt methods, for the synthesis of a range of oxovanadium(IV) complexes is presented. This methodology eliminations expensive equipment and toxic solvents, whilst reducing the reaction times to < 5 minutes. The compounds synthesized > 11-fold more cytotoxic than cisplatin and remain non-toxic towards normal cells.



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Fast, facile and solvent-free dry melt synthesis of oxovanadium(IV) complexes: Simple design with high potency towards cancerous cell