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Synthesis, Characterization and Antioxidant Activity of Two Novel Oxovanadium (IV) Curcuminoids

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Abstract

The reaction of bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione (curcumin) and two novel ligands of bis[4-tetrabenzylglucose-3-methoxyphenyl]-1,6-heptadiene-3,5-dione (bis(tetrabenzylglucose)curcumin) (BTBGC) and bis[4-tetraacetylglucose-3-methoxyphenyl]-1,6-heptadiene-3,5-dione (bis(tetraacetylglucose)curcumin) (BTAGC) with vanadium in methanol, in a 2:1 molar ratio, which yield the complexes of ML_2 where M is $[VO]^{2+}$, have been synthesized and characterized by FT-IR, mass spectrometry, 1H NMR spectroscopy and elemental analysis. These novel compounds were also examined for their antioxidant activity (using *Trolox Equivalent Antioxidant Capacity (TEAC)* antioxidant assay as a measure of their overall ability to scavenge free radicals compared to antioxidant standards such as Trolox); compounds with free hydroxyl groups were more active than those one whose locking such and also the metal complexes showed more activity than Trolox. The antioxidant capacity was decreased in BTBGC, BTAGC and their complexes compared to curcumin and its oxovanadium (IV) complex, corroborating the importance of curcumin's free phenolic OH groups for scavenging oxidants potential. Also, the presence of the methoxy group increases the activity.

Keywords: Curcumin, Bis(tetrabenzylglucose) curcumin, Bis(tetraacetylglucose) curcumin, Vanadium, Antioxidant

Introduction

Curcuminoids are a group of naturally occurring β- diketones with the structure of 1,7-diaryl-1,6-heptadiene-3,5-diones, which were firstly determined in 1910 [1], constitute the yellow colored physiologically active component of the turmeric that is obtained from the powdered root of Curcuma longa Linn. The medicinal activity of curcumin has been known and also the substance further has a potential as the subject of several investigations in the field of biology, medicine and pharmacology over recent decades. One of the most important biological activities of curcumin is its antioxidant property [2-4], which has been attributed to the presence of a phenolic group that is important for its property. Its activity is also enhanced by the presence of a methoxy group in the ring [5]. Moreover, curcumin has applicable potentials such as antitumor [6-8], HIV antiproteases [9] and anti-inflammatory activities [10, 11].

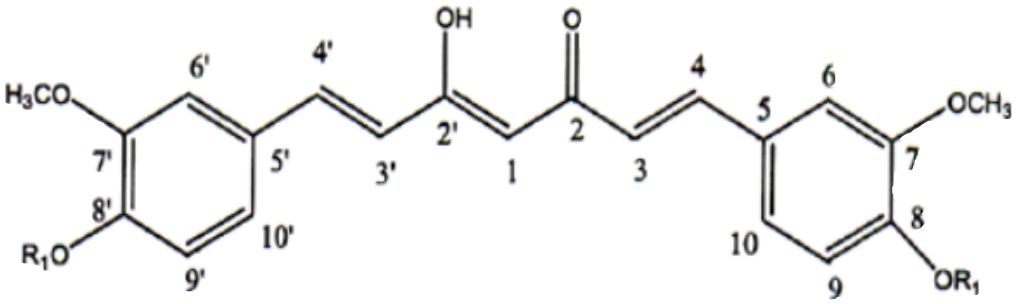
A variety of curcumin metallo complexes has been synthesized and characterized, usually with biological studies in mind. Oxovanadium (IV) ion and peroxovanadate complexes are of interest candidates as chemotherapeutic agents [12-14]

In vitro studies showed that vanadium has various effects in lipid and protein metabolism [15], and also in experimental models of diabetes, it has demonstrated physiological effect on insulin [16, 17].

Some oxovanadium (IV) complexes can act as antidiabetic agents. For example, vanadium-containing drug candidates, bis(maltolato)oxovanadium (IV) (BMOV) and bis (ethylmaltolato)oxovanadium (IV) (BEOV) are unsurpassed as orally available glucose- and lipid-lowering insulin mimetics, whether administered acutely or chronically [18-20].

Oxovanadium (IV) complexes of curcumin with antioxidant activity, which were recently synthesized and characterized, could improve synergistically the potency of an oxovanadium (IV) based hypoglycemic agent [21, 22]. Oxovanadium (IV) curcumin ($VO(Cur)_2$) has attract as an anti-cancer agent, an inhibitor of synoviocyte proliferation and also proved to be exceptionally non-toxic *in vivo*, compared to uncomplexed curcumin or oxovanadium (IV) ion alone [23].

Scheme 1: The Proposed Structure of Curcumin and Curcumin Derivatives used as Ligands in this Study



Curcumin (Cur)	$R_1 = H$
Bis(tetrabenzylglucose)curcumin (BTBGC)	$R_1 = TBG$
Bis(tetraacetylglucose)curcumin (BTAGC)	$R_1 = TAG$

The antioxidant activity of curcumin arises mainly from scavenging of several biologically relevant free radicals that are produced during physiological processes [24, 25]. Although a lot of work has been done to show antioxidant properties of curcumin, search for new synthetic derivatives in different model systems has demonstrated a range of potencies dependent upon particular substituents on the aromatic moiety [26] to develop compounds with better antioxidant activities.

In this paper, I describe the synthesis and characterization of oxovanadium (IV) complexes by the 1,3-diketones, curcumin and two its new derivatives, to include novel ligands of bis(tetrabenzyl-glucose)curcumin and bis(tetraacetylglucose)curcumin (Scheme 1). Also, the antioxidant activity of these compounds was studied.

Experimental

Chemical and Materials

All solvents (Sigma/Aldrich/Fisher) and chemicals were reagent grade and used without further purification, except curcumin. Oxovanadium (IV) acetylacetone, (Aldrich chemical, Milwaukee, WI), MTT (3-4,5-dimethylthiazole-2-ylate-2,5-diphenyltetrazoliumbromide) (Sigma); Curcumin (Sigma, 65-70% typically, from curcuma longa (turmeric)), acetic anhydride (Fisher), ADDP (1,1'-(azodicarbonyl) dipiperidine) (Aldrich), P(nBu)3 (tri-n-butylphosphine) (Aldrich), ABTS (2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) diammonium salt) (Sigma). Potassium persulfate (Aldrich), Trolox ((s)-(-)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) (Aldrich), TBG (2,3,4,6-tetra-O-benzyl-D-glucopyranose) (Aldrich), TBA (di-2,3,4,6-tetra-O-acetyl-D-glucopyranose) (Aldrich). BHT(2,6-di-tert-butyl-4-methylphenol) (Aldrich).

Analytical Instruments

IR spectra were record in the solid state (KBr disk) in the range 400-4000 cm^{-1} using an ATI Mattson Galaxy Series FT-IR 5000 spectrometer and Shimadzu FTIR-8300 spectrophotometer. Elemental analyses were carried out on a Carlo Erba analytical instrument. Mass spectra (+ion) were obtained with a Macromass LCT (electrospray ionization, ESI), or a Bruker BiflexIV (Matrix-Assisted Laser Desorption Ionization-Time of Flight, MALDI-TOF). ^1H NMR spectra of samples in $CDCl_3$ were recorded on a Bruker AM-300 instrument at 300.13 MHz.

Separation, Preparation and Characterization of Curcuminoids and their Complexes

Isolation of Curcumin (Cur)

Curcuminoids were isolated by modification of the previous method [27]. Commercial curcumin (65-70%) was dissolved in acetone and impregnated with Silica gel (70-230 mesh), loaded onto a column of Silica gel (70-230 mesh), and eluted with CHCl3/MeOH/AcOH (98:5:2). Different phases from column were collected and solvent was evaporated under vacuum.

^1H NMR (300 MHz, $CDCl_3$): 3.93 (6H, s, $2OCH_3$), 5.78 (1H, s, 1H), 6.46 (2H, d, J = 16.0 Hz, 3,3'-H_2), 6.92 (2H, d, J = 8.4 Hz, 9,9'-H_2), 7.04 (2H, d, J = 2.1 Hz, 6,6'-H_2), 7.10 (2H, dd, J = 8.4,2.1 Hz, 10,10'-H_2), 7.58 (2H, d, J = 16.0 Hz, 4,4'-H_2). IR (KBr, cm^{-1}): ~3478 (ν_{O-H}), ~3120 ($\nu_{=C-H}$), ~2937 (ν_{C-H}), 1626 ($\nu_{C=O}$), 1585, 1513 ($\nu_{C=C}$), 1452 (ν_{C-H}), 1285, 1140 ($\nu_{C-C,C-O}$), 963 ($\nu_{H-C=C-H}$ trans), 852 (ν_{C-H}); Mass spectrum: m/z = 369 [M+H]+; Anal. Calcd. for $C_{21}H_{20}O_6$ (%): C, 68.47; H, 5.47. (Found): C, 68.23; H, 5.67.

Preparation and Characterization the Ligands

Bis(tetrabenzylglucose)curcumin (BTBGC)

This compound was prepared by using Mitsonubo reaction [28]. Cur (0.2 g, 0.54 mmol), di-2,3,4,6-tetra-O-benzyl-Dglucopyranose (0.59 g, 1.08 mmol) and ADDP (0.34 g, 1.33 mmol) were added to a flask that had been evacuated; filled by Ar, 13 ml dry CH_2Cl_2 and 2 ml acetone were added. $P(nBu)_3$ (350 ppm, 1.35 mmol) was added dropwise by syringe. The resultant solution was refluxed for 18 h. The progress of reaction was monitored by TLC technique. When the reaction completed, cooled, filtrated under vacuum and washed by CH_2Cl_2. The filtrate was evaporated under reduced pressure. The residue was

washed by cold methanol and filtrated. The resultant solid was collected and dried overnight in vacuum (59% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 3.62-3.80 (16H, s, $BnCH_2$), 3.85 (6H, s, $2OCH_3$), 4.50-5.22 (10H, m, glucose-H), 5.82 (1H, s, 1H), 6.50 (2H, d, J = 15.8 Hz, 3,3'-H2), 7.05 (2H, d, J = 8.1 Hz, 9,9'-H_2), 7.08 (2H, s, 6,6'-H_2), 7.15 (2H, d, J = 8.1 Hz, 10.10'-H_2), 7.19 (3H, m, Bn-H), 7.30 (2H, m, Bn-H), 7.55 (2H, d, J = 15.8 Hz, 4,4'-H_2); IR (KBr, cm^{-1}): ~3600-3200 (ν_{O-H}), ~3100-2900 (ν_{C-H}), 1630 ($\nu_{C=O}$), 1505, 1455 ($\nu_{C=C}$), 1427 (ν_{C-H}), 1261-1088 ($\nu_{C-O,C-C-C}$), 1029 ($_{C-H}$); Mass spectrum: *m/z* = 1435 $[M+Na]^+$; 913 [MG+\ Na]$^+$; Anal. Calcd. for $C_{89}H_{88}O_{16}$(%); C, 75.62; H, 6.27. Found: C, 75.44; H, 6.40.

Bis(tetraacetylglucose)curcumin (BTAGC)

This compound was prepared in the same way as BTBGC. Di-2,3,4,6-tetra-O-acetyl-D-glucopyranose (0.59 g, 1.08 mmol) was used instead of di-2,3,4,6-tetra-O-benzyl-Dglucopyranose (55% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 2.08 (s, 6H, $COCH_3$), 2.11 (s, 6H, $COCH_3$), 2.10 (s, 6H, $COCH_3$), 2.16 (s, 6H, $COCH_3$), 3.93 (6H, s, $2OCH_3$), 4.08-5.17 (10H, m, glucose-H), 5.82 (1H, s, 1H), 6.44 (2H, d, J = 15.8 Hz, 3,3'-H_2), 6.91 (2H, d, J = 8.3 Hz, 9,9'-H_2), 7.30 (2H, s, 6,6'-H_2), 7.10 (2H, d, J = 8.3 Hz, 10.10'-H_2), 7.55 (2H, d, J = 15.8 Hz, 4,4'-H_2); IR (KBr, cm-1): ~3600-3200 (ν_{O-H}), ~3200-3000 (ν_{C-H}), 1632 ($\nu_{C=O}$), 1521, 1463 ($\nu_{C=C}$), 1390 (ν_{C-H}), 1260- 1141 ($\nu_{C-O,C-C-C}$), 1087 (ν_{C-H}); Mass spectrum: *m/z* = 1052 $[M+Na]^+$; 720 $[M-G+Na]^+$; Anal. Calcd. for $C_{49}H_{54}O_{24}$ (%); C, 57.20; H, 5.49. Found: C, 57.35; H, 5.28.

The Complexes

General Method

The complexes were prepared according to the literature procedure [29]. Curcuminoid (0.50 mmol) was added to ~10 ml degassed methanol (acetone was used for completely dissolving curcuminoid) and the suspension was gently heated and stirred until dissolution occurred. $VO(acac)_2$ (0.25 mmol) was dissolved in ~10 ml degassed methanol and added dropwise to the curcuminoid solution. The reaction mixture was refluxed for ~2 h under Ar and then cooled to room temperature. After cooling, solid was precipitated. The mixture was filtrated, washed with cold methanol, collected and dried overnight in vacuum at room temperature.

Oxovanadium (IV) curcumin, $[VO(Cur)_2]$ [29]

(89% yield); IR (KBr, cm^{-1}): ~3497 (ν_{O-H}), ~3124, 2935 (ν_{C-H}), 1626 ($\nu_{C=O}$), 1591, 1489 ($\nu_{C=C}$), 1391 (ν_{C-H}), 1261-1151 ($\nu_{CO,\ C-C-C}$), 966 ($\nu_{V=O}$), 847 (ν_{C-H}); MS (+ES-MS, positive electrospray MS): *m/z* = 802 $[M+H]^+$ Anal. Calcd. For $C_{42}H_{38}O_{13}V$ (%); C, 62.92; H, 4.78. Found: C, 62.85; H, 5.02.

Oxovanadium (IV) bis(tetrabenzylglucose)curcumin, $[VO(BTBGC)_2]$

(65% yield); IR (KBr, cm^{-1}): ~3100-2900 (ν_{C-H}), 1627 ($\nu_{C=O}$), 1500, 1452 ($\nu_{C=C}$), 1390 (ν_{C-H}), 1261- 1129 ($\nu_{C-O,C-C-C}$), 1070 (ν_{C-H}), 968 ($\nu_{V=O}$); Mass spectrum (MALDI-TOF): *m/z* = 2915 $[M+Na+2H]^+$; Anal. Calcd. For $C_{178}H_{174}O_{33}V.H_2O$ (%); C, 73.46; H, 6.10. Found: C, 73.15; H, 6.31.

Oxovanadium (IV) bis(tetraacetylglucose)curcumin, [VO(BTAGC)$_2$]
(72% yield); IR (KBr, cm^{-1}): ~3100-3000 (ν_{C-H}), 1627 ($\nu_{C=O}$), 1512, 1461 ($\nu_{C=C}$), 1375 (ν_{C-H}), 1255- 1132 ($\nu_{C-O,C-C-C}$), 1076 (ν_{C-H}), 983 ($\nu_{V=O}$); Mass spectrum (MALDI-TOF): *m/z* = 2148 $[M+Na+2H]^+$; Anal. Calcd. For $C_{98}H_{110}O_{49}V.H_2O$ (%); C, 55.45; H, 5.22. Found: C, 55.63; H, 5.47.

Antioxidant Studies

Trolox Equivalent Antioxidant Capacity (TEAC), Antioxidant Assay

The curcuminoids and their complexes were tested using the TEAC antioxidant assay as a measure of their overall ability to scavenge free radicals compared to antioxidant standards such as Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), α-tocopherol (α-Toc) and BHT (butylhydroxytoluene). An improved $ABTS^{*+}$ (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) diammoniuim salt) radical cation decolorization assay [30] was used to determine relative TEAC values.

ABTS was dissolved in water (7 mM), subsequently, reacted with aqueous potassium persulfate (2.45 mM), and placed in the dark place for 16 h before use. Thus, ABTS oxidizes to the $ABTS^{*+}$ radical cation. The $ABTS^{*+}$ product solution, after equilibrating to 30° C (Fisher Isotemp circulating water bath), was diluted with MeOH to an absorbance of 0.70 (±0.02) at 734 or 745 nm. The Stock solutions of the compounds in MeOH were diluted so that addition of 20 µl to 2 ml of $ABTS^{*+}$ solution caused a reduction of 20-80% in the absorbance as a result of the reduction to ABTS. To obtain this range, final concentrations for the compounds ranged from 2.5-15 µM. After the solutions were initially mixed, the A734 readings were taken at 30° C after 1, 3 and 6 min. These readings were done in triplicate. The percentage inhibition of absorbance at 734 nm was calculated and plotted as a function of compound concentration. The slopes were then compared to the standard Trolox, with its TEAC value normalized to 1.

Results and Discussion

Spectroscopic Characterization

The Ligands and their Complexes

Commercial curcumin was separated into its individual component by column chromatography, followed by recrystallization. Two Curcumin derivatives, BTBGC and BTAGC and also two novel oxovanadium (IV) curcuminoid complexes, $VO(BTBGC)_2$ and $VO(BTAGC)_2$ were synthesized and characterized.

All of the ligands and their complexes are subjected to elemental analysis. The results obtained are in good agreement with those calculated values for the suggested formula in sharp indicating the purity of the prepared compounds.

Further characterization evidence of the ligands and their complexes comes from their mass spectra, which show intense peaks for $[L+Na]^+$, $[L-G+Na]^+$, $[VOL_2+H]^+$ and or $[VOL_2 + Na+2H]^+$, and confirm a stoichiometry of 2:1 curcuminoid to oxovanadium (IV) (See figures S1 and S2). The structures of the ligands are also confirmed by IR and ^{1}H NMR spectra, which will be discussed in detailed manner together with their metal complexes later.

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^{1}H NMR of the Compounds

For the ligands, BTAGC and BTBGC, protection of the OH hydrogen by glucose derivatives groups was confirmed by absence of a signal at δ ~ 9.5-10 ppm, typical of phenol ring OH hydrogen in curcuminoids, in the ^{1}H NMR spectra (See Figure S3). The presences of a sharp singlet for the methoxymethane proton in the ligands were observed in the region of 3.85-3.93 ppm. The glucose proton signals were found in the range of 4.08-5.22 ppm. Protons of benzene rings can be seen in the range of 6-8 ppm, while acetate protons are appearance in 2.08-2.16 ppm. In addition, there are signals which belong to protons of ethyl in 1-ethylbenzyle in 3.62-3.80 ppm and finally protons of curcumin chain are displayed from 5.80 to 7.55 ppm.

IR Spectra and Mode of Binding

In the FT-IR spectroscopic data, the most characteristic vibrations are selected by comparing the IR spectra of the ligands and their complexes (See figures S4 and S5). All the ligands showed $\nu_{C=O}$ in the typical 1600-1630 cm^{-1} range, which shifted to lower energy in the oxovanadium (IV) complexes of the same ligands. Oxovanadium (IV) complexes also had no broad band in the 2600-3400 cm^{-1} range, related to the stretching of intramolecular H in the enol function, as noted for a previously synthesized oxovanadium (IV) 1,7-diaryl-1,6-heptadiene-3,5-dione, with a different pattern of hydroxylation on the aromatic rings [31]. Oxovanadium (IV) complexes showed a $\nu_{V=O}$ medium intensity band at ~968-996 cm^{-1}.

Antioxidant Assay

Testing for biological activity included comparison of antioxidant potential among the ligands and their complexes.

Figure S1: Mass Spectrum of BTBGC Ligand

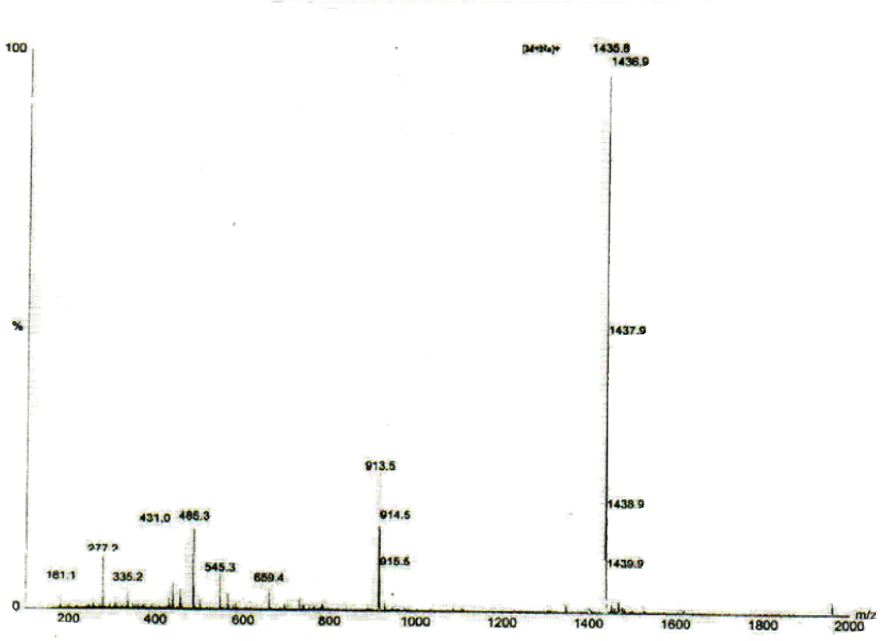

Figure S2: Mass Spectrum of $VO(BTBGC)_2$ Complex

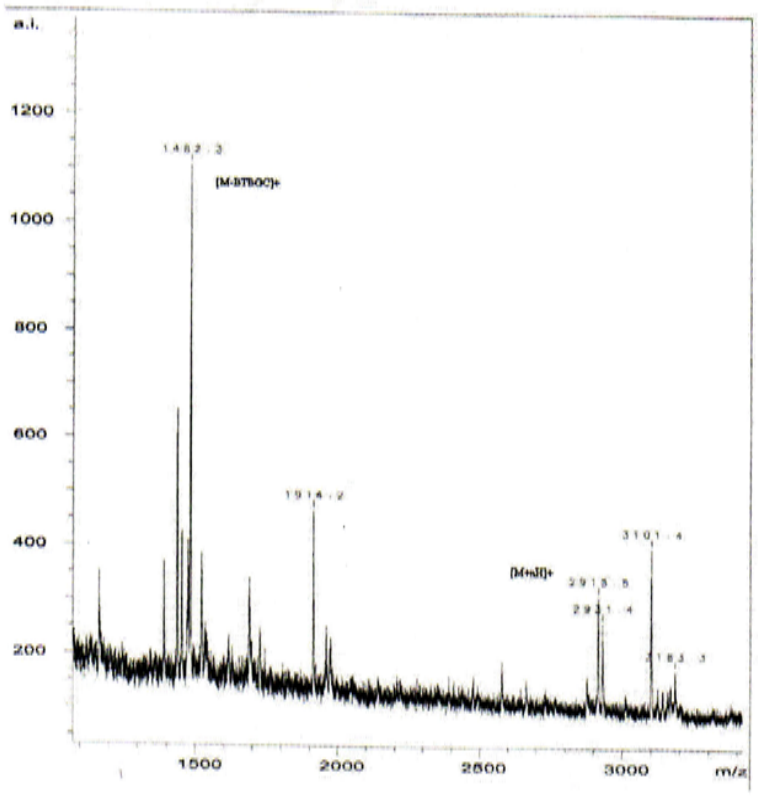

Figure S3: ^1H NMR Spectrum of BTBGC Ligand in $CDCl_3$

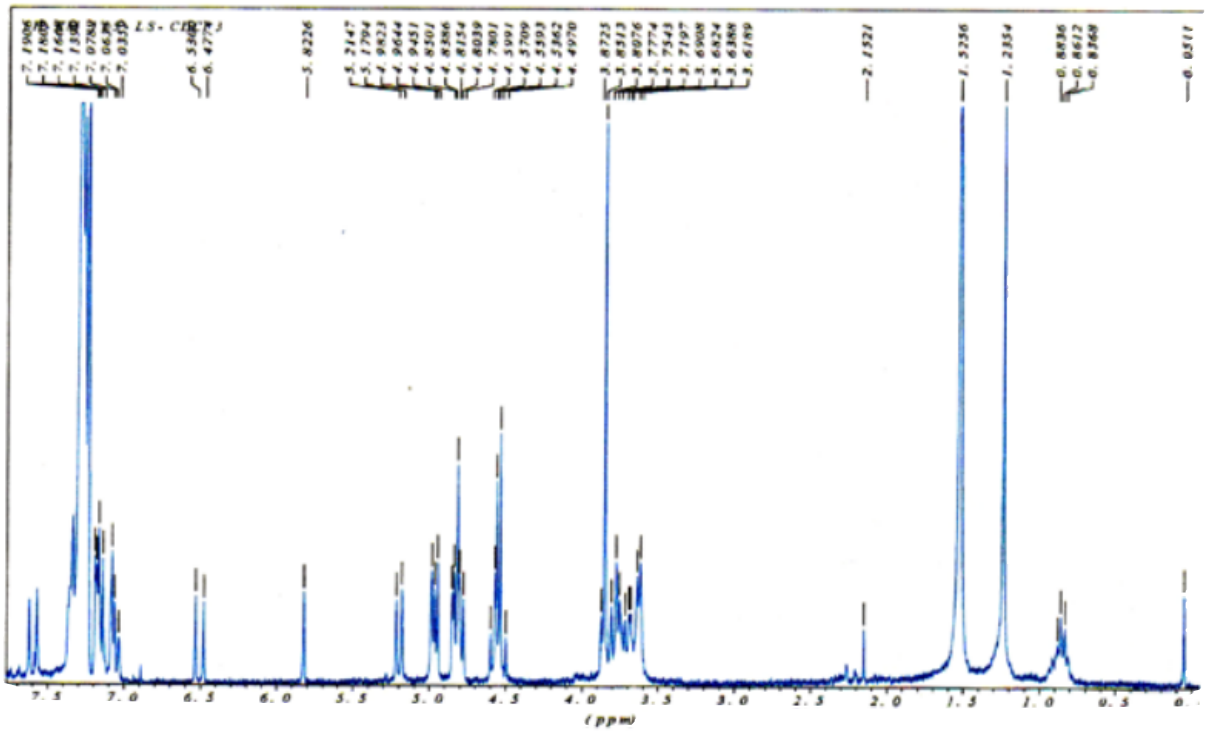

Figure S4: FT-IR Spectrum of BTBGC Ligand

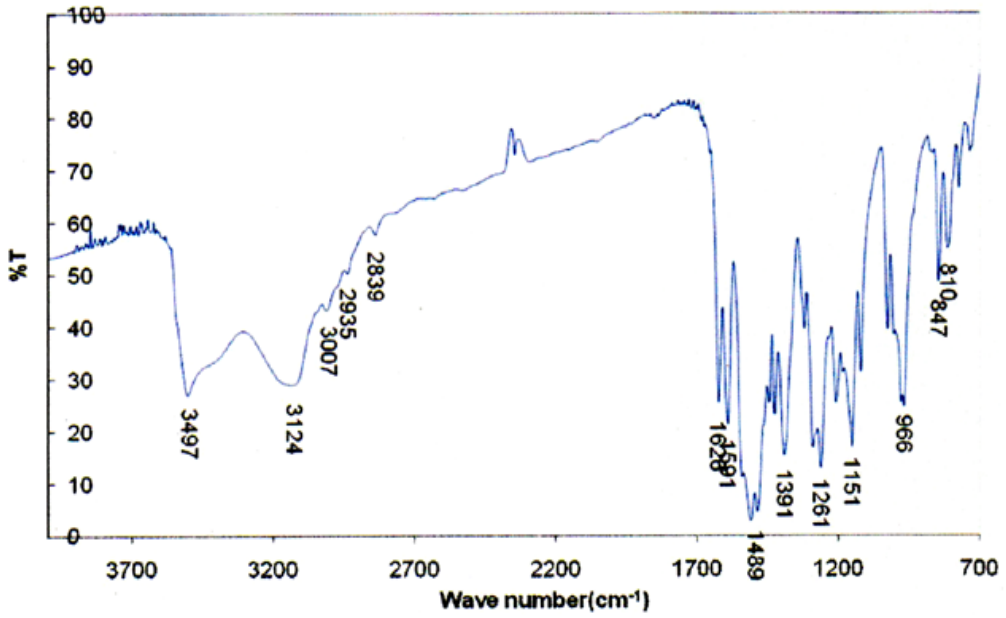

Figure S5: FT-IR Spectrum of $[VO(BTBGC)_2]$ Complex

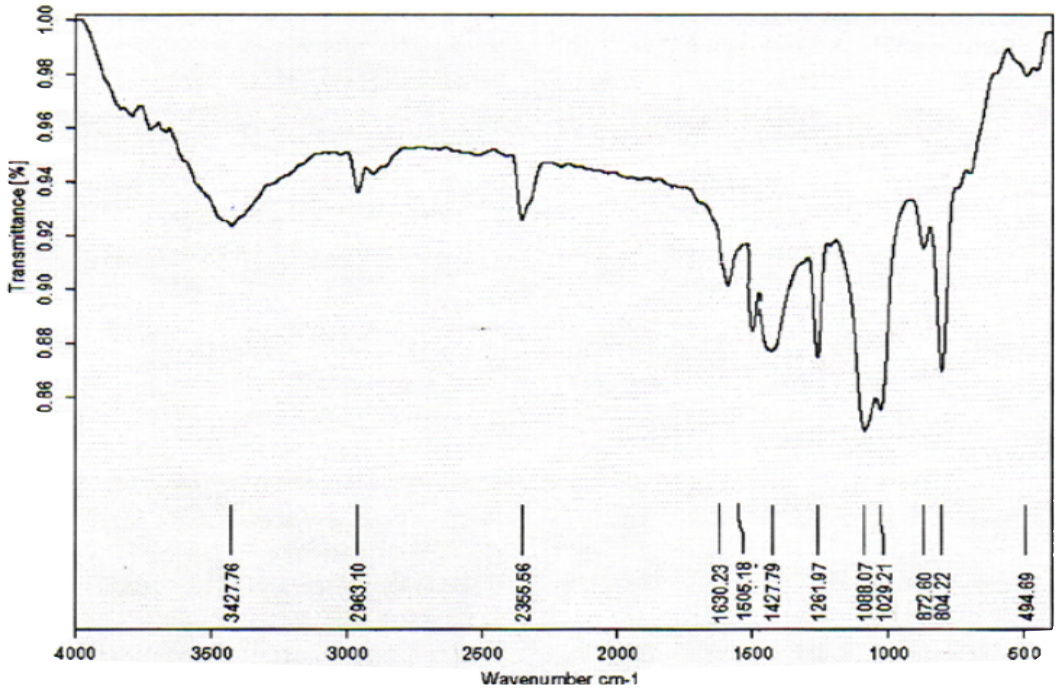

Table 1: The Antioxidant Assay Results for the Ligands and their Oxovanadium (IV) Complexes

Compounds	1 min	3 min	6 min
Cur	0.87	1.01	1.09
BTBGC	0.16	0.22	0.29
BTAGC	0.17	0.25	0.31

$VO(Cur)_2$	2.05	2.27	2.40
$[VO(BTBGC)_2]$	0.31	0.46	0.59
$[VO(BTAGC)_2]$	0.37	0.48	0.56

It's indicated that the predominant determinant of antioxidant capacity was the ligand, with $VO(Cur)_2$ roughly twice as effective as were curcumin alone. Meanwhile $VO(BTBGC)_2$ and $VO(BTAGC)_2$ had very low TEAC values compared to the oxovanadium (IV) curcumin complex. The exceptions were seen for the two novel ligands, which they had too low response to be quantified by the assay conditions we used (Table 1); comparing of these issues with the previous studies [29] have a good agreement that curcumin and its oxovanadium (IV) complex have the most antioxidant activities in compare to the other ligands and their complexes, which were considered in our studies. This suggests that blocking of phenolic OH groups reduced their ability to intercept the free radical-induced chain reaction. On the other hand, I can claim that the phenolic group is an essential for the free radical scavenging activity, which these radicals were formed by a singleelectron transfer (SET) mechanism, furthermore the presence of the methoxy group increases the activity.

Conclusions

In this work, two novel curcumin derivatives ligands and their oxovanadium (IV) complexes have been synthesized, characterized and considered, both chemically and biologically, which indicates that the stoichiometry ratio of the complexes is 1:2 (M:L). By regarding the results of antioxidant studies, it was shown that bis (tetrabenzylglucose)curcumin and bis(tetraacetylglucose) curcumin significantly decreased the antioxidant potential of compounds containing these ligands.

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References

1. H.Y.Y. Pabon, Rec. Trav. Chim. 83 (1964) 379.
2. K.S. Parvathy, P.S. Negi, P. Srinivas, Food. Chem. 120 (2010) 523.
3. A.K. Tuba, G. Ilhami, Chemico-Biol. Inter. 174 (2008) 27.
4. M. Tuorkey, K. Karolin, Biomed. Envir. Sci. 2 (2009) 488.
5. S.V. Jovanovic, C.W. Boone, S. Steenken, M. Trinoga, R.B. Kaskey, J. Am. Chem. Soc. 123 (2001) 3064.
6. T.H. Kim, H.H. Jiang, Y.S. Youn, C.W. Park, K.K. Tak, S. Lee, H. Kim, S. Jon, X. Chen, K.C. Lee, Int. J. Pharm. 403 (2011) 285.
7. S.T. Tharakan, T. Inamoto, B. Sung, B.B. Aggarwal, A.M. Kamat, Biochem. Pharm. 79 (2010) 218.
8. Y. Wen, Y. Ho, R. Shiau, J. Yeh, J. Wu, W. Wang, S. Chiou, J. Organomet. Chem. 695 (2010) 352.
9. A. Sundaryono, A. Nourmamode, C. Gardrat, A. Fritsch, A. Castellan, J. Mol. Struct. 649 (2003) 177.

10. J. Ravindran, G.V. Subbaraju, M.V. Ramani, B. Sung, B.B. Aggarwal, Biochem. Pharm. 79 (2010) 1658.
11. B.B. Aggarwal, K.B. Harikumar, Int. J. Biochem. Cell Biol. 41 (2009) 40.
12. H. Sakurai, Y. Kojima, Y.Y. Oshikawa, K. Kawabe, H. Yasui, Coord. Chem. Rev. 226 (2002) 187.
13. O.J.D. Cruz, Y. Dong, F.M. Uckun, Anti-Cancer Drugs 11 (2000) 849.
14. A.M. Evangelou, Crit. Rev. Oncol. Hematol. 42 (2002) 249.
15. S. Rizvi, M. Zaid, Clin. Exp. Pharmacol. Physiol. 28 (2001) 776.
16. M. Siddiqui, A. Taha, K. Moorttry, J. Biosci. 30 (2005) 483.
17. P. Poucheret, S. Verma, M. Grynpas, J.H. McNeill, J. Mol. Cell. Biochem. 188 (1998) 73.
18. K.H. Thompson, J.H. McNeill, C. Orvig, Chem. Rev. 99 (1999) 2561.
19. J.H. McNeill, V.G. Yuen, H.R. Hoveyda, C. Orvig, J. Med. Chem. 35 (1992) 489.
20. K.H. Thompson, B.D. Liboiron, Y. Sun, K.D. Bellman, I.A. Setyawati, B.O. Patrick, V. Karunaratne, G. Rawji, J. Wheeler, K. Sutton, S. Bhanot, C. Cassidy, J.H. McNeill, V.G. Yuen, C. Orvig, J. Biol. Inorg. Chem. 8 (2003) 66.
21. L.C.Y. Woo, V.G. Yuen, K.H. Thompson, J.H. McNeill, C. Orvig, J. Inorg. Biochem. 76 (1999) 251.
22. T. Storr, D. Mitchell, P. Buglyo, K.H. Thompson, V.G. Yuen, J.H. McNeill, C. Orvig, Bioconjug. Chem. 14 (2003) 212.
23. K.H. Thompson, K. Böhmerle, E. Polishchuk, C. Martins, P. Toleikis, J. Tse, V. Yuen, J.H. McNeill, C. Orvig, J. Inorg. Biochem. 98 (2004) 2063.
24. E. Kunchundy, M.N.A. Rao, Int. J. Pharm. 58 (1990) 237.
25. E. Kunchundy, M.N.A. Rao, Int. J. Pharm. 57 (1989) 173.
26. S. Gafner, S.K. Lee, M. Cuendet, S. Barthelemy, L. Vergnes, S. Labidalle, R.G. Mehta, C.W. Boone, J.M. Pezzuto, Phytochemistry 65 (2004) 2849.
27. O. Vajragupta, P. Boonchoong, L.J. Berliner, Free Rad. Res. 38 (2004) 303.
28. T. Tsunoda, Y. Yamamiya, S. Ito, Tetrahedron Lett. 34 (1993) 1639.
29. Kh. Mohammadi, K.H. Thompson, B.O. Patrick, T. Storr, C. Martins, E. Polishchuk, V.G. Yuen, J.H. McNeill, C. Orvig, J. Inorg. Biochem. 99 (2005) 2217.
30. R. Re, N. Pellegrini, A. Proteggente, A. Pannala, M. Yang, C. Rice-Evans, Free Rad. Biol. Med. 26 (1999) 1231.
31. K. Krishnankutty, V.D. John, Synth. React. Inorg. Metal-Org. Chem. 33 (2003) 343.