











Tetraarylantimony 2,2'-bipyridinecarboxylates: synthesis, photophysical and molecular docking studies

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Abstract

Tetraarylantimony(V) carboxylates based on 5-carboxyl and 6-carboxyl 2,2'-bipyridines (4 compounds) were synthesized for the first time. The structure of one of the compounds was confirmed by X-ray diffraction analysis. It was shown that the carboxyl group participates in the coordination of the antimony(V) cation, but the bipyridine fragment does not. The antitumor activity of the new complexes was assessed by molecular docking, and the most probable targets were determined. It was shown that the affinity of ligands to them is higher than that of the corresponding complexes. The best results were obtained for complex **3a**; its inhibition of VEGFR2 is 74% more effective compared to the native ligand. In addition, the primary photophysical properties of the new carboxylates in acetonitrile solutions were studied. It was shown that the luminescence quantum yield values strongly depend on the position of the carboxyl group: for 5-substituted compounds they reach 65.0%, while for 6-substituted ones they have an extremely low (< 0.1%) value. At the same time, the absorption and emission maxima are within 300–314 nm and 364–403 nm, respectively.

Keywords

2,2'-bipyridine carboxylic acids
antimony(V) complexes
XRD analysis
molecular docking
luminescence

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Key findings

- For the first time antimony(V) complexes based on 2,2'-bipyridinecarboxylic acids have been prepared and characterized by physical methods, including XRD analysis.
- Based on *in-silico* studies some of these complexes could serve as inhibitors of some key proteins (*i.e.* p38a, ERK2, VEGFR2).
- In solutions these complexes exhibited good photophysical properties with absolute quantum yields values up to 65%.

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1. Introduction

Carboxylic acids are well-known ligands for antimony complexes [1–3]. There are various tetraarylantimony carboxylates, synthesized by dearylation of pentaarylantimony by

carboxylic acids [4]. However, there are just a few examples of synthesis of tetraarylantimony carboxylates with pyridine containing carboxylate ligands [5]. In general, only singular examples of Sb(V) chelates with pyridine ligands are described, with all of them being monopyridines

and their annulated analogues. *E.g.*, the interaction of 2-picolinic acid with trimethylantimony [6] or its ether leads to corresponding biscarboxylates [7]. The same product was obtained by the reaction of nicotinic acid with triphenylantimony(V) dibromide [8]. SbCl_3 can also be used as a substrate, leading to the double salt formation [9]. All the reactions are carried out in mild conditions with good to excellent yields (65–94%). When trisarylantimony is used, an additional oxidation is required to obtain the target product (for example, the use of H_2O_2 [10, 11]). The quinoline- and 1,8-naphthiridincarboxylic acids complexes can be obtained using alkyl/arylcarboxylic acids [12–14]. When pyridine-2,6-dicarboxylic acids are used as ligands, MOFs are formed [15–17]. In such case phenantroline can act as coligand for antimony atom [18]. It should be noted that some of the above-mentioned compounds show antileishmanial [1–3, 8], antibacterial [15], antifungal and antitumor [13] activities.

Therefore, synthesis of antimony(V) complexes with heterocyclic ligands opens up new possibilities for antimony-based compounds with valuable applications since both heterocyclic ligands and arylantimony can be both biologically active. 2,2'-Bipyridine and its derivatives are well-known ligands for various metal ions [19, 20] due to their robust redox stability and ease of functionalization [21]. Incorporation of carboxylic groups into the 2,2'-bipyridine framework can further enhance the ligand's coordination capabilities and influence the properties of the resulting antimony complexes [22]. Hence, we consider 2,2'-bipyridinecarboxylic acids to be of interest for the expansion of the range of available oligoazine chelates for novel Sb complexes as well as for the synthesis of biologically active candidates, *e.g.*, those with antitumor and antileishmanial activities.

2. Experimental part

All reagents were purchased from Shanghai Macklin Biochemical Technology and used without further purification. NMR spectra were recorded on a Bruker Avance-400 spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as internal standard. Elemental analyses were performed on a PE 2400 II CHN-analyzer (Perkin Elmer). Mass spectra were recorded on a MicrOTOF-Q II mass spectrometer (Broker Daltonics) with electrospray ionization. The photophysical properties of acetonitrile solutions were measured on Shimadzu 2600 (absorption spectra) and Horiba (luminescence spectra).

The X-ray diffraction analysis was performed on an automatic Rigaku XtaLAB Synergy four-circle diffractometer with a HyPix-6000HE CCD detector and a PhotonJet X-ray source according to a standard procedure (Mo $K\alpha$ radiation, graphite monochromator, and ω scanning in 1° increments) at $T = 295(2)$ K. An empirical correction for absorption was applied. The measured reflection data were indexed, integrated, and scaled using the CrysAlisPro software package

[22]. The structures were deciphered by the internal phasing method according to the SHELXT program [24] and refined by the least squares method for F^2 using the SHELXL program [25]. The decoding and refinement of the structure were carried out in the Olex2 software shell [26]. Nonhydrogen atoms were refined in the anisotropic approximation. Hydrogen atoms at oxygen atoms were identified from the Fourier difference series. All other hydrogen atoms were placed in calculated positions in accordance with stereochemical criteria and refined according to the rider scheme. The results of X-ray diffraction analysis are registered in the Cambridge Structural Database under the CCDC No. 2390672. This data is freely available and can be requested at <https://www.ccdc.cam.ac.uk/>.

The starting compound 6-(6,7-dihydro-4-phenyl-5H-cyclopenta[c]pyridin-1-yl)-2-pyridinecarboxylic acid (**1a**) [20] and methyl 5'-phenyl[2,2'-bipyridine]-5-carboxylate (**2b**) [19] were synthesized as described in the literature.

2.1. 5-*p*-Tolyl-2,2'-bipyridine-5'-carboxylic acid (**1b**)

The ether **2b** (500 mg, 1.64 mmol) was suspended in 100 ml of the mixture of $\text{H}_2\text{O}:\text{EtOH}$ (2:8 by volume), and KOH (277 mg, 4.93 mmol) was added. Then the mixture was stirred under reflux for 2 h. After cooling to room temperature it was kept for 2 h. The solvents were removed under reduced pressure. Obtained residue was dissolved in water (50 ml), and hot filtration was performed. Hydrochloric acid (5 N) was added to the filtrate to adjust pH to 2. The precipitate was filtered off, washed with ethanol and water, and dried. The obtained product was used for next step without further purification. M.p. > 250 °C. Yield 400 mg (1.38 mmol, 84%). ^1H NMR (DMSO- d_6 , δ , ppm): 2.38 (s, 3H, CH_3), 7.33–7.38 (m, 2H, $\text{C}_6\text{H}_4\text{Me}$), 7.72–7.76 (m, 2H, $\text{C}_6\text{H}_4\text{Me}$), 8.27 and 8.43 (both *dd*, 1H, 3J 8.4 Hz, 4J 2.4 Hz, H-4 and H-4'), 8.53 and 8.55 (both *d*, 1H, 3J 8.4 Hz, H-3 and H-3'), 9.06 and 9.18 (both *d*, 1H, 4J 2.4 Hz, H-6 and H-6'). ^{13}C NMR (DMSO- d_6 , δ , ppm): 21.2, 120.8, 122.0, 127.0, 127.3, 130.3, 133.8, 135.8, 136.9, 138.7, 138.9, 147.5, 150.6, 152.8, 158.2, 166.5. ESI-MS, m/z : found 289.10, calcd 289.10 [M-H] $^-$.

2.2. Method for the synthesis of complexes 3

A mixture of Ph_3Sb (100 mg, 0.197 mmol) or (*p*-Tol) $_3\text{Sb}$ (100 mg, 0.173 mmol) and equal amount of corresponding acid **1a** or **1b** in benzene (20 mL) was kept at 20 °C for 24 h. After the solvent evaporation, the residue was recrystallized from acetonitrile with addition of isopropyl alcohol.

2.2.1. Complex 3a ($\text{Ph}_4\text{Sb}\cdot\mathbf{1a}$)

M.p. 160 °C. Yield 102 mg (0.14 mmol, 70%). IR: 3065, 3050, 1645 (CO), 1574, 1477, 1435, 1333, 1248, 1182, 1248, 1182, 1159, 1066, 997, 840, 766, 733, 691, 615, 565 (Sb–O), 513, 453 (Sb–C). ^1H NMR (400 MHz, CDCl_3): 2.06–2.18 (m, 2H, CH_2 -6), 3.02–3.11 (m, 2H, CH_2 -7), 3.50–3.58 (m, 2H, CH_2 -5), 7.39–7.54 (m, 17H, SbPh_4 , Ph), 7.76–7.81 (m, 8H, SbPh_4), 8.03–8.09 (m, 1H, H-5(Py)), 8.23–8.33 (m, 2H, H-3,4(Py)), 8.51–8.55 (m, 1H, H-3'(Py)). ^{13}C NMR (100 MHz, CDCl_3): 25.5, 32.5, 33.9, 123.0, 127.9, 128.6, 128.6, 128.7, 129.3,

129.5, 129.6, 130.8, 133.9, 134.2, 134.4, 135.3, 137.0, 137.5, 138.3, 139.4, 146.9, 153.6. Found, %: C 70.93, H 4.81, N 3.69. $C_{44}H_{35}N_2O_2Sb$. Calculated, %: C 70.89, H 4.73, N 3.76.

2.2.2. Complex 3b (Tol₄Sb•1a)

M.p. 212 °C. Yield 86 mg (0.11 mmol, 62%). IR: 3055, 3009, 2959, 2918, 1647 (CO), 1589, 1491, 1443, 1393, 1337, 1312, 1252, 1211, 1186, 1146, 1061, 1013, 993, 945, 841, 795, 766, 700, 569 (Sb–O), 532, 480 (Sb–C). ¹H NMR (400 MHz, CDCl₃): 2.11–2.20 (m, 2H, CH₂-6), 2.40 (s, 12H, C₆H₄Me), 3.04–3.13 (m, 2H, CH₂-7), 3.50–3.59 (m, 2H, CH₂-5), 7.20–7.30 (m, 8H, Sb(C₆H₄Me)₄), 7.48–7.56 (m, 5H, Ph), 7.66–7.71 (m, 8H, Sb(C₆H₄Me)₄), 7.99–8.08 (m, 1H, H-5(Py)), 8.09–8.21 (m, 2H, H-3,4(Py)), 8.56–8.63 (m, 1H, H-3'(Py)). Found, %: C 71.86, H 5.37, N 3.57. $C_{48}H_{43}N_2O_2Sb$. Calculated, %: C 71.92, H 5.41, N 3.49.

2.2.3. Complex 3c (Ph₄Sb•1b)

M.p. 193 °C. Yield 100 mg (0.14 mmol, 70%). IR: 3053, 2922, 1595 (CO), 1573, 1557, 1479, 1466, 1431, 1389, 1269, 1223, 1186, 1152, 1063, 1022, 997, 860, 820, 797, 762, 733, 694, 567, 529 (Sb–O), 490, 457 (Sb–C). ¹H NMR (CDCl₃, δ, ppm): 2.42 (s, 3H, C₆H₄Me), 7.27–7.33 (m, 2H, C₆H₄Me), 7.39–7.50 (m, 12H, Ph), 7.52–7.58 (m, 2H, C₆H₄Me), 7.70–7.79 (m, 8H, '), 8.30 and 8.44 (both d, 1H, ³J 8.4 Hz, H-3 and H-3'), 8.87–8.91 and 9.07–9.11 (both m, 1H, H-6 and H-6'). ¹³C NMR (100 MHz, CDCl₃): 21.2, 120.0, 121.3, 126.9, 129.2, 129.9, 130.5, 131.5, 134.7, 134.9, 135.3, 136.5, 137.2, 138.0, 138.2, 147.6, 150.7, 154.5, 156.9, 168.1. Found, %: C 70.25, H 4.51, N 3.98. $C_{42}H_{33}N_2O_2Sb$. Calculated, %: C 70.11, H 4.62, N 3.89. Crystals of the compound suitable for X-ray diffraction were obtained by evaporation of its toluene–isooctane solution. Crystallographic data: monoclinic, P 1, a = 25.4326(5) Å, b = 8.06810(10) Å, c = 18.1376(3) Å, α = 90°, β = 102.769(2)°, γ = 90°, V = 3629.66(11) Å³, Z = 4, d_{calc} = 1.317 g/cm³, μ = 0.797 mm⁻¹, 86660 reflections, 9448 independent reflections (*R*_{int} = 0.0812), the number of refinement variables 425, GOOF = 1.042, *R* factors for *F*² > 2σ(*F*²): *R*₁ = 0.0677, w*R*₂ = 0.1119; *R* factors for all reflections: *R*₁ = 0.0420, w*R*₂ = 0.1011. CCDC registration code 2393136. Ph), 7.98 and 8.12 (both d, 1H, ³J 8.4 Hz, H-4 and H-4

2.2.4. Complex 3d (Tol₄Sb•1b)

M.p. 240 °C. Yield 80 mg (0.10 mmol, 60%). IR: 3026, 2968, 2916, 2862, 2344, 1626 (CO), 1587, 1493, 1462, 1329, 1190, 1144, 1113, 1063, 1016, 843, 799, 760, 712, 650, 634, 571, 548, 529 (Sb–O), 484 (Sb–C). ¹H NMR (400 MHz, CDCl₃): 2.40 (s, 12H, Sb(C₆H₄Me)₄), 2.44 (s, 3H, C₆H₄Me), 7.24–7.29 (m, 8H, Sb(C₆H₄Me)₄), 7.30–7.34 (m, 2H, C₆H₄Me), 7.65–7.72 (m, 8H, Sb(C₆H₄Me)₄), 8.08 and 8.20 (both d, 1H, ³J 8.4 Hz, H-4 and H-4'), 8.35 and 8.47 (both d, 1H, ³J 8.4 Hz, H-3 and H-3'), 8.92–8.96 and 9.13–9.18 (both m, 1H, H-6 and H-6'). ¹³C NMR (100 MHz, CDCl₃): 21.2, 21.5, 120.0, 121.3, 126.9, 129.9, 129.9, 132.1, 133.5, 134.7, 134.9, 135.3, 136.4, 138.0, 138.2, 140.6, 147.6, 150.9, 154.7, 156.7,

168.0. Found, %: C 71.36, H 5.46, N 3.74. $C_{46}H_{41}N_2O_2Sb$. Calculated, %: C 71.24, H 5.33, N 3.61.

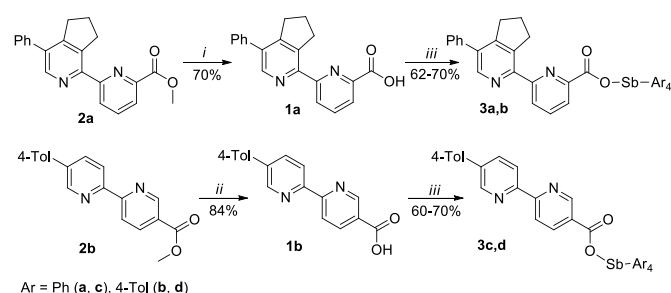
3. Results and discussions

3.1. Synthesis

2,2'-Bipyridine-based carboxylic acids are well-known ligands for various metal cations; however, none of them were reported as ligands for Sb(V). In this study 5-aryl-2,2'-bipyridinecarboxylic acids were investigated as potential ligands. Earlier, we obtained ligand **1a** by hydrolysis of corresponding ether **2a** for the synthesis of Ln(III) complexes [20] (Scheme 1). The same method was used for the synthesis of 2,2'-bipyridine-5-carboxylic acid **1b** from ether **2b**, which we obtained previously [19]. The described procedure for the synthesis of the Sb(V) complexes with aromatic carboxylic acids [7] turned out to be suitable for ligands **1**.

The structure of products **3** was confirmed by the ¹H NMR, ¹³C NMR, IR-spectra data as well as by elemental analysis. In particular, the IR spectra of all compounds contain bands at 1595–1647 cm⁻¹ due to COO group vibrations. Bands at 529–569 cm⁻¹ and 453–484 cm⁻¹, correspondingly, are related to Sb–O and Sb–C bond vibrations [27]. In the ¹H NMR spectra of compounds **3** arylbipyridine protons signals are shifted in comparison to the signals of corresponding carboxylic acids and the signals of aryl substituents of Sb(V) are present.

The structure of complex **3c** was determined by XRD analysis (Figure 1). The antimony atoms have a distorted trigonal-bipyramidal coordination with carbon atoms of three aryl groups in the equatorial plane and with the remaining aryl group carbon atom and carboxylate group oxygen atoms in the axial planes. Antimony atoms deviate from the equatorial plane by 0.143 Å towards the axial carbon atom like in the other tetraarylantimony carboxylates [28]. Two equatorial C_{eq}SbC_{eq} angles in **3c** (103.8(1), 102.4(1)°) are much less than 120°, while the third one is larger (149.1(1)°), which can be explained by carboxylate ligand coordination. It is coordinated to the antimony atom by carbonyl oxygen atoms. The distance Sb...O=C (2.591(2) Å) is much less than the sum of van der Waals radii of Sb and O atoms 3.70 Å [29] and is slightly more than Sb–O bond length 2.591(2) Å.



Scheme 1 Synthesis of Sb(V) complexes. Reagents and conditions: i) KOH / H₂O:EtOH (2:8), reflux, 2 h, then HCl, 20 °C; ii) NaOH, ethanol, 78 °C, 1 h, then HCl, 20 °C; iii) Ar₃Sb / benzene, rt, 24 h.

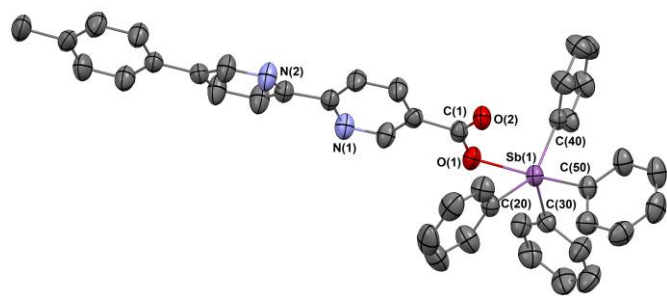


Figure 1 Molecular structure of **3c** showing thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Sb–C_{eq} 2.140(3), 2.126(3), 2.138(2), Sb–C_a 2.164(3), Sb–O_a 2.313(2), C_{eq}SbC_{eq} 103.8(1), 102.4(1), 149.1(1), C_aSbO_a 169.13(9), C_{eq}SbO_a 78.92(9), 84.83(8), 90.19(8), C_{eq}SbC_a 94.1(1), 99.6(1), 97.5(1).

3.2. Photophysical studies

Photophysical properties of synthesized Sb(V) complexes **3** in a dilute solution of acetonitrile (10⁻⁵ M) are summarized in Table 1. Figures 2–5 show absorption and emission spectra of complexes **3** and ligands **1** in CH₃CN.

The results of the measurements showed a significant dependence of the photophysical properties of the obtained complexes with antimony on the position of the carboxyl group in the structure of the initial ligand. Thus, complexes **3a,b** of 6-carboxylic acid **1a** showed extremely negligible emission with values of absolute quantum yields below 0.1%, and a sharp decrease in the emission intensity and a hypsochromic shift of the absorption maxima at 33 nm compared to the initial ligand were observed.

Table 1 Data of photophysical properties of complexes **3** in CH₃CN solution (C = 10⁻⁵ M).

Compound	$\lambda_{\text{abs}}^{\text{max}}$, nm ^a	$\lambda_{\text{em}}^{\text{max}}$, nm ^b	Stokes shift, nm	Φ_f , % ^c
3a	264, 270, 300	364	64	<0.1
3b	262, 300	364	64	<0.1
3c	264, 314	403	89	65.0
3d	263, 312	403	91	54.8

^a Absorption spectra were measured at r.t. in MeCN in range from 245 to 450 nm,

^b Emission spectra were measured at r.t. in MeCN,

^c Absolute quantum yields were measured using the Integrating Sphere of the Horiba-Fluoromax-4 at r.t. in MeCN [30].

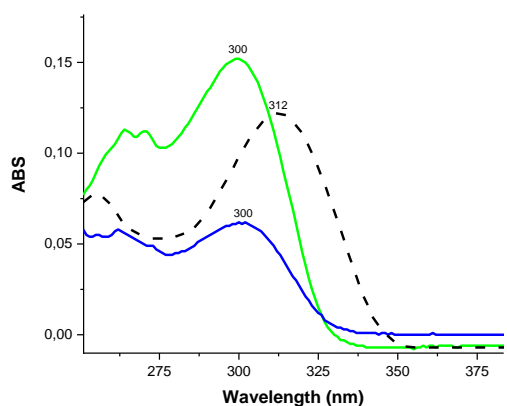


Figure 2 Absorption spectra of Sb(V) complexes **3a** (green line), **3b** (blue line) and ligand **1a** (black dotted line) in CH₃CN (C = 10⁻⁵ M).

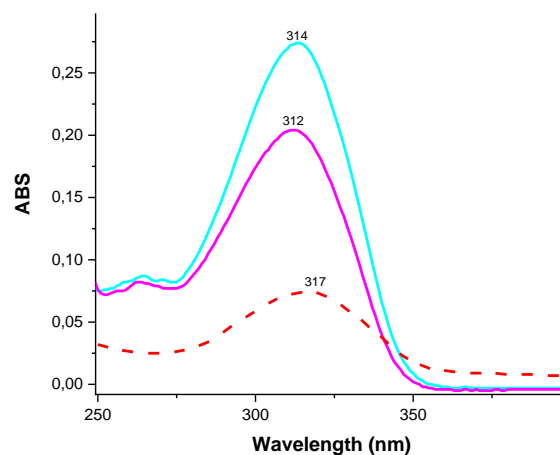


Figure 3 Absorption spectra of Sb(V) complexes **3c** (cyan line), **3d** (magenta line) and ligand **1b** (red dotted line) in CH₃CN (C = 10⁻⁵ M).

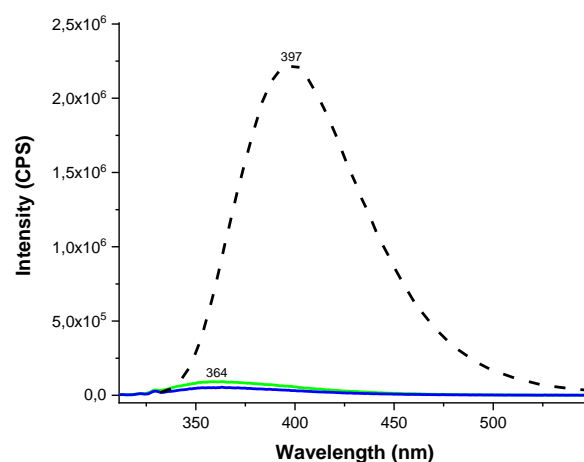


Figure 4 Emission spectra of Sb(V) complexes **3a** (green line), **3b** (blue line) and ligand **1a** (black dotted line) in CH₃CN (C = 10⁻⁵ M).

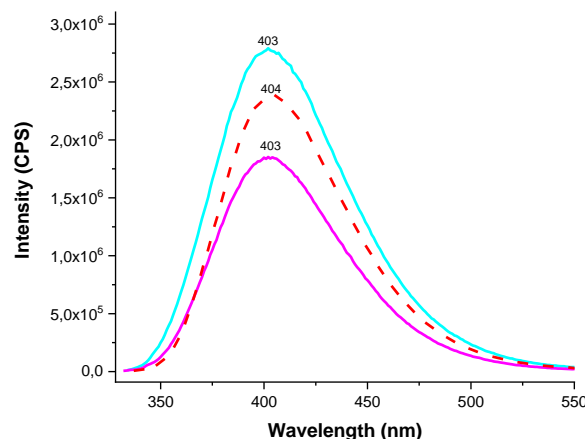


Figure 5 Emission spectra of Sb(V) complexes **3c** (cyan line), **3d** (magenta line) and ligand **1b** (red dotted line) in CH₃CN (C = 10⁻⁵ M).

In contrast, complexes **3c,d** of 5-carboxylic acid **1b** showed quantum yield values of 54.8–65.0%, and there is practically no shift of emission maxima in comparison with the ligand. The emission intensity also did not undergo significant changes. The hypsochromic shift of the absorption maxima when going from ligand to complexes is also stronger in the case of 6-carboxylic compounds compared to 5-carboxylic compounds (12 nm and 3–5 nm, respectively).

3.3. Molecular docking

The next step of our work was an evaluation of possible antitumor activity of some of the obtained Sb(V) complexes. In order to determine a potential mechanism of compounds **3** activity, the molecular docking studies on some of the typical target proteins were conducted based on the structure of their complexes with inhibitors (*i.e.* p38a (pdb: 4ewq) [31], ERK2 (pdb:1tvo) [32], VEGFR2 (pdb: 3efl) [33]). The complexes of corresponding proteins with well-known inhibitors were used for docking (Figure 6).

Molecular docking was done with Arguslab 4.0.1 software [34] using Lamarckian genetic algorithm GADock and empirical scoring function AScore. Water molecules and third-party molecules were removed from the complexes, and hydrogen atoms were added. The studied ligands were prepared for docking using OpenBabel 2.4.1 [35] with the generation of 3D structure by the internal method, and the size of binding sites for calculations was determined automatically relative to the positions of the native ligands in complexes. Validation was performed by redocking of the native ligands with the calculation of their root-mean-square deviation – RMSD (threshold value $\text{RMSD} < 2 \text{ \AA}$). The results of docking studies are given in Table 2.

It should be noted that the antimony atom in the studied structures contributes to the instability of the evaluation function (as well as to the generation of 3D structure, which is partially resolved by the UFF force field in OpenBabel).

The calculation results show no bonding possibility of **3d** at p38a active center. **3c** and **3d** are unable to bind with target receptor VEGFR2 as well.

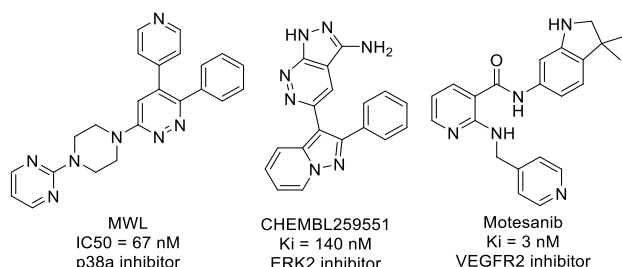


Figure 6 Inhibitors/native ligands of the target proteins for molecular docking.

Table 2 The results of molecular docking studies.

Structure	Docking score, kcal/mol		
	p38a	ERK2	VEGFR2
Protein			
PDB	4ewq	1tvo	3efl
native ligand*	-9.65	-9.06	-10.86
(rmsd)	(1.47Å)	(1.50Å)	(1.69Å)
1a	-10.06	-10.90	-11.00
1b	-10.02	-9.70	-10.93
3a	-12.75	-5.45	-18.89
3b	-5.41	-9.38	-15.60
3c	-9.40	-12.64	48.86
3d	20.36	-13.15	18.77

*native ligands – inhibitors from the corresponding protein complexes (Figure 4).

In the other cases the possibility of formation of stable protein complexes was shown (hit compounds for each target are marked grey in Table 1). It should be noted that free ligands **1a**, **1b** could form more stable complexes with target proteins than their organometallic complexes (*e.g.* docking results for **3b-3d** in p38a protein).

The most promising docking result was obtained for the structure **3a** docked into VEGFR2 active center (Figure 7) according to the docking score (Table 2) that was much better than the results for native inhibitor Motesanib (Figure 4) and corresponding free ligands **1a-b**.

Two possible targets could be presumed for studied organometallic complexes based on the best docking scores across all 3 proteins: 1) VEGFR2 for **3a**, **3b**; 2) ERK2 for **3c**, **3d**. Free ligands **1a,1b** have the same calculated affinity to all 3 targets.

4. Limitations

The studies demonstrated that complexes of 2,2'-bipyridinecarboxylic acids containing a carboxyl fragment in the α -position of the edge pyridine cycle show low luminescence (quantum yields $< 0.1\%$). A way to circumvent this limitation is to switch to the use of β -substituted carboxylic acids as ligands, in which case a significant improvement in the photophysical properties of Sb(V) complexes such as Stokes shift (up to 91 nm) and absolute fluorescence quantum yield (up to 65%) was observed.

5. Conclusions

In this work the Sb(V) complexes of the 2,2'-bipyridinecarboxylic acids have been synthesized for the first time. It was shown that the carboxyl group is involved in coordination with the antimony cation, but the nitrogen atoms of the 2,2'-bipyridine core do not. The primary photophysical properties (absorption and emission maxima, luminescence quantum yields in acetonitrile solution) were studied, and their difference for 5- and 6-carboxyl-substituted compounds was shown. *In silico* studies of their potential cytotoxic activity against the chosen target proteins were conducted. In particular, complexes of the 6-carboxyl-substituted ligand showed better affinity for VEGFR2, and those of the 5-carboxyl-substituted ligand showed better affinity for ERK2.

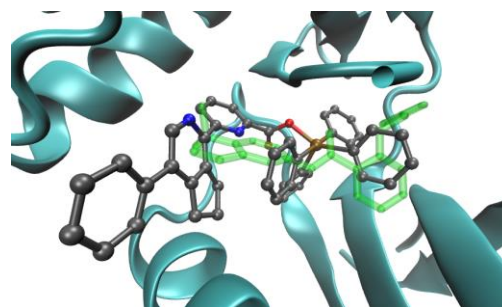


Figure 7 Docked structure **3a** (gray carbon skeleton) into VEGFR2 (cink color) in comparison with native ligand Motesanib (green transparent skeleton).

Overall, the research demonstrates the potential of 2,2'-bipyridinecarboxylic acids as ligands for the design and synthesis of novel antimony(V) complexes with tailored properties. Future research should focus on comprehensive structure-activity relationship studies and in-depth biological evaluations.

• Supplementary materials

No supplementary materials are available.

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• Conflict of interest

The authors declare no conflict of interest.

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