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Synthesis, Spectral, and Single Crystal XRD Studies of Novel Terpyridine Derivatives of Benzofuran-2-Carbaldehyde and Their Cu(II) Complex

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Abstract—A series of novel terpyridine derivatives of benzofuran (NP1–NP3) were synthesised by simple multicomponent one pot reaction among benzofuran-2-carbaldehyde, ammonium hydroxide and three different derivatives of acetyl pyridine with isolated yield up to 98%. All the synthesised molecules were characterised by NMR, HRMS, IR spectroscopies and single crystal XRD (CIF file CCDC no. 2078532 for TP1). Cu(II) complexes were prepared selectively with terpyridine derivative of 2-acetyl pyridine and characterised by single crystal XRD (CIF file CCDC no. 1525025 for TP-Cu). UV–Vis spectral studies were performed with all the prepared molecules.

Keywords: terpyridine, benzofuran, multicomponent, one pot, single crystal XRD

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INTRODUCTION

Terpyridines have been extensively used as ligands in metal chelation due to their aromatic structure, which consist of three pyridine rings with adjacent nitrogen atoms. In this concern, their major applicatory research is usually related with catalysis, optoelectronics and photovoltaic materials [1–3]. Their coordination compounds with transition metals that can change their oxidation state are useful in numerous reactions comprising C–C coupling. However, the central coordinated metal atom is not essential and terpyridine alone has been an operative organ-catalyst in the synthesis of carbonates from CO_2 [4]. In medicinal chemistry, terpyridines and their coordination compounds are well known for their varied range of activity against bacteria, fungi and cancer cells [5–7]. Furthermore, coordination compounds that are constructed on redox-active metals (Fe, Cu) increase nuclease activity by transferring the redox state of the coordinated atom and creating reactive oxygen species (ROS) [5]. Therefore, disruption of redox homeostasis and selective accumulation of complexes may affect DNA and/or mitochondrial damage [8–10]. Recently, Deka et al. reported terpyridine-copper coordination compounds that selectively accumulated in the mitochondria, where they increased ROS levels and oxidative stress, resulting in the activation of apoptosis pathways [11].

Among various scaffold of terpyridine 2,2';6',2''-terpyridine has a significantly higher activity against various cancer cell lines than its analogue, 2,2';6',3''-terpyridine. Subsequently, the activity of 2,2';6',4''-terpyridine is even less active (three orders of magnitude) than the derivative with adjacent nitrogen atoms, which are more suitable for metal coordination. In this case, naturally prevailing metals such as zinc, copper or iron may be accountable for the terpyridine activity. This may be conjectured further for two possible mechanisms of action that consist of generating ROS (in the case of Fe(II) or Cu(II) ions) or those with an ionophoric activity (all metal ions). A comparable mechanism has been recognized for quinoline derivatives such as clioquinol in which the mobilisation of Zn(II) and Fe(II) ions activated the hypoxia-inducible factor (HIF) [12, 13]. However terpyridine substituted by the heterocyclic moieties had a better activity and offered a better intercalating potency and/or DNA degradation [14]. This may be at least somewhat explained by its greater lipophilicity and permeability through the biological membranes. Considering on these hopeful outcomes of terpyridine system and their metal complexes, herein, a series of terminally functionalised terpyridine molecules (TP1 to TP3) and Cu(II) complex of the type [Cu(2,2':6',2''-terpyridine)$(Cl)_2$] (TP1-Cu) was synthesised and characterised by different methods.

EXPERIMENTAL

All the chemicals of Sigma, TCI and S-Define were obtained from local supplier and used without

further purification. Solvents were dried over molecular sieves if necessary. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature using a Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer, TMS was used as internal reference, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad, app = apparent), coupling constants (*J*; Hz), and assignment. ^{13}C and DEPT-135 NMR spectra were measured on Bruker AVANCE III 125 MHz (AV 125) with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. Infrared (IR) spectra were recorded neat by ATR on a Thermo Nicolet iS50 FT–IR spectrometer and are reported in cm^{-1}. HR–MS data were obtained in methanol, with Thermo Scientific Orbitrap Elite Mass spectrometer. Melting point is measured by open capillary method using Sigma Melting Point Apparatus. Single crystal structural data were recorded on Bruker Kappa APEXII (CIF files CCDC nos. 2078532 for TP1; 1525025 for TP-Cu). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by recrystallization or column chromatography silica gel 60 (Merck, 230–400 mesh).

Synthesis of 4'-(benzofuran-2-yl)-2,2':6',2"-terpyridine (TP1). Benzofuran-2-carbaldehyde (A1) (0.5 mmol, 81.5 mg), dissolved in 2 mL ethanol, was added to the solution of 2-acetyl pyridine (K1) (1 mmol; 121 mg) in 3 mL ethanol. The solution was stirred at room temperature for 15 min. Then a small piece of KOH pellet (~0.05 mg) was added followed by 25% (w/v) aqueous ammonia (1.5 mL) and the resultant mixture was stirred at room temperature for 6 h. The reaction was monitored on TLC. After completion of reaction, the obtained solid product was filtered under vacuum onto a sintered funnel. The solid was washed with ice-cold ethanol until the washings are colourless and recrystallized from $CHCl_3$. Greenishwhite solid, yield 180 mg (98%), m.p. 135–136°C. FT-IR (KBr pellet; ν_{max}, cm^{-1}): 1070, 1266, 1315, 1686, 3049; ^{1}H NMR (500 MHz; $CDCl_3$; δ, ppm): 7.3 (t., *J* = 7 Hz, 1H), 7.3 (t., *J* = 7.5 Hz, 3H), 7.5 (s., 1H), 7.8 (t., *J* = 8 Hz, 2H), 8.6 (d., *J* = 8 Hz, 2H), 8.7 (d., *J* = 4.5 Hz, 2H), 8.9 (s., 2H); ^{13}C NMR (125 MHz; $CDCl_3$; δ, ppm): 105.28, 111.63, 116.10, 121.32, 121.61, 123.24, 123.97, 125.54, 128.73, 136.88, 139.48, 149.18, 153.67, 155.34, 155.97, 156.10; DEPT-135: 105.28, 111.63, 116.09, 121.32, 121.61, 123.25, 123.98, 125.54, 136.89, 149.18; HRMS (ESI; ion trap) *m/z*: $[M + H]^+$: calcd. ($C_{23}H_{16}N_3O$): 350.1288, found.: 350.1413.

Synthesis of 4'-(benzofuran-2-yl)-3,2':6',3"-terpyridine (TP2) was synthesised by similar process of TP1, from benzofuran-2-carbaldehyde (A1) (0.5 mmol, 81.5 mg), 3-acetyl pyridine (K2) (1 mmol, 121 mg). White solid, yield 172 mg (92%), m.p. 148–150°C. FT-IR (KBr pellet; ν_{max}, cm^{-1}): 1070, 1266, 1315, 1686, 3049; ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 7.3 (t., *J* = 7.5 Hz, 1H), 7.4 (t., *J* = 3.5 Hz, 2H), 7.6 (d., *J* = 8.5 Hz, 1H), 7.6 (d., *J* = 7.5 Hz, 1H), 8.1 (s., 2H), 8.5 (d., *J* = 8 Hz, 2H), 8.7 (d., *J* = 4 Hz, 1H), 9.4 (s., 2H). ^{13}C NMR (125 MHz, $CDCl_3$; δ, ppm): 105.52, 11.61, 114.48, 121.77, 123.62, 126.07, 128.41, 134.42, 134.49, 139.66, 148.42, 150.37, 152.73, 155.58; DEPT-135 (125 MHz; $CDCl_3$, δ, ppm): 105.52, 111.61, 114.48, 121.77, 123.63, 126.07, 134.49, 148.42, 150.37; HRMS (ESI; ion trap) *m/z*: $[M + H]^+$: calcd. ($C_{39}H_{30}O_5N_3$): 620.2180, found.: 620.2148.

Synthesis of 4'-(benzofuran-2-yl)-4,2':6',4"-terpyridine (TP3) was synthesised by similar process of TP1, from benzofuran-2-carbaldehyde (A1) (0.5 mmol, 81.5 mg), 4-acetyl pyridine (K3) (1 mmol, 121 mg). Off-white solid, yield 184 g (98%), m.p. 157–159°C. FT-IR (KBr pellet; ν_{max}, cm^{-1}): 1058, 1258, 1318, 1406, 1633; ^{1}H NMR (500 MHz, $CDCl_3$): 7.3 (t., *J* = 7.5 Hz, 1H), 7.4 (t., *J* = 7.5 Hz, 2H), 7.6 (d., *J* = 8.5 Hz, 1H), 7.7 (d., *J* = 8 Hz, 1H), 8.1 (d., *J* = 5.5 Hz, 4H), 8.2 (s, 2H), 8.8 (d, *J* = 5.5 Hz, 4H); ^{13}C NMR (125 MHz; $CDCl_3$; δ, ppm): 105.77, 111.61, 115.65, 121.12, 121.83, 123.74, 126.26, 128.34, 139.89, 145.73, 150.59, 152.40, 155.38, 155.44; DEPT-135 (125 MHz; $CDCl_3$; δ, ppm): 105.77, 111.61, 115.65, 121.12, 121.83, 123.74, 126.26, 150.59; HRMS (ESI; ion trap) *m/z*: $[M + H]^+$: calcd. ($C_{23}H_{16O}N_3$): 350.1288, found.: 350.1295.

Synthesis of Cu(II) complex of 4'-(benzofuran-2-yl)-2,2':6',2"-terpyridine (NP1-Cu(II)). Terpyridine TP1 (1 mmol, 366 mg), dissolved in 2 mL chloroform was added to the solution of copper(II) chloride (1 mmol; 0.99 mg) in 3 mL ethanol. The solution was stirred at room temperature for 2 h. The reaction was monitored on TLC. After completion of reaction, the obtained solid product was filtered under vacuum onto a sintered funnel. The solid was washed with ice-cold chloroform and recrystallized from ethanol. Dark green solid, yield 472 mg (95%), m.p. > 300°C. The structure of synthesised coordination compound was confirmed by single crystal XRD.

RESULTS AND DISCUSSION

A well-established terpyridine synthesis from aromatic aldehyde and acetyl pyridine involves the intermediate synthesis of chalcone, followed by the formation of 1,5-diones and cyclization-aromatization with ammonium hydroxide [15]. A significant advantage of this method is that it makes use of multicomponent single pot reaction. Present work shows the synthesis novel terpyridine derivatives of benzofuran by simple multicomponent one pot reaction between benzofuran-2-carbaldehyde, ammonium hydroxide and various derivatives of acetyl pyridine (Scheme 1).

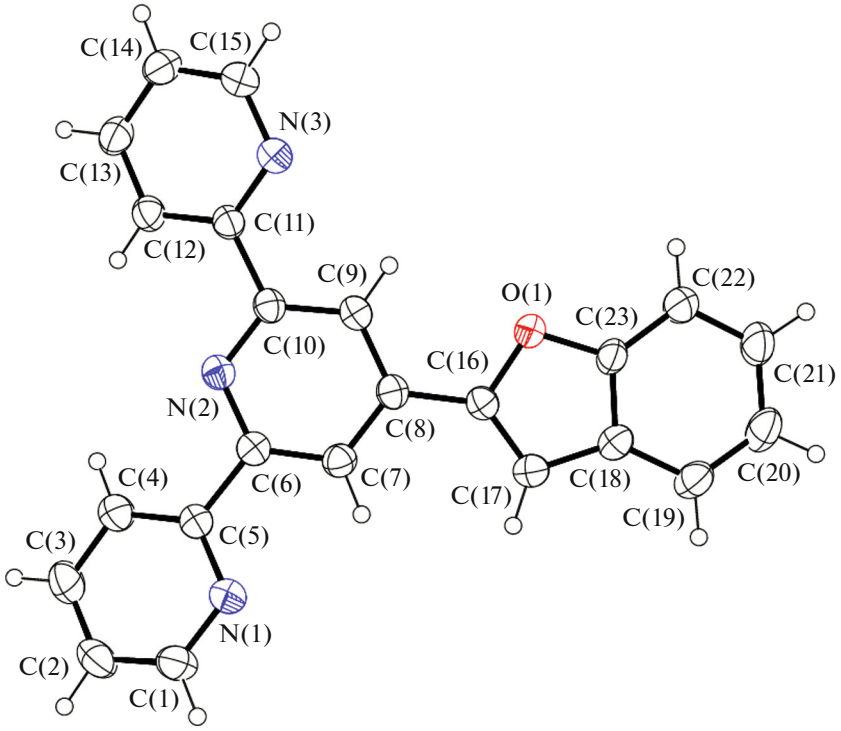
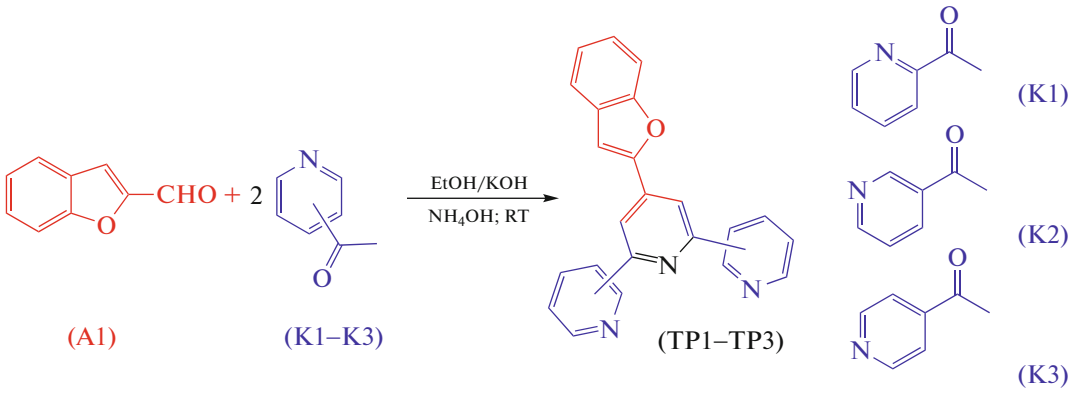


Fig. 1. Molecular structure of TP1 displacement ellipsoid plot drawn at 40% probability.



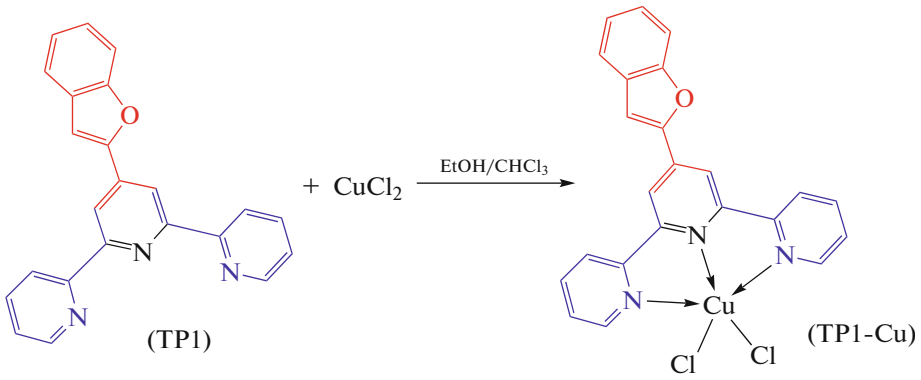
Scheme 1.

The structures of the synthesized molecules were confirmed by NMR spectroscopy, HRMS and IR spectrometry. The ^{1}H NMR spectra of all the molecules are having all their peaks in aromatic region with suitable number of hydrogen. The symmetric structure of TP3 is clearly observed in its ^{1}H NMR spectrum. ^{13}C NMR spectra of all these molecules are also having all the possible peaks in aromatic region. DEPT-135 spectra for all the structures show the presence of all six quaternary carbons, i.e. carbon without hydrogen. The crystal of TP1 was developed from ethanol for single crystal XRD analysis (Fig. 1). The crystal data and structure refinement for TP1 are listed in Table 1. The UV–Vis spectrums for all the three molecules were recorded with very dilute solution in THF (Fig. 2). All these molecules are having their absorbance maxima (λ max) in the range of 425 to 445 nm.

A metal chelate formation is possible only with *o*-terpyridine (TP1), therefore Cu(II) complex (chelate)—Cu(II) coordination compound of 4'-(benzofuran-2-yl)-2,2':6',2''-terpyridine (TP1-Cu) was synthesised by the reaction of TP1 with copper(II) chloride (Scheme 2) [13].

Table 1. Crystallographic data and structure refinement for TP1 and complex TP1-Cu

Parameter	Value	
	TP1	TP1-Cu
Empirical formula	$C_{23}H_{15}N_3O$	$C_{23}H_{15}N_3OCl_2Cu$
Formula weight	349.38	483.82
Temperature, K	296(2)	296(2)
Wavelength, Å	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a, Å	6.2691(6)	12.0147(6)
b, Å	17.6364(17)	8.0670(4)
c, Å	15.6999(16)	20.5984(9)
Volume, Å^3	1725.3(3)	1968.17(16)
Z	4	4
ρ_{calcd}, mg/m^3	1.345	1.633
μ, mm^{-1}	0.085	1.403
F(000)	728	980
Crystal size, mm	0.350 × 0.300 × 0.250	0.250 × 0.200 × 0.150
Theta range for data collection	1.742 to 24.998.	2.717 to 24.995
Index ranges	$-7 \le h \le 7$, $-20 \le k \le 20$, $-18 \le l \le 18$	$-14 \le h \le 14$, $-9 \le k \le 9$, $-24 \le l \le 24$
Reflections collected	18594	20709
Independent reflections (R_{int})	3025 (0.0461)	3462 (0.0330)
Completeness to θ = 24.998°, %	99.2	99.9
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max and min transmission	0.7455 and 0.6458	0.7460 and 0.6409
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3025/0/244	3462/95/271
Goodness-of-fit on F^2	1.058	1.024
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0453$, $wR_2 = 0.0945$	$R_1 = 0.0283$, $wR_2 = 0.0777$
R indices (all data)	$R_1 = 0.0740$, $wR_2 = 0.1096$	$R_1 = 0.0405$, $wR_2 = 0.0858$
Largest diff. peak and hole, e Å^{-3}	0.130 and –0.188	0.301 and –0.275



Scheme 2.

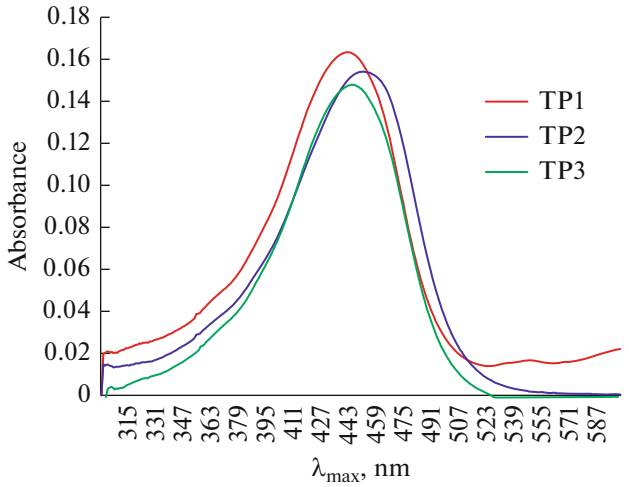


Fig. 2. UV–Vis spectrum of TP1, TP2 and TP3.

Simple metal complexes can be prepared with remaining two ligands, however they require different protocol, therefore it has not been presented in this manuscript. The structure of complex TP1-Cu was initially evaluated by IR and mass spectrum. Finally the structure of this complex was confirmed by single crystal XRD (Fig. 3). The crystal of TP1-Cu(II) was developed in biphasic solvent system, i.e. chloroform–ethanol. A crystal structure shows that Cu(II) has coordinated with three N atoms of TP1 by secondary valence. Also it has two chloride ions attached by primary (ionic) valance. The crystal data and structure refinement for TP1-Cu are listed in Table 1. The UV–Vis spectrum of TP1-Cu was also recorded with very dilute solution in THF (Fig. 4). It has shown the absorbance maxima (λ_{max}) at 490 nm.

The UV absorption maxima (λ_{max}) are a unique characteristic of a particular molecule. In order to see the effect of metal chelation on UV absorption maxima of ligand molecule (TP1), the UV–Vis spectrums for TP1 and its Cu(II) chelate were recorded in THF. The comparison UV spectrums of ligand TP1 (λ_{max} = 224) and its chelate (λ_{max} = 490) shows the increase in λ_{max}, i.e. bathochromic shift. This indicates the chelation of TP1 with the Cu(II) metal ion [13].

CONCLUSIONS

Different novel terpyridine derivatives were synthesised from benzofuran-2-carbaldehyde. The structures of all these newly synthesised compounds were confirmed by NMR, HRMS and IR spectrum. The UV–Vis spectrums for all three compounds were also recorded in THF. Cu(II) coordination compound was synthesised with 4'-(benzofuran-2-yl)-2,2':6',2''-terpyridine. The structure of the synthesised coordination compound was confirmed by single crystal XRD. The UV–Vis spectrum of this coordination compound was also recorded in THF. These synthesized molecules will be studied for their DNA binding activities and cytotoxicity.

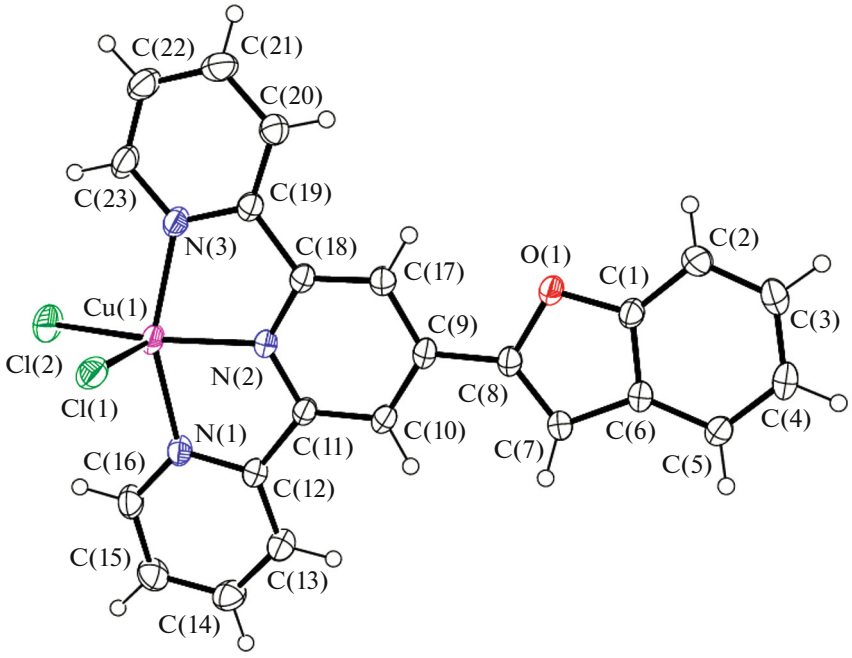


Fig. 3. Molecular structure of TP1-Cu displacement ellipsoid plot drawn at 40% probability.

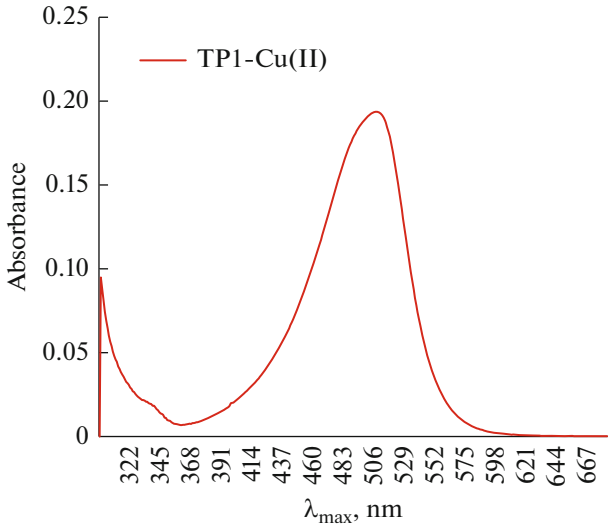


Fig. 4. UV–Vis spectrum of TP1-Cu.

FUNDING

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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