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ORIGINAL PAPER

Preparation, Characterization and Crystal Structures of a Key Intermediate, and a Significant Impurity, in the Synthesis of Repaglinide

Gui-Mei Tang[1] · Yong-Tao Wang[1] · Yu-Song Wu[1]

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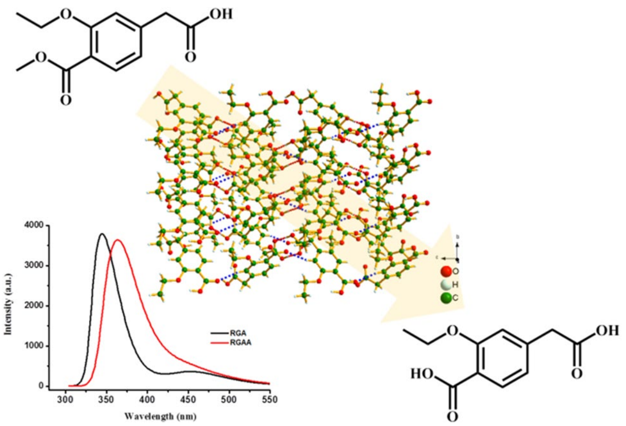
Abstract

The crystal structure of 2-(3-ethoxy-4-(methoxycarbonyl)phenyl) acetic acid (**RGA**), an important intermediate in the preparation of Repaglinide, has been carried out. Hydrogen bonds between the carboxylate groups link the molecules into dimers while weak C–H···π interactions link these dimers into a one-dimensional chain lying along the crystallographic *b* axis. 4-(Carboxymethyl)-2-ethoxybenzoic acid (**RGAA**), an impurity observed in the preparation of Repaglinide, has been simply synthesized by the hydrolysis of **RGA** under basic conditions. Hydrogen bonds between the carboxylate groups link the molecules into dimers while weak C–H···O interactions connect these dimers into a one-dimensional chain lying along the crystallographic *c* axis. The compound **RGAA** has also been characterized by FT-IR and UV–Vis spectra, and by ^{1}H NMR analysis. **RGA**: monoclinic, $P2_1/n$, $a = 12.848(3)$ Å, $b = 4.5539(10)$ Å, $c = 22.328(5)$ Å, $\alpha = 90°$, $\beta = 101.703(5)°$, $\gamma = 90°$, $V = 1279.2(5)$ Å^3. **RGAA**: monoclinic, $P2_1/n$, $a = 14.0877(11)$ Å, $b = 5.1814(3)$ Å, $c = 14.5857(11)$ Å, $\alpha = 90°$, $\beta = 91.578(3)°$, $\gamma = 90°$, $V = 1064.26(13)$ Å^3. The thermal behaviors and fluorescence properties of **RGAA** were also investigated.

Graphic Abstract

The crystal structures of one key intermediate of Repaglinide and its derivative have been characterized, where their luminescence properties and thermal behavior have been investigated.



Keywords Repaglinide · Intermediate · Infrared spectra · UV–Vis and NMR spectra · X-ray diffraction · Crystal structures · Thermal behavior · Photoluminescence

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10870-019-00811-7) contains supplementary material, which is available to authorized users.

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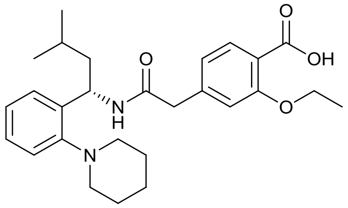
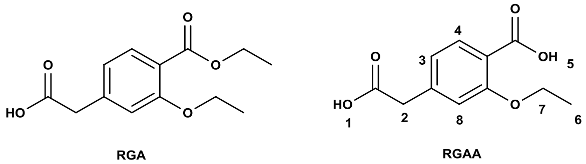


Scheme 1 The structure of the Repaglinide



Scheme 2 The structures of the **RGA** and **RGAA**

Introduction

Repaglinide, (*S*)-2-ethoxy-4-(2-((3-methyl-1-(2-(piperidin-1-yl)phenyl)butyl)amino)-2-oxoethyl) benzoic acid (Scheme 1), is a new class of oral hypoglycemic agent for type-II non-insulindependent diabetes, which stimulates the secretion of insulin from pancreatic beta cells, acting via calcium channels [1–6]. Compared with other antidiabetic agents, Repaglinide gives a significantly better biological profile [7–10]. The 2-(3-ethoxy-4-(methoxycarbonyl)phenyl) acetic acid (**RGA**) is one of the key intermediates for the synthesis of Repaglinide. A derivative of **RGA**, 4-(carboxymethyl)-2-ethoxybenzoic acid (**RGAA**) can be often observed during the preparation of Repaglinide, which is a crucial impurity affected the purity and the efficacy of the drug. Hydrolysis of **RGA** under basic condition easily leads to the formation of **RGAA** as a impurity [11]. To date there is still little information about the relationship between the solid-state structures and the properties of these compounds although the synthesis and development of the Repaglinide motif has been reported [12–20]. Thus, researching the solid-state structural information and other properties of the key intermediate of Repaglinide and its derivative still remains a big challenge.

Herein, we present the preparation of a pivotal intermediate of Repaglinide namely, 2-(3-ethoxy-4-(methoxycarbonyl)phenyl) acetic acid (**RGA**), and a derivative of this latter compound, 4-(carboxymethyl)-2-ethoxybenzoic acid (**RGAA**) (Scheme 2), which has been easily obtained through the hydrolysis of **RGA** under basic conditions. Both **RGA** and **RGAA** have both been characterized by FT-IR, UV–Vis, ^{1}H-NMR, MS and by single-crystal X-ray structural analyses. Additionally, the fluorescence properties of both **RGA** and **RGAA**, and the thermal behavior of **RGAA**, have been investigated.

Experimental

Materials and Measurements

2-(3-Ethoxy-4-(methoxycarbonyl)phenyl) acetic acid (**RGA**), sodium hydrate, and ethyl acetate were purchased from Shandong Solar Power Material Limited Corporation. The reagents and solvents employed were used as received without further purification.

Elemental analyses were performed on an Elementar vario EL III microanalyser. The FT-IR spectrum was recorded from KBr pellets in the range 400–4000 cm^{-1} on a Bruker spectrometer. The UV–Vis spectrum for **RGAA** was recorded on Shimadzu UV-2600 spectrometer. The^{1}H NMR spectra were recorded using a Bruker Advances 400 at 400 MHz for sample held at room temperature and dissolved in DMSO-d_6. Thermogravimetric analysis (TGA) data were collected with a TA SDT Q600 analyzer in N_2 at a heating rate of 10 °C min^{-1} from room temperature to 800 °C. At room temperature, solid-state fluorescent studies were conducted on a HITACHI F-4500 system.

Crystallization of 2-(3-Ethoxy-4-(methoxycarbonyl)phenyl) Acetic Acid (RGA)

The solution of **RGA** (1 mmol, 0.252 g) and water (10 mL) was stirred at 80 °C for 10 min. The solution was filtered and allowed to stand. The needle crystals suitable for single-crystal diffraction were obtained after 1 week. Yield (0.227 g, 90%).

Synthesis of 4-(Carboxymethyl)-2-ethoxybenzoic Acid (RGAA)

To a mixture solution of distilled water (10 mL) and NaOH (25 mmoL, 1.0 g), 2-(3-ethoxy-4-(methoxycarbonyl)phenyl) acetic acid (10 mmol, 2.38 g) was added. The reaction mixture was refluxed on a steam bath for 4 h. After cooling to room temperature, the pH value of the solution was adjusted to 1 by adding concentrated HCl solution. The solid formed was collected and washed with water. Yield (86.6%, 1.9391 g). The compound was recrystallized in distilled water. The colorless crystals suitable for single-crystal diffraction were obtained after several days. M.p. 138–140 °C. Elemental analysis calcd (%) for $C_{11}H_{12}O_5$ (224.21): C, 58.9; H, 5.4; N, 35.7; found: C, 58.7; H, 5.3; N, 35.8. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.441 (s, 2H), 7.550 (d, $J = 8$ Hz, 1H), 7.000 (s, 1H), 6.861 (d, $J = 8$ Hz, 1H), 4.059

(q, $J = 8$ Hz, 2H), 3.594 (s, 2H), 1.31 (t, $J = 8$ Hz, 3H). IR (KBr, cm^{-1}): 3424(br), 3288(w), 3215(w),1728(s), 1614(m), 1576(m), 1443(m), 1408(m), 1302(m), 1225(m), 1179(m), 1036(m), 914(w), 945(m),772(m), 692(m), 613(w), 459(w).

X-ray Crystallography

Data collection on single crystals of **RGA** and **RGAA** were carried out with a Bruker APEX II CCD diffractometer equipped with a graphite crystal monochromator Mo Kα radiation ($\lambda = 0.71073$ Å). The lattice parameters were obtained by a least-squares refinement of the diffraction data. All the measured independent reflections were used in the structural analysis, and semi-empirical absorption corrections were applied using the SADABS program [21]. The program SAINT was used for integration of the diffraction profiles [22]. The structure was solved by direct methods using the SHELXS program of the SHELXTL package and refined with SHELXL [23, 24]. All non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was performed by full-matrix least-squares methods with anisotropic thermal parameters for all the non-hydrogen atoms based on F^2. All hydrogen atoms were found in difference electron density maps. The hydrogen atoms on the oxygen atoms were refined, all others were placed in calculated positions and included in the refinement using the riding model with displacement parameters derived from the parent carbon atoms. Calculations for the crystal structure discussions were carried out with PLATON for Windows [25]. A summary of the crystallographic data and structure refinements are listed in Table 1. Corresponding hydrogen bonding data for **RGA** and **RGAA** is summarized in Table 2.

Table 1 Crystal data and structure refinement parameters for **RGA** and **RGAA**

Compound reference	**RGA**	**RGAA**
Chemical formula	$C_{13}H_{16}O_5$	$C_{11}H_{12}O_5$
Formula mass	252.26	224.21
Crystal system	Monoclinic	Monoclinic
a (Å)	12.848(3)	14.0877(11)
b (Å)	4.5539(10)	5.1814(3)
c (Å)	22.328(5)	14.5857(11)
α (°)	90.00	90.00
β (°)	101.703(5)	91.578(3)
γ (°)	90.00	90.00
Unit cell volume (Å^3)	1279.2(5)	1064.26(13)
Temperature (K)	296(2)	273(2)
Space group	$P2_1/n$	$P2_1/c$
No. of formula units per unit cell, Z	4	4
Radiation type	Mo Kα	Mo Kα
Absorption coefficient (μ mm^{-1})	0.101	0.111
No. of reflections measured	11,875	9042
No. of independent reflections	3313	1790
R_{int}	0.1062	0.0283
Final R_1 values ($I > 2\sigma(I)$)^a	0.0597	0.0449
Final $wR(F^2)$ values ($I > 2\sigma(I)$)^b	0.1105	0.1198
Final R_1 values (all data)^a	0.1875	0.0548
Final $wR(F^2)$ values (all data)^b	0.1512	0.1344
Goodness of fit on F^2	0.961	0.981
CCDC number	1,500,755	1,500,756

$^aR_1 = \sum||F_o| - |F_c||/\sum|F_o|$

$^bwR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$

Table 2 Hydrogen bond geometries in the crystal structure of **RGA** and **RGAA**

Compound	D–H···A^a	H···A (Å)	D···A (Å)	D–H···A (°)
RGA	O(5)–H(5A)···O(4)^a	1.71(5)	2.657(3)	175(4)
RGAA	O1–H1···O5	1.75(3)	2.562(2)	148(3)
	O4–H4···O3^b	1.73(3)	2.659(2)	174(3)
	C5–H5···O2^c	2.36	3.243(2)	159

Symmetry codes: ^{a}– x, – y, 1 – z; ^{b}1 – x, 1 – y, 2 – z; ^{c}x, 3/2 – y, 1/2 + z

Results and Discussion

FT-IR Spectra

As shown in Fig. S1, there exists a broad peak at 3424 cm^{-1}, arising from the carboxylate –OH group while the band at 1728 and 1179 cm^{-1} is due to the symmetric and asymmetric $\nu_{C=O}$ stretching vibration of carboxylic group. The asymmetric deformation vibration bands of methyl and methylene are expected to be at 1408–1443 cm^{-1}. The bands observed at 1225–1302 cm^{-1} in **RGAA** are indicative of the structure of ethyl–O–Ar. The bands at 1036–692 cm^{-1}of **RGAA** could be attributed to in-plane and out-plane deformation vibrations of the phenyl ring.

UV–Vis Absorbance Spectra

The electronic spectrum data of **RGAA** has been examined at 2.68×10^{-5} mol L^{-1} in ethyl acetate (Fig. S2). The UV–Visible spectrum of the **RGAA** shows a strong absorption band at 240 nm, which may be assigned to $\pi^* \rightarrow \pi$ electronic transition of the aromatic nucleus [26, 27].

^{1}H NMR Spectra

The ^{1}H NMR spectrum for the target compound was recorded in DMSO-d_6 as solvent and the data are given in the experimental section; The hydrogen atomics labeling are shown in Scheme 2. As shown in Fig. S3, the single peak for the carboxyl groups occurs at 12.411 ppm (H_1 and H_5). The signals located at the region of 7.559–6.851 ppm are assigned to the hydrogen protons (H_3, H_4 and H_8) of phenyl ring hydrogen proton. The three doublet signals observed at 1.327, 1.310 and 1.293 ppm can be ascribed to the methyl hydrogen protons (H_6). The four doublet signals located at 4.084–4.033 ppm indicates the existence of the methylene hydrogen proton (H_7). Additionally, the single peak at 3.594 ppm can be assigned to methylene hydrogen proton (H_2).

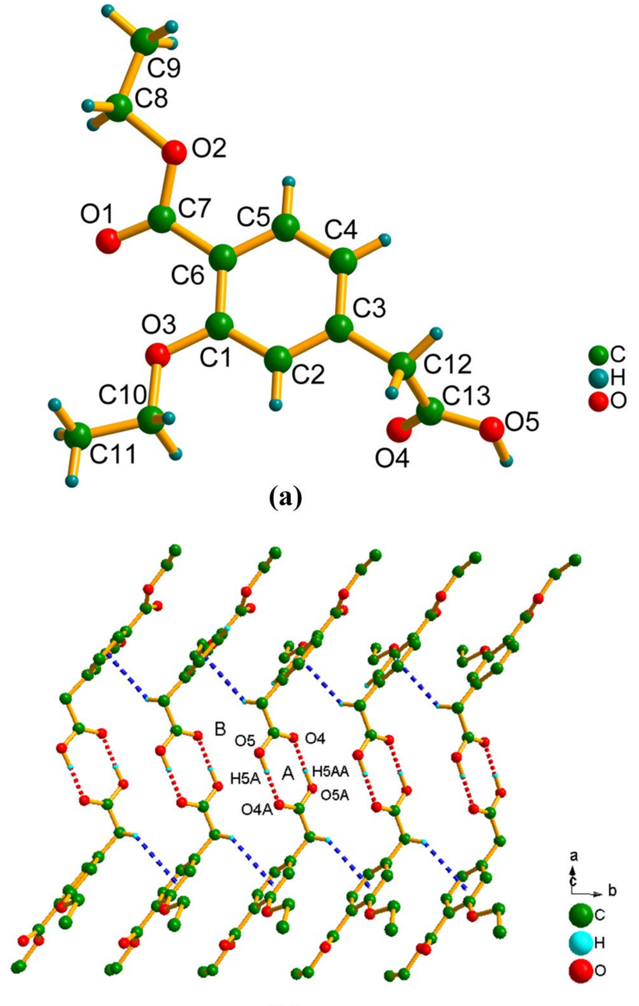
Crystal Structure Analysis

Description of the Structure of RGA

Single crystal X-ray diffraction study reveals that **RGA** crystallizes in the monocline space group $P2_1/n$ (Table 1), with one molecule of **RGA** comprising the asymmetric unit (Fig. 1a). Two molecules form a dimer by hydrogen bonding between the carboxylic acid groups (O(5)–H(5A)···O(4)^a, 2.657(3) Å, ^{a}– x, – y, 1 – z) (Table 2). In addition, there is a weak C–H···π interaction between the alkyl carbon atom adjacent to the carboxylic acid group and the aromatic ring of an adjacent dimer, C(12)–H(12B)···Cp (where Cp is the centroid of the ring): 134° and H(12B)···Cp: 2.930 Å. These hydrogen bond interactions ling the **RGA** dimers into a one-dimensional (1D) chain along the crystallographic *b* axis (Fig. 1b). There is only one type of hydrogen-bonded pattern A–D, noted as R_2^1 (8) (Fig. 1b(A)).

Description of the Structure of RGAA

X-ray diffraction analysis study reveals that the asymmetric unit of compound **RGAA** contains one molecule of **RGAA** (Fig. 2a). The target compound belongs to the monocline system with the space group $P2_1$/c. Within each molecule there is an intramolecular hydrogen bond between one of the carboxylate hydrogen atoms and the ether oxygen (O1–H1···O5: 2.562(2) Å) while there are intermolecular hydrogen bonds (O4–H4···O3^c 2.659(2) Å, c: 1 – x, 1 – y, 2 – z) between the carboxylate oxygen atoms of two adjacent RGAA molecules generating a hydrogen bonded dimer. These dimers are linked by C–H···O hydrogen bonds involving a carbon from an aromatic ring and a carboxylate oxygen (C5–H5A···O2^c, 3.243(2) Å, c: x, 3/2 – y, 1/2 + z) (Table 2) in a head–tail pattern, which results in a 1D chain along the crystallographic *c* axis (Fig. 2b).



(a)

(b)

Fig. 1 **a** A perspective view of **RGA**. **b** A view of the hydrogen bonding interactions and resulting in the 1D chain lying along the *b* axis

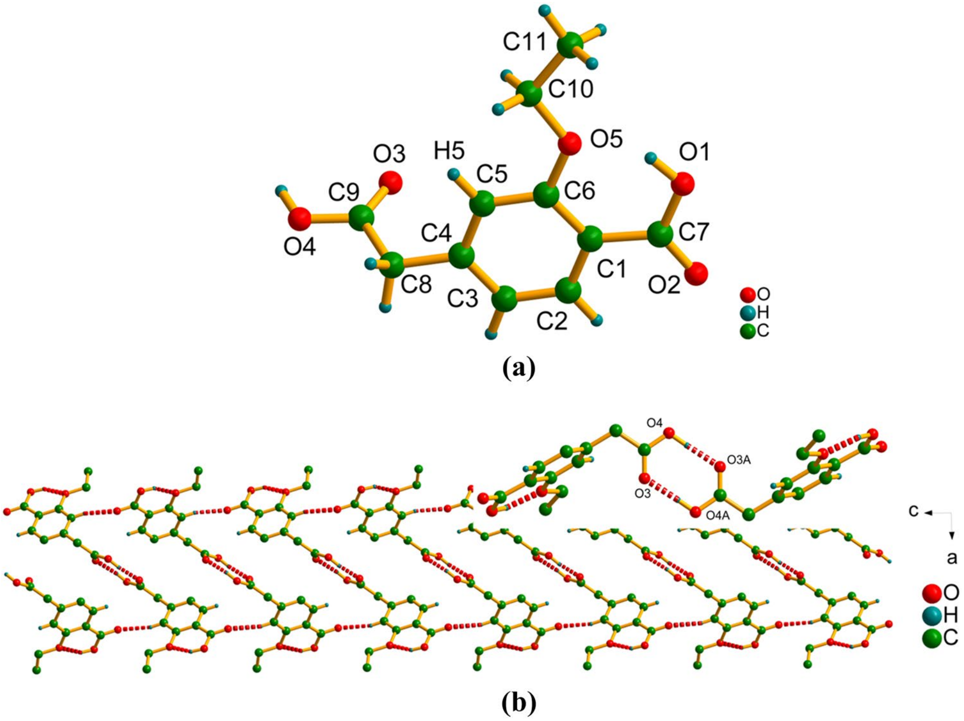
Thermogravimetric Analysis (TGA)

The thermal stability of **RGAA** was carried out by thermogravimetric analyses (TGA) [28, 29]. This was performed on samples comprising crystals of **RGAA** under a N_2 atmosphere with a heating rate of 10 °C min^{-1} (Fig. S4). The TGA curve shows that the compound is thermally stable up to 191 °C, presumably as a result of hydrogen bonds in the solid compound. As the temperature rises there is a rapid weight loss indicating total decomposition of the compound, which is essentially complete by 326 °C.

Photoluminescent Properties

Luminescent compounds based aromatic rings are of great current interest because of their various applications in chemical sensors, photochemistry, and electroluminescent display. The title compounds, having aromatic rings, display interesting luminescent property. The solid-state photoluminescence of **RGAA** and **RGA** was investigated at room

Fig. 2 **a** A perspective view of **RGAA**. **b** A view of the hydrogen bonding interactions and resulting in the 1D chain lying along the *c* axis



temperature. As shown in Fig. S5, there exist the maximal peaks at 364 and 345 nm ($\lambda_{ex} = 284$ nm) for **RGAA** and **RGA**, respectively, which may be ascribed to the $\pi^* \rightarrow \pi$ or $\pi^* \rightarrow n$ transitions. In comparison with **RGA**, the maximum emission band of **RGAA** is red-shifted 19 nm, which may be tentatively assigned to the difference of the functional groups [30–33].

Conclusions

In summary, the pivotal intermediate of Repaglinide and its derivative have been structurally characterized. The single-crystal X-ray diffraction study reveals that both compounds **RGA** and **RGAA** have hydrogen bond interactions involving the carboxylate groups linking the molecules into hydrogen bonded dimers; further hydrogen bond interactions link into polymers. As well, their fluorescent properties make them promising candidates for photo-luminescent materials. Further investigation and development of the compounds with the skeleton of the RGA intermediate is underway in our laboratory.

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Appendix: Supplementary Material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC references numbers are 1500755 and 1500756 for compounds **RGA** and **RGAA,** respectively. Copies of this information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

References

1. Culy CR, Jarvis B (2001) Drugs 61:1625–1660
2. Plosker GL, Figgitt DP (2004) Pharmacoeconomics 22:389–411
3. Scott LJ (2012) Drugs 72:249–272
4. Barbara JE, Kandel S, Stanley FA, Buckley DB (2014) Drug Metab Rev 45:179–180
5. Gertz M, Sall C, Houston JB, Galetin A (2014) Drug Metab Rev 45:258
6. Barbara JE, Muranjan S, Stanley F, Kollu C, Kandel S, Otwell C, Buckley DB (2015) Drug Metab Rev 47:120
7. Salman M, Babu SJ, Ray PC, Biswas S, Kumar N (2002) Org Process Res Dev 6:184–186
8. Grell W, Hurnaus R, Griss G, Mark RSERM, Luger P, Nar H, Wittneben H, Muller P (1998) J Med Chem 41:5219–5246
9. Panelo A, Wing JR (2005) Diabetes Care 28:1789
10. Wolffenbuttel BHR, Nijst L, Sels J, Menheere P, Muller PG, Kruseman ACN (1993) Eur J Clin Pharmacol 45:113–116

11. Sundaram DTSS, Mitra J, Rajesh C, Islam A, Prabahar KJ, Rao BV, Douglas SP (2015) Synth Commun 45:2092–2098
12. Zhang Y, Liu TT, Niu ZH, Fu YJ, Yang JX, Song YX, Zhao SC (2016) J Chem Res 11:506–510
13. Zhou XY, Zhu J, Bao ZJ, Shang ZH, Wang T, Song JF, Sun J, Li W, Adelusi TI, Wang Y, Lv DM, Lu Q, Yin XX (2016) Sci Rep 6:28023
14. Amin MM, Arbid MS (2017) Appl Physiol Nutr Metab 42:181–192
15. Awasthi R, Kulkarni GT, Ramana MV, Pinto TDA, Kikuchi IS, Ghisleni DD, Braga MD, De Bank P, Dua K (2017) Int J Biol Macromol 97:721–732
16. Kassem AA, Abd El-Alim SH, Basha M, Salama A (2017) Eur J Pharm Sci 99:75–84
17. Okunlola A, Adebayo AS, Adeyeye MC (2017) Int J Biol Macromol 94:544–553
18. Prior SL, Dunseath GJ, Luzio SD, Stephens JW (2017) Diabetic Med 34:65–66
19. Xu YT, Lu J, Zhou DD, Wang YD, Li JJ, Wang MY, Zhang HJ (2017) Drug Metab Pharmacok 32:S65–S66
20. Yamazaki T, Desai A, Goldwater R, Han D, Howieson C, Akhtar S, Kowalski D, Lademacher C, Pearlman H, Rammelsberg D, Townsend R (2017) Clin Pharm Drug Dev 6:54–65
21. Sheldrick GM (1996, 2003) SADABS. University of Göttingen, Göttingen
22. Bruker AXS Inc. (1998) SAINT software reference manual. Bruker AXS Inc., Madison
23. Sheldrick GM (1997) SHELXTL NT version 5.1. Program for solution and refinement of crystal structures. University of Göttingen, Göttingen
24. Sheldrick GM (2008) Acta Crystallogr A 64:112–122
25. Accelrys (2014) Material studio release notes, release 7.0. Accelrys Software
26. Montazerozohori M, Mojahedi Jahromi S, Masoudiasl A, McArdle P (2015) Spectrochim Acta A 138:517–528
27. Wang P, Zhao L (2015) Spectrochim Acta A 135:342–350
28. Wang JH, Tang GM, Wang YT, Qin TX, Ng SW (2014) CrystEngComm 16:2660–2683
29. Wen YH, Dou RT, Yao K, Xu GF (2015) J Coord Chem 68:38–54
30. Chang XH, Zhao Y, Han ML, Ma LF, Wang LY (2014) CrystEngComm 16:6417–6424
31. Cheng L, Wang JQ, Gou SH (2011) Inorg Chem Commun 14:1201–1203
32. Wang CC, Wang JH, Tang GM, Wang YT, Cui YZ, Ng SW (2015) J Coord Chem 68:3918–3931
33. Tang G-M, Chi R-H, Wan W-Z, Chen Z-Q, Yan T-X, Dong Y-P, Wang Y-T, Cui Y-Z (2017) J Lumin 185:1–9

Affiliations

Gui-Mei Tang[1] · **Yong-Tao Wang**[1] · **Yu-Song Wu**[1]

✉ Yong-Tao Wang
ceswyt@qlu.edu.cn

[1] Department of Chemical Engineering, Qilu University of Technology (Shandong Academy of Sciences), Jinan 250353, China