Synthesis, characterization, crystal structure of the coordination polymer Zn(II) with thiosemicarbazone of glyoxalic acid and their inhibitory properties against some metabolic enzymes

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ABSTRACT

A new coordination polymer Zn(II) with thiosemicarbazone glyoxalic acid H\(_2\)GAT was obtained in this study. According to the X-ray diffraction data, the coordination of the Zn(II) ion is carried out by one sulfur atom, in the thiol form, one nitrogen atom of the azomethine group and two oxygen atoms of the carboxylate groups, one of which belongs to neighbouring complex molecule. The oxygen atom of the water molecule completes Zn(II) ion environment to a distorted square-pyramidal structure. The binding of the monomer complex into polimer occurs through the bridge oxygen atom of carboxylate group. This complex is effective inhibitor of the α-glycosidase, butyrylcholinesterase (BChE), cytosolic carbonic anhydrase I and II isoforms (hCA I and II), and acetylcholinesterase enzymes (AChE) enzymes with \(K_I\) values of 1.45 ± 0.23 µM for hCA I, 2.04 ± 0.11 µM for hCA II, 3.47 ± 0.88 µM for α-glycosidase, 0.47 ± 0.10 µM for BChE, and 0.58 ± 0.13 µM for AChE, respectively.

1. Introduction

Thiosemicarbazone aldehydes and keto-acids possess have antimicrobial, antiviral and anti-cancer activity and are inhibitors of the synthesis of DNA [1–7]. Metal complexes with these ligands may have a mononuclear, binuclear and polymeric structure [8]. Only mononuclear and binuclear structures are known for complexes of Zn(II) with similar ligands [9], while with other ligands mononuclear [10], binuclear [11] and polymeric [12] structures are known.

In this work, we synthesised the polymeric complex Zn(II) with thiosemicarbazone of glyoxalic acid and studied its X-ray structures. It was shown, that the bond between the monomeric units is carried out through one oxygen atom of the carboxylate group, which belong to neighbouring molecule of complex.

Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are significant enzymes that catalyze the breakdown of acetylcholine (ACh) and butyrylcholine (BCh) that function as neurotransmitter molecules, which are recorded as drug purposes for Alzheimer’s disease (AD) [13–16]. Carbonic anhydrase enzymes are metabolic enzymes, which catalyze the rapid conversion of CO\(_2\) to a proton (H\(^+\)) and bicarbonate (HCO\(_3^-\)). This mechanism is common for most organisms and as an outcome, pending the evolvement of life seven genetically various families of this enzyme (classified as α-, ζ-, β-, δ-, γ-, η- and θ-CAs) evolved [17,18]. Especially CA inhibitors (CAIs) have usage clinically for almost sixty years as antiglaucoma, diuretics or for the treatment of epilepsy, obesity, convulsants, glaucoma, and more recently cancer. Hence, the interaction of CA isozymes with different types of novel synthesised derivatives had great importance [19–21].

One therapeutic factor in the therapy of type 2 DM is α-glycosidase inhibitors, reversible inhibitor compounds of α-glycosidase, and an enzyme present in the brush border of the small intestine [22]. α-Glycosidase can create glucose compound by opening and hydrolysing linear and branched isomaltose oligosaccharide molecules, resulting in hyperglycemia. Indeed, identifying and characterising the inhibitor compounds of the α-glycosidase enzyme that can be therapeutically utilised is significant [23].

In the present study, we explain the design, synthesis, and evaluation of Zn(II) polynuclear complex as useful BChE, α-glycosidase, AChE, hCA inhibitor agents. Compared with standard compounds, such as acetazolamide, tacrine, and acarbose, this is another goal of this study.

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2. Experimental

All reactants and solvents were of reagent grade. The ligand H₂GAT was prepared according to the procedure described earlier. Carbon, nitrogen, hydrogen and sulfur analyses were performed using Perkin Elmer 2400 Series H Elemental Analyser, IR spectra were recorded on a NicoletIS10 Spectrometer using KBr discs in the range 4000–400 cm⁻¹.

2.1. Synthesis of the ligand C₃H₅N₃SO₂-H₂GAT

To a solution of 0.91 g (0.01 mol) of thiosemicarbazide in 30 ml of water was added 0.69 g (0.01 mol) of glyoxylic acid dissolved in 30 ml of water. The obtained solution was stirred for 2 min., after which a yellow microcrystalline powder was precipitated.


M. p. 165°C (Table 1). IR (KBr, cm⁻¹): 3626(m), 3324(ms), 3282(s), 3171(vs), ν(NH), ν(OH); 1760(s), 1630(as), ν(C=O), ν(as(COO)); 1599(s), ν(CN); 1463(ms), ν (COO); 1377(vs), 1312(ms), 1272(ms), ν(C=OH); 1202(vs), ν(NCS); 723(vs), 708(s), ν(CS).

2.2. Synthesis of the complex [Zn(HGAT)·H₂O]ₙ

To a solution of 0.15 g (1 mmol) of thiosemicarbazone of glyoxylic acid dissolved in 20 ml of water was added Zn(NO₃)₂·H₂O (molar ratio Zn:H₂GAT 1:1) in 20 ml of water. The resulting yellow solution was stirred at room temperature for 5 min and then was allowed to stand. Slow evaporation grew yellow crystals (Scheme 1). Analytical and spectroscopic data correspond to the minimal formula ZnC₃H₆N₃O₃S·H₂O.

Anal. Found: C, 15.69; H, 2.64; N, 18.03; S, 13.97%. ZnC₃H₆N₃O₃S Calc. for: C, 15.65; H, 2.90; N, 18.05; S, 14.01%. M. p. > 250°C (Table 1). IR (KBr, cm⁻¹): 3373(ms,br), 3288(vs), ν(NH₂), ν(NH); 1685(m), 1635(vs), ν(C=O), ν(as(COO⁻)); 1585(s), ν(CN); 1462(m), ν(COO⁻); 1462(m), 1276(s), 1191(vs), 1162(s), ν(NCS); 789(m), ν(C=S).

2.3. X-ray diffraction analysis

Suitable crystal of 1 was selected for data collection which was performed on a D8-QUEST diffractometer equipped with graphite-monochromatic Mo-Kα radiation at 296 K. The structure was solved by direct methods using SHELXS-2013 [24] and refined by full-matrix least-squares methods on F² using SHELXL-2013 [25]. All non-hydrogen atoms were refined with anisotropic parameters. The H atom was located from different maps and then treated as riding atoms with a C−H distance of 0.93 Å. The following procedures were implemented in our analysis: data collection: BrukerAPEX2 [26]; program used for molecular graphics were as follow: MERCURY programs [27]; software used to prepare material for publication: WinGX [28]. Details of data collection and crystal structure determinations are given in Table 2.

2.4. Carbonic anhydrase activity assay

In this work, for recording inhibitory effect of novel complex, both CA isoenzymes were separated and purified by Sepharose-4B-L-tyrosine sulfanilamide affinity chromatography in a single stage [30]. The column chemical material of affinity chromatography containing Sepharose-4B-L-tyrosine-sulfanilamide was created conforming to a former procedure [31]. The protein molecules flow in the column eluates was spectrophotometrically obtained at 280 nm as explained formerly [32]. CA isoenzymes’ activity investigation was obtained using the spectrophotometric style of Verpoorte et al. [29] as described formerly [33]. In this work, changes in absorbance were recorded during 3 min at 348nm using p-Nitrophenylacetate was used as a substrate which converted by both isoenzymes to the p-nitrophenolate ion compound [34].

![Scheme 1. Synthesis Zn(II) polymer complex with thiosemicarbazone of glyoxylic acid (H₂GAT).](image-url)

### Table 1

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Empirical formula (weight)</th>
<th>Yield %</th>
<th>Color</th>
<th>M.p. (°C)</th>
<th>Analysis, found (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂GAT</td>
<td>C₃H₅N₃SO₂</td>
<td>95</td>
<td>Yellow</td>
<td>165</td>
<td>C, 24.48; H, 3.42; N, 28.55; S, 21.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Zn(HGAT)·H₂O]ₙ</td>
<td>C₃H₆N₃O₃SZn</td>
<td>71</td>
<td>Yellow</td>
<td>&gt; 250</td>
<td>C, 15.69; H, 2.64; N, 18.30; S, 13.97; O, 28.48</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

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2.5. Acetylcholinesterase and butyrylcholinesterase activities assays

The inhibitory efficacy of novel complex on BChE/AChE activities was obtained conforming to the spectrophotometric procedure of Ellman et al. [35] Butrylcholine iodide (BChI) and also acetylthiocholine iodide (AChI) compounds were used as substrates of both reactions [36]. In this part, 5,5′-Dithio-bis(2-nitro-benzoic)acid (DTNB) was used for the estimation of BChE/AChE activities. Briefly, 100µL of buffer solution (pH 8.0, Tris/HCl, 1.0 M) and diverse concentration of sample solutions (50–200µL) dissolved in deionised water were added to 50µL of BChE/AChE solutions (5.32×10–3 EU) [37]. Then the mixture was incubated for 10 min at 20°C. Finally, 50µL of DTNB (0.5 mM and 25 ml) of BChI/AChI were added to incubated mixture. Also, the reaction was initiated by the addition of 50µL of BChI/AChI. Activities of these enzymes were evaluated spectrophotometrically at a wavelength of 412 nm [38].

2.6. α-Glycosidase enzyme assay

Inhibitory effect of novel complex on α-glycosidase enzyme activity was performed using p-nitrophenyl-D-glycopyranoside (p-NPG) as the substrate, conforming to the method of Tao et al. [39]. Firstly, 200µL of phosphate buffer (PB) was mixed with 40µL of the homogenate solution in phosphate buffer (0.15 U/mL, pH 7.4). Also, 50µL of p-NPG in PB (5 mM, pH 7.4) after preincubation was added and again incubated at 30°C. The absorbances were spectrophotometrically measured at 405 nm, according to previous studies [40,41].

3. Results and discussions

3.1. Infrared spectra

The spectrum of H2GAT shows a band at 1760 cm−1, which is attributed to ν(C=O) of the carboxylic group. In the IR spectra of complex, this band is absent. The involvement of nitrogen azomethine in connection with metal ions shows itself ν(C=N) band at 1625 cm−1 in H2GAT shifting to a lower frequency in the complex. Two strong ν(C=S) bands at 1129 cm−1 and 839 cm−1 in H2GAT disappeared in the complex. This observation suggests enolization of Schiff base and coordination of the thiol sulfur to the metal ions. In this complex, two new bands observed in the regions 2950–2850 cm−1, which are assigned to ν(CH) of the hydrocarbon chain. The most significant shifts are observed in the 1700–1500 cm−1 region; in particular, only one absorption, at 1685 cm−1, is observed in the spectrum of [Zn(HGAT)·H2O]n (Δν = 35 cm−1 with respect to the free H2GAT), where the ligand is deprotonated. A split ν(CO) band is observed for [Zn(HGAT)H2O]n. While three intense absorptions are present in the spectrum of [Zn(HGAT)H2O]n in the 1700–1600 cm−1 region. As far as the absorptions involving the CN and CS groups are concerned, the variations of the frequency values upon coordination suggest an ONS terdentate ligand behaviour. Points of interest are the lack of the ν(NH) absorption in [Zn(HGAT)H2O]n, the presence of bands in the 2950–2850 cm−1 region, which confirm the nature of the glyoxylic
moiety, and the shifts in frequencies of the absorptions of CN and CS groups as a consequence of coordination of the nitrogen and sulfur atoms to the metal. For compound Zn(II) complex the H$_2$O bands in the spectra of the complex are observed at 789 cm$^{-1}$, 758 cm$^{-1}$ and 627 cm$^{-1}$, respectively, indicates the presence of coordinated water [42].

3.2. Thermal analysis (TG)

The thermogram of [Zn(HGAT)·H$_2$O]$_n$ complex shows five decomposition steps within the temperature range of 22–990 °C decomposition steps within the temperature range of 255–990 °C. The first step of decomposition water molecule, mass loss of 7.828% (7.86% theoretical). The subsequent three steps (2nd, 3rd, and 4th) (255–990 °C) correspond to the removal of the organic part of the ligand leaving metal oxide as a residue. The overall weight loss amounts to 59.23%. The residue of zinc oxide is 40.77% of the initial sample and corresponds to the content of zinc in the material (40%). This indicates the absence of a noticeable electronic excellent interaction between Zn(II) ions at room temperature undoubtedly, this is due to the large Zn(II) distance, which is 3.84%.

![Scheme 2. Important bond distances (Å) for the Zn–O fragments.](image)

![Fig. 2. Determination of Lineveawer-Burk graphs for Zn(II) complex of hCA I (A) and hCA II (B) isoenzymes, achetylcholinesterase (AChE) (C), butyr-ylcholinesterase (BChE) (D) and α-glycosidase (α-Gly) (E) enzymes.](image)
The molecular structure of complex Zn(II) (1), with the atom numbering scheme, is shown in Fig. 1a. The asymmetric unit of the complex 1 consists of one Zn(II) ion, one H2GAT ligand and one co-ordinated water molecule. The Zn(II) ion is coordinated by two oxygen [Zn1–O1=2.020(7) and Zn1–O1ii =2.192(7)Å], one nitrogen [Zn1–N1ii =2.068(8)Å] and one sulfur [Zn1–S1ii =2.406(3)Å] atoms from two different H2GAT ligands, and one water molecule [Zn1–O3=1.994(7)] thus showing distorted square pyramidal geometry [(ii) −x+3/2, y−1/2, −z+1/2]. The coordination Zn(II) polymer complex are formed by binding monomeric units through one oxygen atom of carboxylate group. The structures of the bi- and polynuclear Zn(II) complexes with one bridging oxygen atom of carboxylate group are very rarely found in the literature[43] and metal ions usually are bonded with both oxygen atoms of the carboxylate group. It is noteworthy that in the resulting polymer structure, the bond between the Zn(II) ion and the oxygen atom of the neighbouring complex is shorter, (2.02Å) than the bond Zn(II) with oxygen of the native ligand (2.192Å). There is also a weak bond of the Zn(II) ion with the free carboxylate oxygen atom of the neighbouring complex (2.875Å) (scheme 2). The Zn(II) ions and H2GAT ligands are 1D coordination polymers running parallel to the [010] direction (Fig. 1b). The Zn(II)⋯Zn(II) separation is 3.842Å. Ne⋯S further joins adjacent 1D coordination polymers, Ne⋯N and O⋯O hydrogen bonds, generating 3D supramolecular network (Fig. 1c).

### 3.4. Biochemical results

Both hCA II, I, and also BChE, α-glycosidase, and AChE were evaluated in the enzyme inhibition stage of this paper. Enzymes results of this study:

(1) The defined key role of CAI molecules as antiglaucoma compounds and diuretics factor, it has recently appointed which they have capability as anticonvulsant, antiobesity, antiinfective and anticancer drugs [44]. For the hCA I enzyme, Zn(II) polynuclear complex had K_i value 1.45 ± 0.23µM, also had IC_{50} value 1.08µM, respectively (Fig. 2 and Table 5). Also, for the hCA II isoform, Zn(II) polynuclear complex had K_i value 2.04 ± 0.11µM, also obtained IC_{50} value 2.12µM, respectively (Fig. 2 and Table 5). In this article, acetazolamide (AZA) compound, used as a CA inhibitor for the medical therapy of epileptic seizure, glaucoma, duralectasia, and

### Tables

#### Table 3

Selected bond distances and angles for 1 (Å, °).

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn1–O1</td>
<td>2.020(7)</td>
</tr>
<tr>
<td>Zn1–N1</td>
<td>2.192(7)</td>
</tr>
<tr>
<td>Zn1–S1</td>
<td>2.406(3)</td>
</tr>
<tr>
<td>O3–Zn1–O1</td>
<td>112.2(3)</td>
</tr>
<tr>
<td>O3–Zn1–N1</td>
<td>105.8(3)</td>
</tr>
<tr>
<td>O3–Zn1–S1</td>
<td>96.70(14)</td>
</tr>
<tr>
<td>N1–Zn1–S1</td>
<td>100.0(2)</td>
</tr>
<tr>
<td>N1–Zn1–O1</td>
<td>80.6(2)</td>
</tr>
</tbody>
</table>

Symmetry codes: (ii) −x+3/2, y−1/2, −z+1/2.

#### Table 4

Hydrogen-bond parameters for 1(Å, °).

<table>
<thead>
<tr>
<th>D–H⋯A</th>
<th>D–H</th>
<th>H⋯A</th>
<th>D⋯A</th>
<th>D⋯H⋯A</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3−H3A−S1iii 0.83(2)</td>
<td>2.66(7)</td>
<td>3.411(9)</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>N3−H3B−N2iv 0.86(2)</td>
<td>2.11(3)</td>
<td>2.961(14)</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>O3−H3C−O2v 0.82(2)</td>
<td>1.93(4)</td>
<td>2.731(10)</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>O3−H3D−S1vi 0.83(2)</td>
<td>2.36(3)</td>
<td>3.180(8)</td>
<td>171</td>
<td></td>
</tr>
</tbody>
</table>

Symmetry codes: (iii) −x+1/2, y+1/2, −z+1/2; (iv) −x+1, −y+2, −z+1; (v) −x+2, −y, −z+1; (vi) −x+3/2, y−3/2, −z+1/2.

#### Table 5

The enzyme inhibition results of Zn(II) complex against human carbonic anhydrase isoenzymes I and II (hCA I and II), AChE, BChE, and α-glycosidase enzymes.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC_{50} (µM)</th>
<th>Ki (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCA I r 2</td>
<td>1.08</td>
<td>0.9597</td>
</tr>
<tr>
<td>hCA II r 2</td>
<td>2.04</td>
<td>0.9366</td>
</tr>
<tr>
<td>AChE r 2</td>
<td>0.86</td>
<td>0.9097</td>
</tr>
<tr>
<td>BChE r 2</td>
<td>0.73</td>
<td>0.9662</td>
</tr>
<tr>
<td>α-Gluc r 2</td>
<td>0.73</td>
<td>0.9662</td>
</tr>
<tr>
<td>Zn(II) complex</td>
<td>1.45 ± 0.23</td>
<td>0.9839</td>
</tr>
<tr>
<td>AZAa</td>
<td>2.87 ± 0.48</td>
<td>0.9811</td>
</tr>
<tr>
<td>TACb</td>
<td>1.73 ± 0.10</td>
<td>0.9811</td>
</tr>
<tr>
<td>ACRc</td>
<td>1.45 ± 0.23</td>
<td>0.9839</td>
</tr>
</tbody>
</table>

a AZA (acetazolamide) was used as a positive control for hCA I and II.
b TAC (tacrine) was used as a positive control for AChE and BChE enzymes.
c Acarbose (ACR) was used as a positive control for α-gly enzyme. This has taken of Refs.[49,50].
idiopathic intracranial hypertension, for both isoforms, showed Ki values of 2.87 ± 0.48 and 4.07 ± 0.90 µM, for hCA I and II, respectively (Table 5 and Fig. 2). IC50 values of Zn(II) polynuclear complex and standard (acetazolamide) molecules were: Zn(II) complex (1.08 µM, r²: 0.9597) < acetazolamide (2.38 µM, r²: 0.9790) for hCA I while these compound exhibited for hCA II isoform the following order: Zn(II) complex (2.12 µM, r²: 0.9366) < acetazolamide (3.82 µM, r²: 0.9662). CA inhibitor compounds are a class of pharmaceuticals that suppress the activity of CA. Their clinical use has been established as antiepileptics, diuretics, anti-glaucoma agents, in the management of mountain sickness, gastric and duodenal ulcers, idiopathic intracranial hypertension, osteoporosis or neurological disorders [45].

(2) Inhibitors of BChE and AChE are neurotoxic compounds capable of causing peripheral, central or both peripheral cholinergic and central cholinergic crises [46]. Zn(II) polynuclear complex has also recorded application as medicines developed for the therapy of AD and myasthenia gravis. BChE and AChE enzymes were effectively inhibited by Zn(II) polynuclear complex. It was obtained that Ki values were 0.58 ± 0.13 µM for AChE and 0.47 ± 0.10 µM for BChE, respectively (Table 5). Also, Tacrine (TAC) molecule was used as a control for BChE and AChE enzymes it had Ki values 1.13 ± 0.15 and 1.73 ± 0.40 µM, respectively (Table 5). IC50 values of Zn(II) polynuclear complex and standard (Tacrine) molecules were: Zn(II) complex (0.86 µM, r²: 0.9097) < tacrine (2.70 µM, r²: 0.9988) for AChE while this compound was for BChE enzyme: Zn(II) polynuclear complex (0.73 µM, r²: 0.9671) < tacrine (2.02 µM, r²: 0.9811). The AD is the main reason for dementia disease, and mild to moderate cases are generally treated with AChE inhibitors. Inhibitors of AChE and BChE enzymes are neurotoxic molecules capable of causing peripheral or central cholinergic crises. A number of these molecules have also found application as drugs developed for the treatment of myasthenia gravis and AD. These are based on the premise that increasing the availability of ACh at ACh receptors in the brain cells, results in better neuron to neuron transport that will improve cognitive function [47,48].

(3) Diabetes mellitus (DM) is a common disease worldwide. There are more than 400 million people suffering from DM. Diabetic complications related to hyperglycemia majorly occur of cancer, diabetic retinopathy, mood disorders, neuropathy, nephropathy and others. The inhibitor compounds of α-glycosidase have wide-ranging applications in illuminating the α-glycosidase mechanism of action at in evolving chemotherapeutic agents and molecular levels for the cure of carbohydrate-mediated diseases like cancer, diabetes, hepatitis, obesity, HIV, and cardiovascular diseases [49]. Inhibitor compounds of this metabolic enzyme are antidiabetic factor. α-Glycosidase was effectively inhibited by Zn(II) polynuclear complex. It was obtained that Ki values was 3.47 ± 0.88 µM for this enzyme (Table 5). Also, acarbose molecule was used as a control for this enzyme it had Ki value 12.60 ± 0.78 (Figs. 2 and 3). IC50 values of Zn(II) polynuclear complex and standard (ACR) molecules were: Zn(II) polynuclear complex (3.72 µM, r²: 0.9839) < ACR (22.80 µM) for this enzyme [50,51].

4. Conclusions

Thus, by the interaction of zinc nitrate with thiosemicarbazone of glyoxylic acid to forms a coordination polymer. In this polymer, monomeric complex units are bounded by Zn(II) ions through the oxygen atom of the carboxylate group. The surrounding of the zinc ion is distorted square pyramids, trimmed with sulfur atoms in the thiol form, nitrogen and two bridging oxygen atoms of the carboxylate group, one of which refers to its ligand of the monomeric unit and the second to the neighbouring molecule. It should be noted, that the earlier received by us coordination polymer Cu(II) with this ligand is formed due to the deprotonated amino group so that the complex Cu(II) acts as a monoanionic ligand. In this polymer complex, the sulfur atom is coordinated in the thionic form [1b]. Additionally, this novel complex studied in the in work can be acceptable candidate drugs, the same as CAIs, for therapy of some diseases like epilepsy, gastric and duodenal ulcers, glaucoma, mountain sickness, osteoporosis, or neurological disturbances. Indeed, novel complex effectively inhibited some metabolic enzymes like α-glycosidase, hCA I, hCA II, BChE and AChE enzymes at the micromolar levels.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2018.10.012.
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