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PII: S0968-0896(16)30738-6
DOI: http://dx.doi.org/10.1016/j.bmc.2016.09.042
Reference: BMC 13295

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 11 August 2016
Revised Date: 15 September 2016
Accepted Date: 16 September 2016

Please cite this article as: Wei, M., Chai, W-M., Wang, R., Yang, Q., Deng, Z., Peng, Y., Quinazolinone derivatives: synthesis and comparison of inhibitory mechanisms on α-glucosidase, *Bioorganic & Medicinal Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bmc.2016.09.042

Quinazolinone derivatives: synthesis and comparison of inhibitory mechanisms on α-glucosidase

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Abstract

In this study, eight quinazolinone derivatives were designed and synthesized. Their inhibitory activities on α-glucosidase were assessed in vitro. Two compounds: 2-(4-chlorophenyl)-quinazolin-4(3H)-one (CQ) and 2-(4-bromophenyl)-quinazolin-4(3H)-one (BQ) were found to be potent inhibitors of α-glucosidase with IC_{50} values of 12.5 ± 0.1 μM and 15.6 ± 0.2 μM, respectively. Spectroscopy methods were performed to analyze the inhibitory mechanisms of both compounds on α-glucosidase. The results revealed that they reversibly inhibited α-glucosidase in a non-competitive manner. CQ and BQ could statically quench the fluorescence spectra by formation of an inhibitor-α-glucosidase complex. The interaction between CQ and α-glucosidase depended on hydrogen bonds, electrostatic and hydrophobic force, while the driving force of the binding between BQ and the enzyme was hydrophobic. The docking results showed that BQ was less active than CQ against α-glucosidase because of its weaker interaction with the enzyme. In brief, the quinazolinone derivatives identified in this work were potentially promising candidates for developing as novel anti-diabetic agents.

Kewords: quinazolinone, α-glucosidase, fluorescence, docking.

1. Introduction

Diabetes Mellitus is a health-threatening chronic metabolic disease, arose from insufficient insulin secretion and characterized by hyperglycemia.[1] Enhanced postprandial glucose which associated with diabetes mellitus type II will increase the risk of developing atherosclerosis, stroke and other coronary diseases.[2] Thus, reduced the postprandial glucose by inhibiting the digestive enzymes such as α-glucosidase is an effective approach for the treatment of diabetes mellitus type II and diabetic complications.[3] α-Glucosidase (EC 3.2.1.20) is an enzyme which located in the small intestine epithelium, catalyzing the final step in the hydrolysis of disaccharides and polysaccharides to glucose. The activity of α-glucosidase is directly related to the concentrations of blood glucose, and inhibition of α-glucosidase is crucial due to the potential effects of decreased postprandial blood glucose levels. α-Glucosidase inhibitors, such as voglibose and acarbose, are clinically utilized for retarding the rapid generation of blood glucose. However, they often result in some side effects including diarrhea, abdominal pain and other gastrointestinal disorders in chronic therapy.[4,5] Therefore, the search for efficient and safe α-glucosidase inhibitors is desirable for the therapy of postprandial hyperglycemia.

Quinazolinone derivatives endowed with rich pharmacological properties and biological activities, which have been reported to possess anti-virus,[6] anti-bacterial,[7,8] anti-inflammatory,[9] anti-cancer,[10-12] anti-allergic,[13] anti-fungal,[14] anti-rheumatic,[15] anti-convulsant,[16-20] and CNS depressant[21,22] activities. Hence, quinazolinone derivatives have been gained a great interest in pharmaceutical chemistry field.[23-28]

Inspired by previous work,[29-31] we designed and synthesized eight quinazolinone derivatives, and their inhibitory activities on α-glucosidase were assessed in vitro. Two derivatives: 2-(4-chlorophenyl)-quinazolin-4(3H)-one (CQ) and 2-(4-bromophenyl)-quinazolin-4(3H)-one (BQ) were identified as potent inhibitors on α-glucosidase. Although CQ has been apprised of exhibiting anti-α-glucosidase activity,[32] the inhibitory mechanisms of these two compounds on α-glucosidase were never been covered. The aims of current study were to investigate and compare the inhibitory mechanisms of quinazolinone derivatives on α-glucosidase by using kinetic, fluorescence quenching and molecular docking methods. The findings of this work would provide a comprehensive understanding about the inhibitory mechanisms of quinazolinone derivatives on α-glucosidase and benefit to developing novel anti-diabetic agents.

2. Experimental

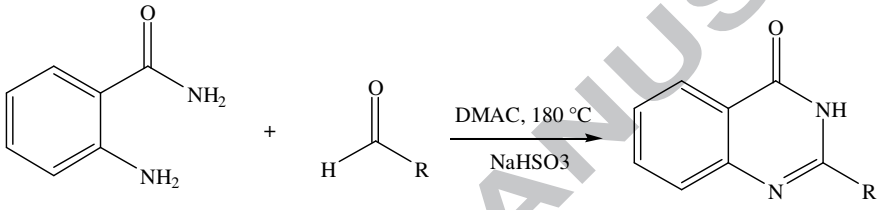
2.1. Chemicals

α-Glucosidase (*from Saccharomyces cerevisiae*), *p*-nitrophenyl-α-D-glucopyranoside (pNPG) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Acarbose was obtained from Aladdin. (Shanghai, China). Anthranilamide, substituted aldehydes were purchased from *9 Ding chemistry* (shanghai) Co.

2.2. Synthesis and structure characterization of quinazolinone derivatives

Quinazolinone derivatives were synthesized from the condensation of anthranilamide (0.2 mmol) and substituted aldehydes (0.4 mmol) in the presence of

$NaHSO_3$ (0.4 mmol) in DMAc (Scheme 1). The mixtures were stirred at 180□ overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether) to afford the desired product. The structures of quinazolinone derivatives were characterized by ^{1}H NMR coupled with FTIR and ESI-MS analysis.



CQ: R=4-Cl-Ph
BQ: R=4-Br-Ph
FQ: R=4-F-Ph
NQ: R=4-NO_2-Ph
DMQ: R=4-$(CH_3)_2$N-Ph
2-MQ: R=2-Me-Ph
3-MQ: R=3-Me-Ph
TQ: R=Thiophene-2-yl

Scheme 1 The synthesis of quinazolinone derivatives

2-(4-chlorophenyl)-quinazolin-4(3H)-one (CQ).[33]

White solid; mp: 299-300 °C

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.63 (s, 1H), 8.25 (d, J=8 Hz, 2H), 8.21 (d, J=8 Hz, 1H), 7.90 (t, J=8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8 Hz, 2H), 7.59 (t, J = 8 Hz, 1H).

FTIR (KBr, ν cm^{-1}): 3451.0, 3195.7, 3133.8, 3088.7, 1677.6, 1603.4, 1560.5, 1345.7, 840.9, 763.0.

ESI-MS: m/z $[M+H]^+$ calcd for $C_{14}H_{10}ClN_2O$ 257.0482, found 257.0460.

2-(4-Bromophenyl)-quinazolin-4(3H)-one (BQ).[34]

White solid; mp: 296-297 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.64 (s, 1H), 8.20 (m, 3H), 7.90 (m, 1H), 7.81 (t, J = 8.0 Hz, 3H), 7.60 (m, 1H).

FTIR (KBr, ν cm^{-1}): 3451.0, 3028.9, 2942.2, 2915.2, 1677.8, 1602.7, 1560.2, 1481.6, 1347.6, 961.0, 798.4.

ESI-MS: m/z $[M+H]^+$ calcd for $C_{14}H_{10}BrN_2O$ 300.9976, found 301.0002.

2-(4-Fluorophenyl)-quinazolin-4(3H)-one (FQ).[35]

White solid; mp: 293-294 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.57 (s, 1H), 8.27 (m, 2H), 8.17 (d, J = 8.0 Hz, 1H), 7.84 (m, 1H), 7.73 (m, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 2H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{14}H_{10}FN_2O$ 241.0777, found 241.0773.

2-(4-Nitrophenyl)-quinazolin-4(3H)-one (NQ).[36]

Brown solid; mp: 363-364 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.82 (s, 1H), 8.41 (m, 4H), 8.19 (m, 1H), 7.87 (m, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.59 (m, 1H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{14}H_{10}N_3O_3$ 268.0722, found 268.0728.

2-(4-(Dimethylamino)-phenyl)quinazolin-4 (3H)-one (DMQ).[37]

White solid; mp: 296-297 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.18 (s, 1H), 8.12 (t, J = 8.0 Hz, 3H), 7.78 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 3.02 (s, 6H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{16}H_{16}N_3O$ 266.1293, found 266.1278.

2-(2-Methylphenyl)-quinazolin-4(3H)-one (2-MQ).[38]

White solid; mp: 214-216 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.45 (s, 1H), 8.19 (m, 1H), 7.84 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55 (m, 2H), 7.44 (m, 1H), 7.35 (m, 2H), 2.40 (s, 3H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{15}H_{13}N_2O$ 237.1028, found 237.1026.

2-(3-Methylphenyl)-quinazolin-4(3H)-one (3-MQ).[39]

White solid; mp: 210-212 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.47 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.0 (m, 2H), 7.84 (m, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.43 (m, 2H), 2.42 (s, 3H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{15}H_{13}N_2O$ 237.1028, found 237.1006.

2-(Thiophene-2-yl)-quinazolin-4(3H)-one (TQ).[33]

White solid mp: 275-276 °C.

^{1}H NMR (400 MHz, DMSO-d6): δ 12.66 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.81 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H).

ESI-MS: m/z $[M+H]^+$ calcd for $C_{12}H_9N_2OS$ 229.0436, found 229.0438.

2.3. Enzyme Assay

α-Glucosidase activity assay was performed on the basis of Ranilla et al.[40] with a slightly modification. The reaction system involved with 50 μL of sample with different concentrations, 50 μL of α-glucosidase solution (7U/mL) and 200 μL of 5mM *p*-nitro-phenyl-α-D-glucopyranoside solution in 0.1M potassium phosphate buffer (pH=6.8). The absorbencies were measured every 10s at 405nm in ambient temperature. The relative enzymatic activity was calculated as follows: The relative activity (%) = (slope of reaction kinetics equation obtained by reaction with inhibitor)/(slope of reaction without inhibitor)×100. Acarbose was used as a positive control. The inhibitory mechanism assay was applied with varying the concentration

of the enzyme in the reaction mixture. The inhibition type was then assayed by the Lineweaver-Burk plot, and the inhibition constant was determined from the secondary plot.

2.4. The fluorescence quenching analysis

The fluorescence quenching analysis was carried out via a Varian Cary Eclipse fluorescence spectrophotometer in the range of 300-500 nm, and the excitation wavelength was set at 280 nm. Briefly, 50 μL of samples with different concentrations were mixed with 50 μL of α-glucosidase (0.1 mg/mL) and 900 μL of 0.1 mM sodium phosphate buffer. All the data was obtained at 25 °C.

The dynamic quenching data were ascertained from the Stern-Volmer equation.[41]

$F_0/F = 1 + K_q\tau_0[Q] = 1 + K_{sv}[Q]$……. (1)

In the equation, F_0 and F are the fluorescence intensities of α-glucosidase in the absence and presence of quinazolinone derivatives. K_{sv} is the Stern-Volmer quenching constant. K_q is the quenching velocity constant of biomolecular reaction. τ_0 is the average lifetime of the fluorophore absence of quencher. [Q] is the concentration of quinazolinone derivatives.

The fluorescence data were further estimated by the modified Stern-Volmer equation.[42]

$\log [(F_0 - F)/F] = \log K + n \log [Q]$……(2)

Where K is the binding constant, n represents the number of binding sites.

2.5. Molecular docking

The X-ray structure of α-glucosidase was downloaded from the RCSB protein Data Bank. The water molecules in α-glucosidase were removed, whereas Gasteiger charges and polar hydrogen atoms were added to the macromolecule by using the AutoDock tools. The 3D structures of quinazolinone derivatives were generated by

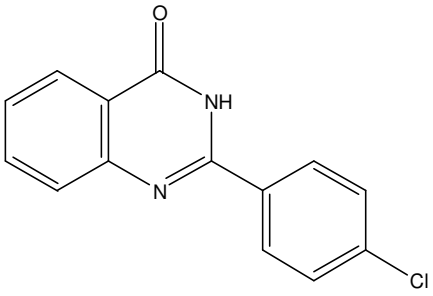
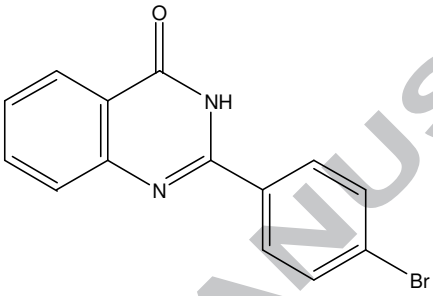
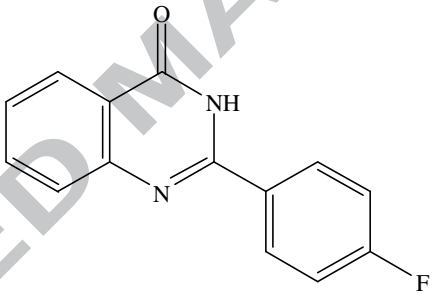
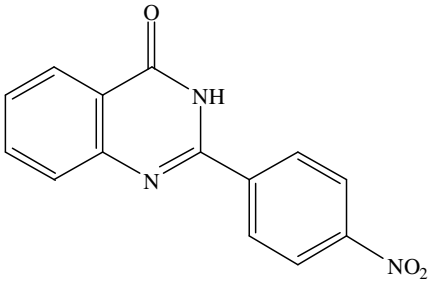
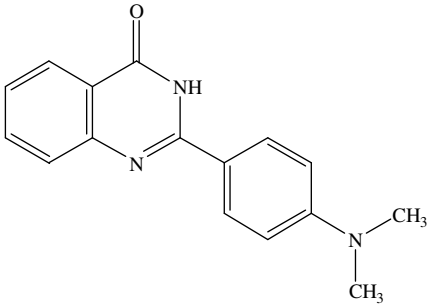
Chem Bio Draw Ultra 8.0. Docking calculations were achieved using the default parameters. The docked conformation with lowest free energy was selected as the optimal binding pattern.

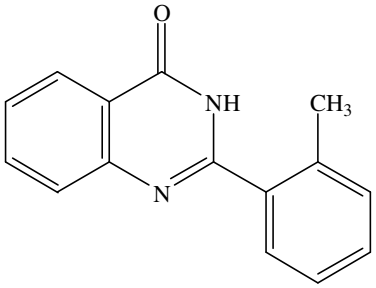
3. Results and Discussion

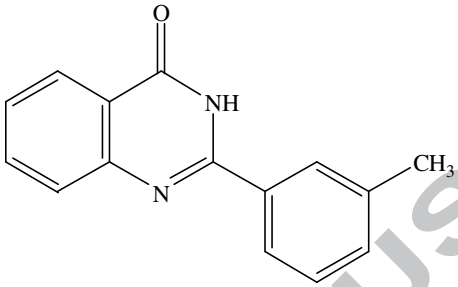
3.1. The effects of quinazolinone derivatives on α-glucosidase activity

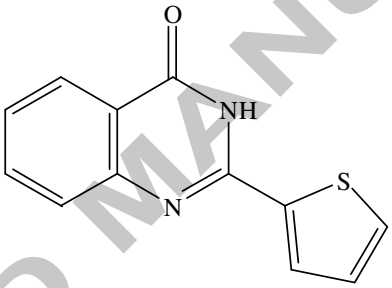
The effects of quinazolinone derivatives on the hydrolyzation of *p*-nitrophenyl-α-D-glucopyranoside catalyzed by α-glucosidase were studied. The concentrations leading to 50% activity loss (IC_{50}) were listed in Table 1. Substitution of chlorine at C4' on phenyl ring in CQ and substitution of bromine at C4' on phenyl ring in BQ were found as effective inhibitors on α-glucosidase with the IC_{50} values of 12.5 ± 0.1 μM and 15.6 ± 0.2 μM, respectively. When the fluorine group was present at C4' (FQ, IC_{50} >57.2 μM), a significantly decreased in activity on α-glucosidase was observed. Whereas nitro group at C4' phenyl ring (NQ), dimethylamino group at C4' phenyl ring (DMQ), methyl group at C2' phenyl ring (2-MQ), methyl group at C3' phenyl ring (3-MQ) and thiophene group at quinazolinone ring (TQ) completely diminished the activity on α-glucosidase. These results indicated that the presence of chlorine and bromine at C4' phenyl ring were distinctly responsible for the potent activity. Compared with the positive control acarbose (IC_{50}=0.475 ± 0.001 mM), CQ and BQ were prominent α-glucosidase inhibitors, and with a possibility to adopt as novel anti-diabetic agents.

Table 1. Inhibition of quinazolinone derivatives on α-glucosidase

Compound	Structure	IC_{50} (μM)
CQ		12.5 ± 0.1
BQ		15.6 ± 0.2
FQ		>57.2
NQ		NA
DMQ		NA

2-MQ  NA

3-MQ  NA

TQ  NA

Values are expressed as mean of triplicate determinations ± standard deviation

3.2. Inhibitory mechanisms of CQ and BQ on α-glucosidase

To ascertain the mechanisms of CQ and BQ on α-glucosidase, the plots of the enzyme activity versus the concentrations of enzyme in the presence of different amount of compounds were constructed in Fig. 1. The plots showed a good linear relationship, all the straight lines passing through the origin. Moreover, the slopes of the lines reduced with raising the concentrations of CQ and BQ, which indicated that the presence of CQ and BQ did not lessen the amount of α-glucosidase, but it resulted in the suppression of enzymatic activity. These results clearly suggested that both CQ and BQ inhibited α-glucosidase in a reversible way.

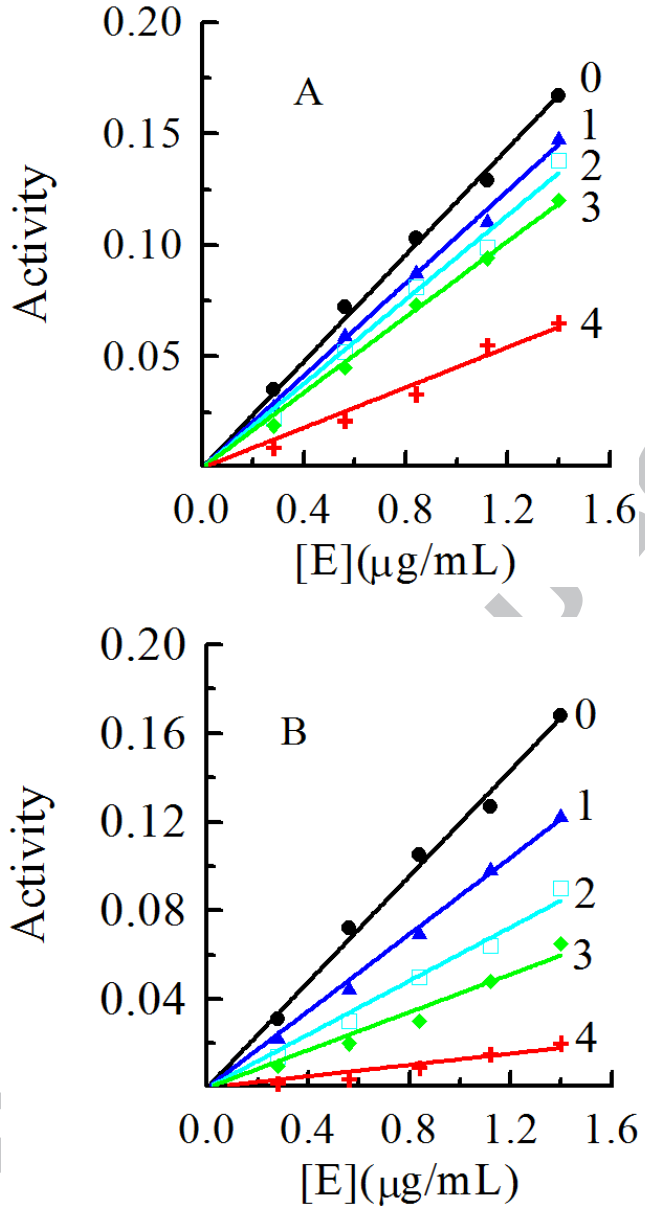


Figure 1 The inhibitory mechanisms of CQ (A) and BQ (B) on α-glucosidase. The concentrations of CQ and BQ for curves 0-4 were 0, 8, 12, 16, 24 μM.

3.3. The inhibition modes of BQ and CQ on α-glucosidase

The Lineweaver-Burk reciprocal plots (Fig. 2A, 2B) were applied to analyze the inhibition modes of CQ and BQ on α-glucosidase. The vertical axis intercept ($1/V_m$) added and the horizontal axis intercept ($-1/K_m$) untouched with mounting the concentrations of inhibitors, which revealed that CQ and BQ caused a proper

noncompetitive inhibition. The enzyme inhibitor constants (K_I) of CQ and BQ were acquired from the secondary plots (Fig. 2A-1, 2B-1). They were calculated to be 9.1 and 10.6 μM, respectively. The K_I value of CQ was smaller than that of BQ, this manifested that CQ showed a better binding affinity than BQ to α-glucosidase.

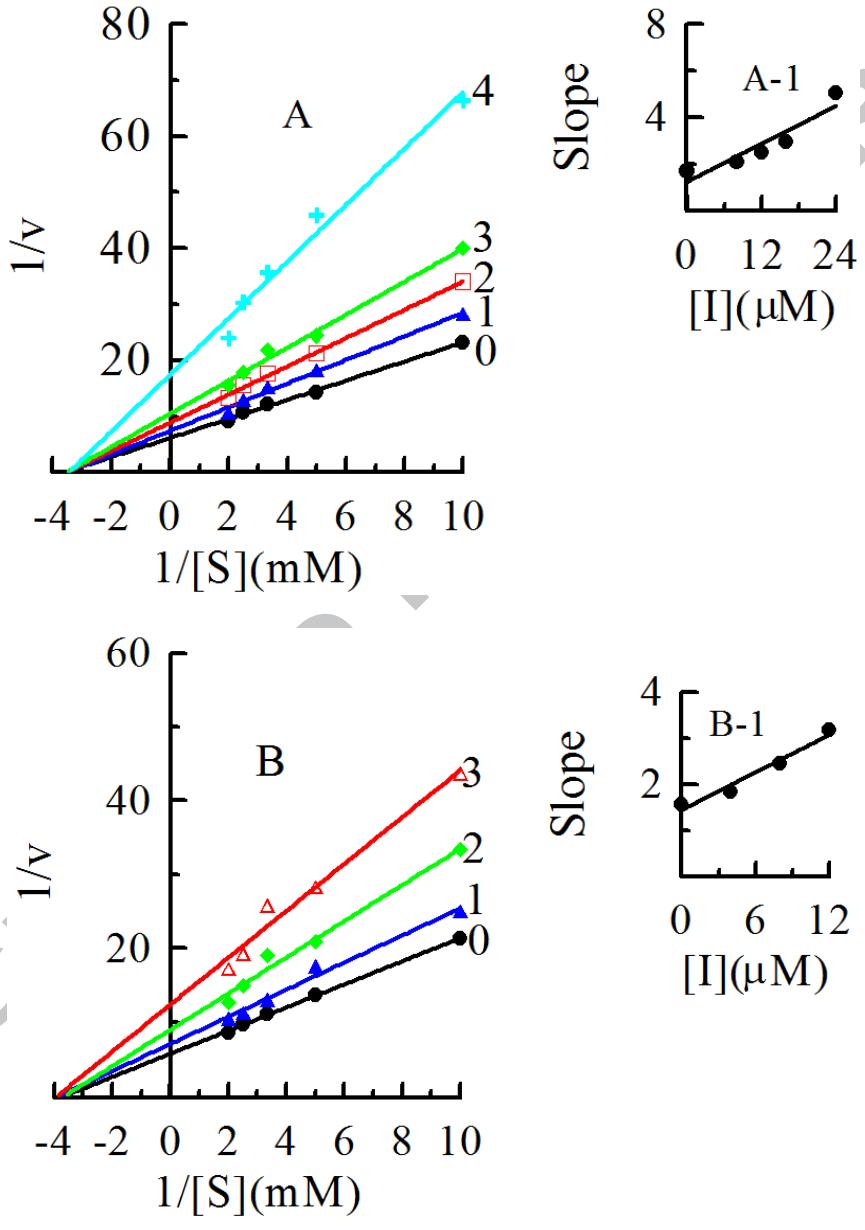


Figure 2 Lineweaver-Burk plots for inhibition of CQ (A) and BQ (B) on α-glucosidase. The concentrations of CQ for curves 0-4 were 0, 8, 12, 16, 24 μM; curves 0-3 for the concentrations of BQ were 0, 8, 12, 16 μM. The inhibition constant K_I of CQ and BQ was determined from the secondary plot A-1 and B-1, respectively.

3.4. Fluorescence quenching of α-glucosidase by CQ and BQ

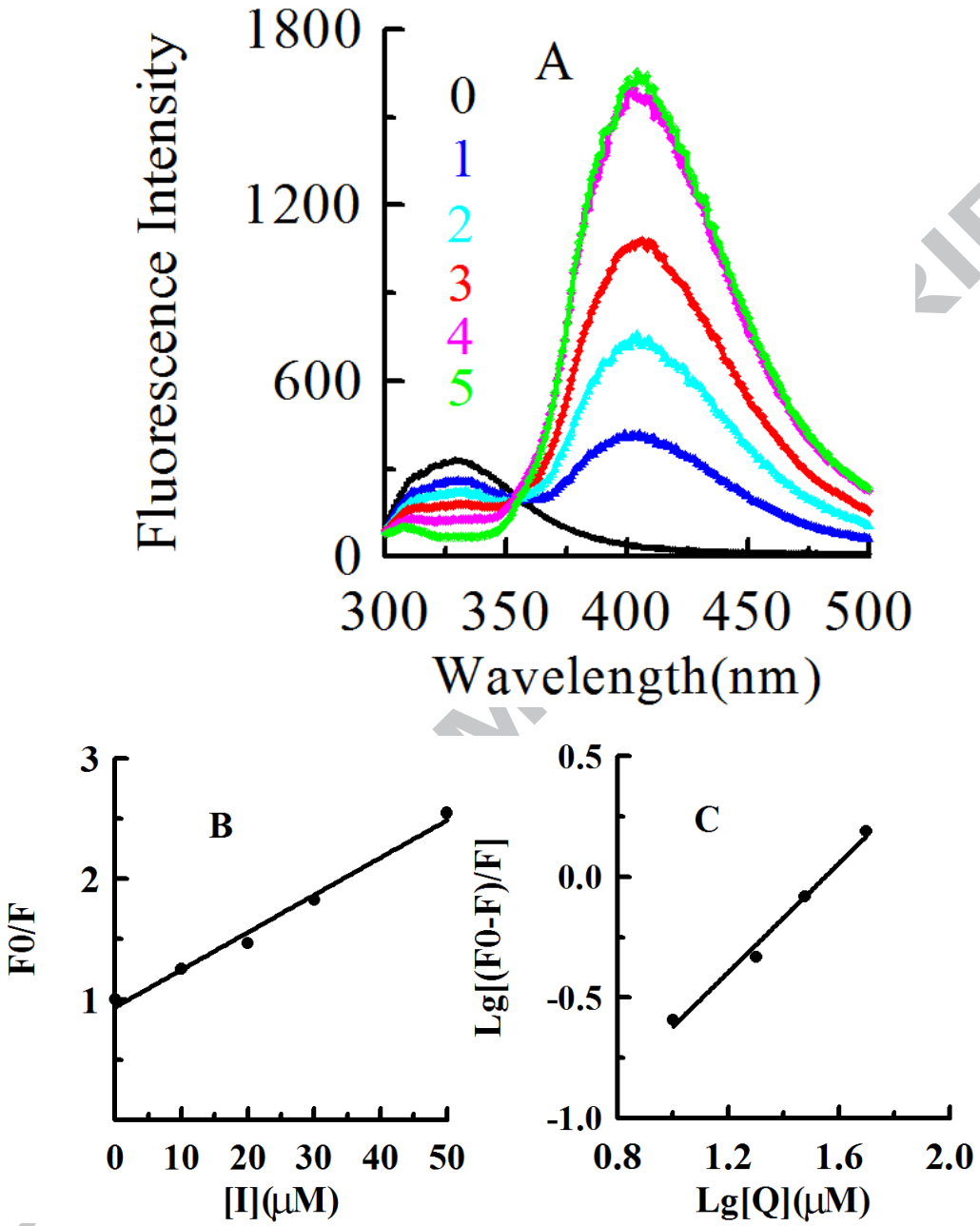


Figure 3 (A) Fluorescence emission spectra of α-glucosidase in the presence of CQ at different concentrations, the concentration of CQ for curves 0-4 were 0, 10, 20, 30, 50 μM, the curves 5 is fluorescence emission spectra of CQ at the concentration of 50 μM. (B) The stem-volmer plots for the fluorescence quenching of α-glucosidase at different concentrations of CQ. (C) Plot of lg [(F0 – F)/F] against lg [Q] for α-glucosidase various concentrations of CQ. F0 and F are the fluorescence intensities of α-glucosidase in the absence and presence of CQ.

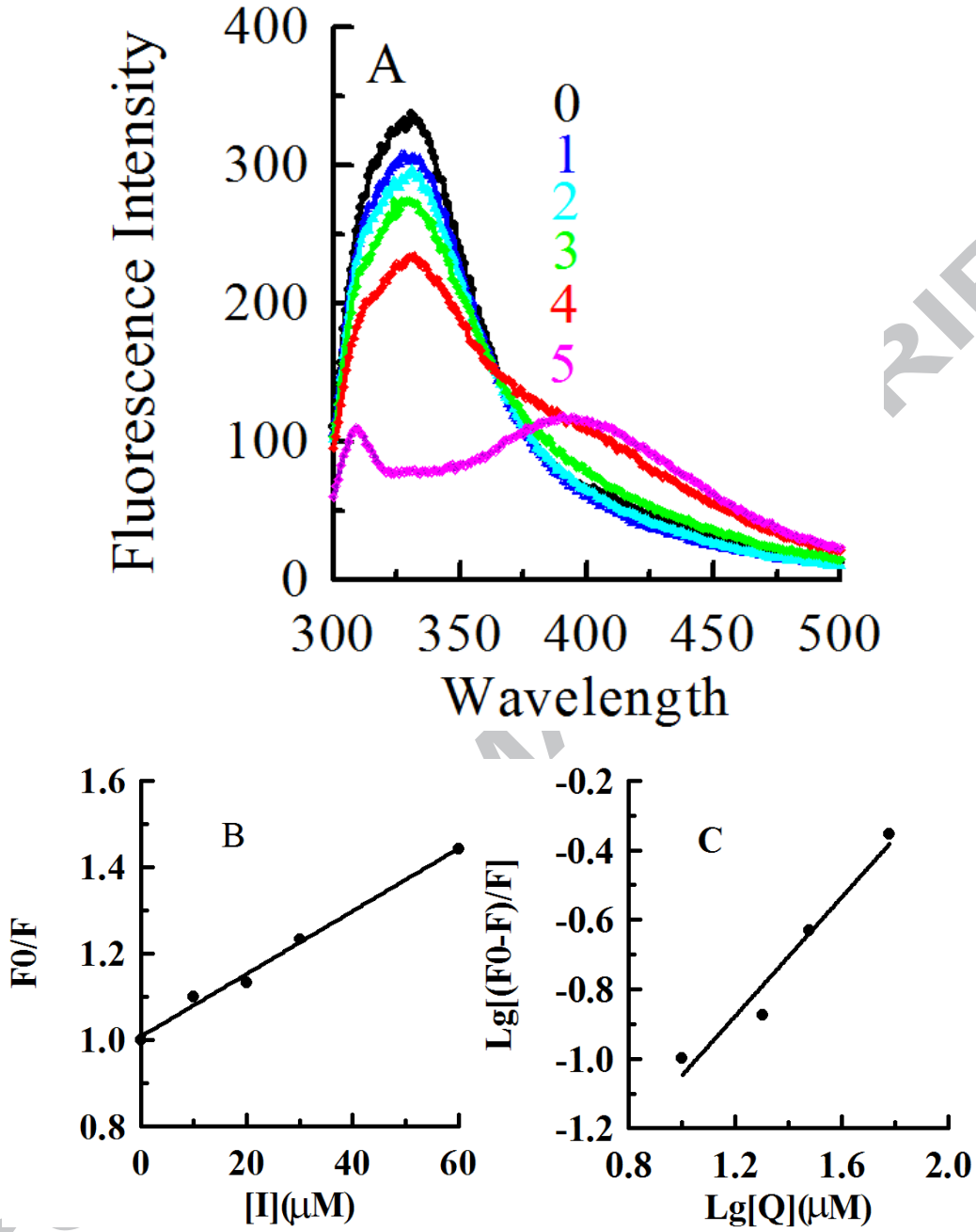


Figure 4 (A) Fluorescence emission spectra of α-glucosidase in the presence of BQ at different concentrations, the concentration of BQ for curves 0-4 were 0, 10, 20, 30, 60 μM, the curves 5 is fluorescence emission spectra of BQ at the concentration of 60 μM. (B) The stem-volmer plots for the fluorescence quenching of α-glucosidase at different concentrations of BQ. (C) Plot of lg [(F0 – F)/F] versus lg [Q] for α-glucosidase various concentrations of BQ. F0 and F are the fluorescence intensities of α-glucosidase in the absence and presence of BQ.

Fluorescence quenching analysis was executed to investigate the intrinsic interaction mechanisms of CQ and BQ on the α-glucosidase. As shown in Fig. 3A and Fig. 4A, α-glucosidase displayed a strong fluorescence peak at 330nm, which resulted from the tyrosine residues of α-glucosidase. While, CQ and BQ had a high emission peak at 404 and 390nm, respectively. Neverthless, as added different quinazolinone derivatives, the fluorescence intensity of α-glucosidase descended gradually with increasing the concentrations of the test compounds. The relative fluorescence intensity of enzyme was decreased to 39.3% when the concentration of CQ was extended to 50 μM, whereas the relative fluorescence intensity of enzyme was only reduced to 69.3% when the concentration of BQ was rose to 60 μM. These results showed that CQ was a better fluorescence quencher and easier to combine with the enzyme. In addition, with increasing the concentrations of CQ and BQ, the highest emission peak around 330nm no obvious red shift or blue shift, which proved that CQ and BQ did not affect the conformation of α-glucosidase. Intriguingly, there were accompanied increases in the fluorescence emission at 404 and 390nm with the accretion of CQ and BQ (Fig. 3A, 4A) respectively which caused by the fluorescence of quinazolinone derivatives.

For further identify the interaction mechanisms of quinazolinone derivatives on the α-glucosidase, the fluorescence quenching data were calculated from the plots of F_0/F versus [Q] (Fig. 3B, 4B) based on the previous studies.[41] For CQ and BQ, the values of K_q were determined to be 3.10×10^{12} L/mol·s and 7.26×10^{11} L/mol·s, respectively. The K_q values of BQ and CQ were much greater than the maximum scatter collision quenching constant 2.0×10^{10} L/mol·s.[43] Undoubtedly, BQ and CQ evoked quenching were considered as static quenching by formation of an inhibitor-α-glucosidase complex.

The binding constants (K) and number of binding sites (n) were obtained through the plots of lg [(F_0 − F)/F] versus lg [Q] (Fig. 3C, 4C). The results (Table 2) showed the binding constant (K) was CQ>BQ, which further confirmed that CQ was a better fluorescence quencher and more preferable to connect with the enzyme.[44] The number of binding sites (n) of BQ and CQ were close to 1.

Table 2. Quenching constants of quinazolinone derivatives on α-glucosidase

compound	T(□)	K_{sv} (L/mol)	K_q (L/mol.s)	K (L/mol)	n
CQ	25	3.10×10^{4}	3.10×10^{12}	1.78×10^{4}	1.13
BQ	25	7.26×10^{3}	7.26×10^{11}	1.25×10^{4}	0.85

3.5. Molecular docking

With the purpose of acquiring a better comprehension on the mutual effects between quinazolinone derivatives and α-glucosidase, molecular dockings were implemented using ActoDock tools. The conformations with lowest free energy was considered to be the most actively optimal formation. As shown in Fig. 5, hydrogen bonds were generated between CQ and amino residues: the oxygen atom on the quinolinone ring and the chlorine atom on the benzene ring could interact with B chain of residues Ala451 and Ser44, respectively. Besides, there existed an electrostatic interaction between CQ and A chain of residue Asp441. Furthermore, it was found that CQ inserted into the hydrophobic region of α-glucosidase interacting with A chain residues His348, Ala444 and B chain Arg450, Ala454. These results vividly displayed that the binding of CQ with α-glucosidase was driven by hydrogen bonds, electrostatic and hydrophobic interaction. For compound BQ (Fig. 6), it could be visible that a hydrophobic pocket constituting A chain of residues His348, Ala444 and B chain of residues Ala454 surrounded and grasped the ligands. The molecular

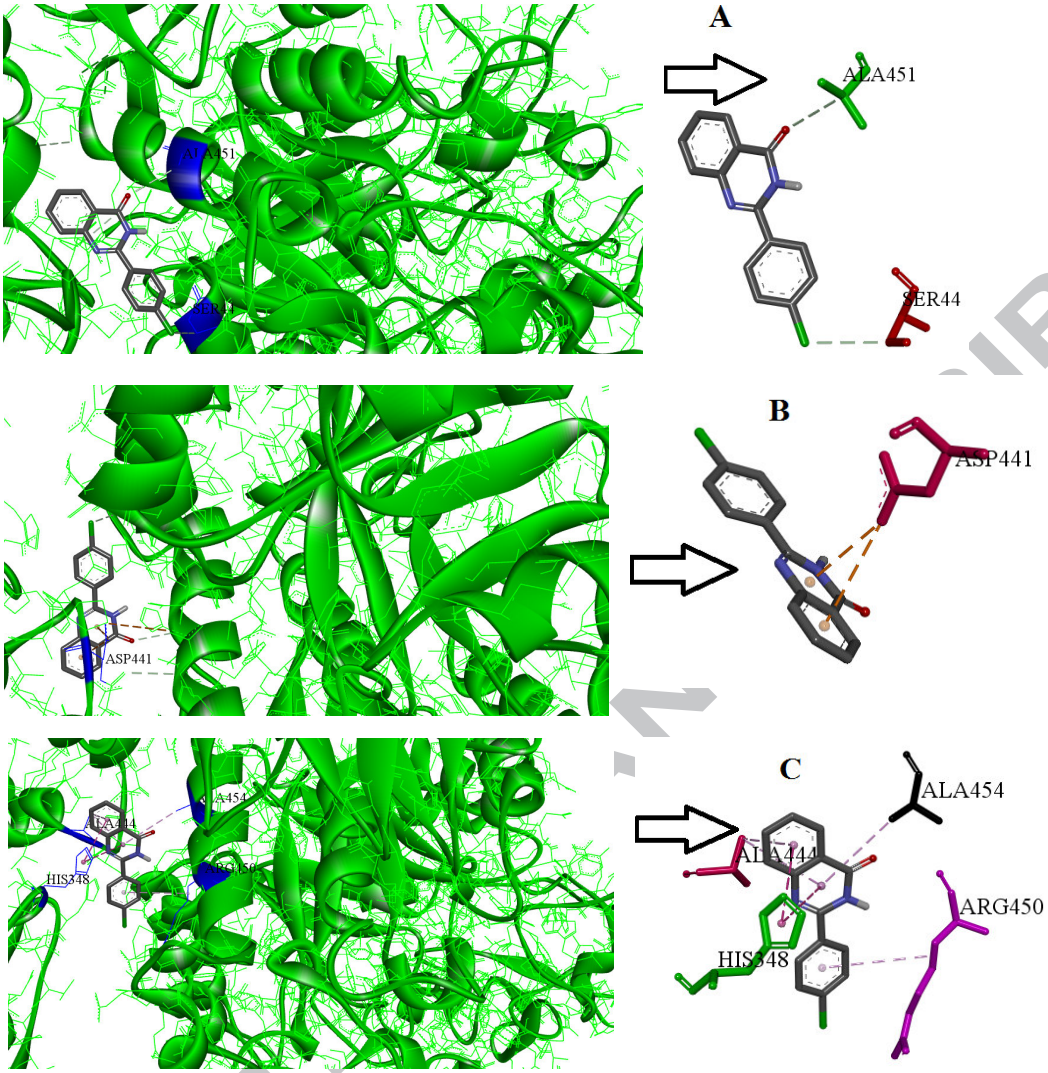


Figure 5 Molecular docking results of CQ with α-glucosidase. (A) Hydrogen bonds between CQ and amino residues. (B) Electrostatic interaction between CQ and residue Asp441. (C) Hydrophobic interaction of CQ with amino residues.

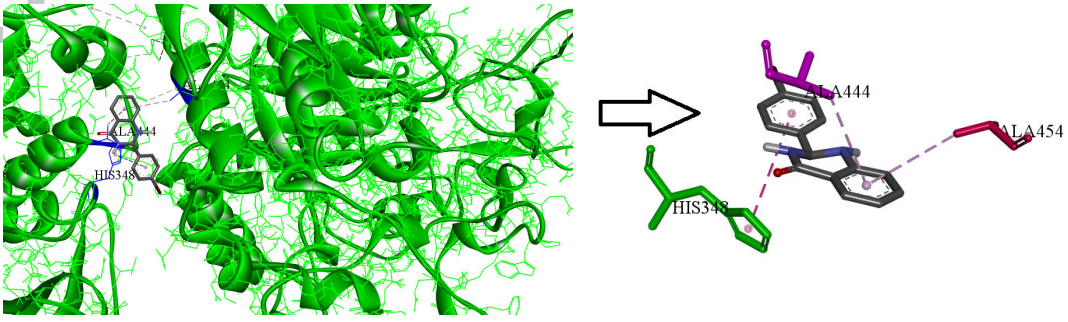


Figure 6 Hydrophobic interaction of BQ with α-glucosidase.

docking endorsed and visualized the consequence that the key driving force of the binding between BQ and the enzyme was hydrophobic interaction. The docking results clearly showed that CQ and BQ had different interaction with the enzyme. We speculated that there existed two main reasons lead to the difference between the chloro group and the bromo group: (1) the electronegativity of chlorine atom is higher than that of bromine atom, it allowed CQ easier to generate hydrogen bonds and electrostatic interaction with the amino acid residues; (2) the radius of chlorine atom is smaller than that of bromine atom, which makes CQ could be better embedded into the enzyme and interacted with the amino acid residues. Molecular docking analysis further evidenced that BQ was less active than CQ against α-glucosidase because of its weaker interaction with the enzyme.

4. Conclusion

In summary, compound CQ and BQ possessed excellent α-glucosidase inhibitory activities comparing with the positive control acarbose. Both of those two compounds reversibly inhibited the enzyme in a non-competitive manner. And they statically quenched the fluorescence spectra by formation of an inhibitor-α-glucosidase complex. Molecular docking studies revealed that BQ was less active than CQ against α-glucosidase because of its weaker interaction with the enzyme. Inhibition the activity of α-glucosidase was critical to control postprandial hyperglycemia. Hence, the quinazolinone derivatives identified in this work were potentially promising candidates for developing as novel anti-diabetic agents.

Acknowledgments

Financial support from National Natural Science Foundation of China (No. 21162012 and 31501414), the open project programs of CAS Key Laboratory of Molecular Recognition and Function, Chinese Academy of Sciences and key laboratory of Functional Small Organic Molecule, Ministry of Education, Jiangxi Normal University (NO.KLFS-KF-201408 and KLFS-KF-201419) is gratefully acknowledged.

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