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2,3-DIHYDRO-QUINAZOLIN-4(1H)-ONE AS A FLUORESCENT SENSOR FOR Hg^{2+} ION AND ITS DOCKING STUDIES IN CANCER TREATMENT

Abstract: The 2,3-dihydro-quinazolin-4(1H)-one was synthesised via the deployment of SBA-Pr-SO_3H and its application was explored as a highly selective fluorescent sensor for Hg^{2+} ion; fluorescence intensity was decreased selectively by Hg^{2+} ions. Furthermore, this compound also indicated for its superb anti-interference ability among other ions. It is important to mention that this compound could be employed to detect a very low amount of Hg^{2+} ions, which are highly toxic and general contaminants. The docking study shows that the molecule, 2,3-dihydro-quinazolin-4(1H)-one, is a good inhibitor for the 5ACC enzyme.

Keywords: 2,3-dihydro-quinazolin-4(1H)-one, fluorescent sensor, SBA-Pr-SO_3H, Hg^{2+} ion, sensors

Introduction

Quinazoline is an organic compound which was initially extracted from the Chinese plant aseru [1, 2] and was synthesised by Gabriel in 1903 for the first time [3]. 2,3-dihydro-quinazolin-4(1H)-one fused N-containing heterocycles are endowed with significant various biological, medicinal, and pharmacological activities. Their pharmacological and biological features comprise anti-tumour, antifungal, analgesic, diuretic, anti-allergic, painkiller, vasodilator, and diuretic actions [4-7]. Cancer leads to the changes in the normal cell to malignant tumours due to uncontrolled growth of abnormal cells and it is one of the most dangerous health issues in humans [8]. Finding safe, most effective drugs for the treatment of various forms of cancers remains a major challenge [9]. With the broad range of pharmaceutical activity as well as its importance, various preparation methods have been reported in recent years for quinazoline. The available protocols comprise: (1) $SnCl_2$ catalysed reductive cyclization of 2-nitrobenzamide with various ketones or aldehydes [10], (2) Lewis or Brønsted acid-catalysed anthranilamide

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reaction with ketones or aldehydes [11, 12] and (3) Lewis-, or Brønsted acid-catalysed ammonium salts and isatoic anhydride reaction with ketones or aldehydes [13-15].

Fluorescent sensors comprise fluorophore and a binding site, to provide a signal through the fluorophore in response to the incident at the binding sites [16]. The first fluorescent sensor was reported by Goplschroder in 1867 for the detection of aluminium ions (Al^{3+}) [17]. This led to the birth of analytical chemistry in view of the development of some fluorescent sensors to determine many other metal ions. New fluorescent sensors focus more on detecting metal ions and neutral species. Fluorescent sensors have been used in various fields such as biology, physiology, pharmacology, and environmental sciences [18].

Mercury is a dangerous and toxic metal, which appears indeed in the earth's crust. Low amounts of mercury ions can even increase the risk of different kinds of diseases, which can cause lots of health problems such as central nervous system defects, arrhythmia, and kidney damage [19-22]. In view of the increased attention to this element, efficient methods like atomic absorption spectroscopy, voltammetry, etc., have been deployed to detect the mercury ions in the environmental and biological analysis [23]. Among various kinds of available detection methods, fluorescent sensors are one of the best choices in terms of their sensitivity, selectivity, response speed, and easy operation [24, 25].

One of the computational modelling methods is molecular docking, which simplifies the prevision for the preferable binding orientation of a molecule (ligand) to another one (receptor), when two molecules collaborate to form an abiding complex. Knowing preferable orientation may be useful to forestall the strength of binding association between two molecules such as biologically related molecules like proteins, etc., which has an important role in signal transduction. In addition, the affiliate orientation of ligand and receptor may change the kind of signal produced. So, molecular docking helps to predict both strength and sort of signal produced [26, 27]. Especially, activation or inhabitation of an enzyme may be predicted by the interaction between small molecules (ligand) and protein objects. This kind of information may assist in the preparation of a raw substance for logical drug design [28-30].

In continuous our previous research [31-34], herein, the metal ion detection ability of the 2,3-dihydro-quinazolin-4(1H)-one, among different metal ions, and their molecular docking anticancer properties are reported.

Experimental section

The general synthesis of the 2,3-dihydro-quinazolin-4(1H)-one

The 2,3-dihydro-quinazolin-4(1H)-one **4** was provided by the reaction of isatoic anhydride **1** (1 mmol, 0.163 g), propynyloxy-benzaldehyde **2** (1 mmol), ammonium acetate **3** (1.2 mmol), and SBA-Pr-SO_3H (0.02 g) as catalyst under the solvent-free condition at 120 °C (Fig. 1) according to our previous work [35], and it was briefly explained in the supporting information.

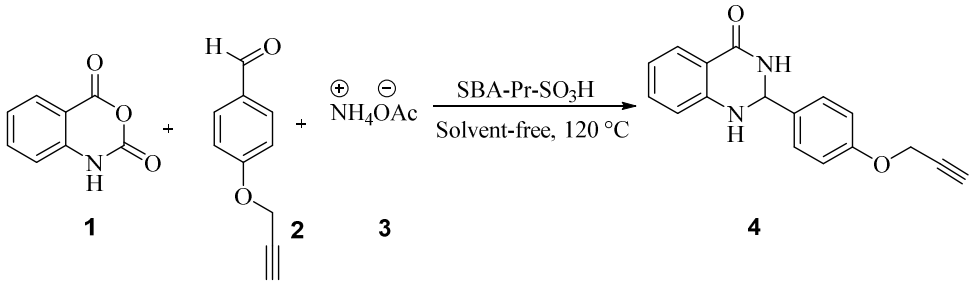

Fig. 1. The synthesis of 2,3-dihydro-quinazolin-4(1H)-one

Fluorescence studies

The PL studies showed that 2,3-dihydro-quinazolin-4(1H)-one possessed an absorption peak at 250 nm. Its fluorescence response was investigated in CH_3CN (2.5 mL, $2.78 \cdot 10^{-4}$ g L^{-1}) by adding different metal cations (200 µL of M^{n+}, $1 \cdot 10^{-2}$ M) including Hg^{2+}, Na^{+}, Mg^{2+}, Al^{3+}, Mn^{2+}, Cd^{2+}, Fe^{2+}, Cu^{2+}, Cd^{2+}, Ca^{2+}, Ag^{+}, K^{+}, Ni^{2+}, Cr^{3+}, Zn^{2+}, Pb^{2+} and Co^{2+} ions. Its emission spectrum was registered at 410 nm after excitation at 250 nm (Fig. 2). Its fluorescence intensity was reduced by adding the Hg^{2+} ions among other ions. A schematic model of the binding method of Hg^{2+} ion to this compound was shown in Figure 3.

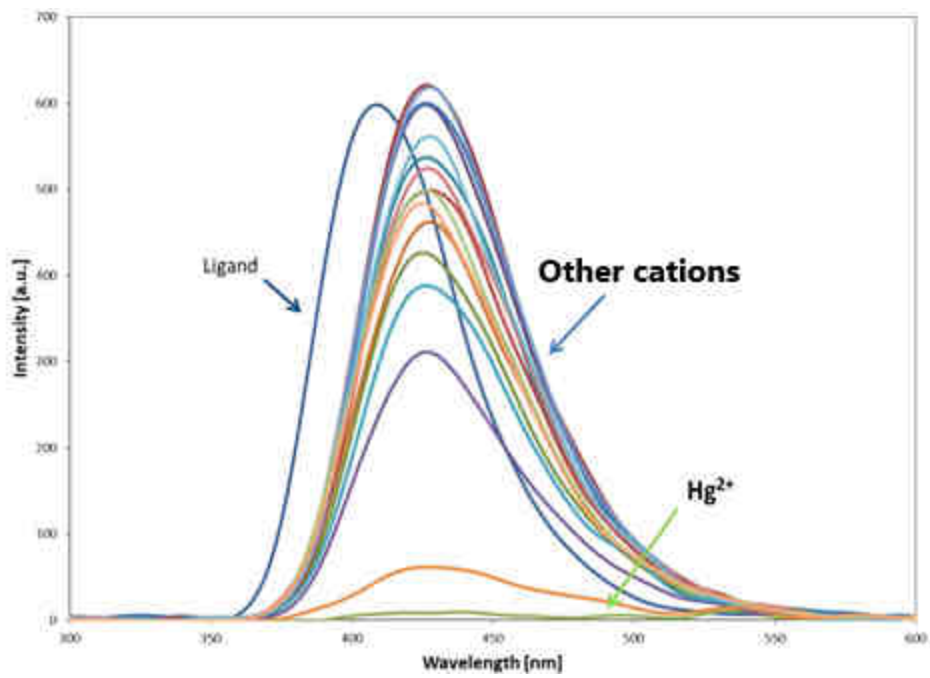

Fig. 2. Fluorescence emission spectrum of the sample dissolved in acetonitrile (10^{-4} M) in the presence of the various metal cations containing Hg^{2+}, Na^{+}, Mg^{2+}, Al^{3+}, Mn^{2+}, Cd^{2+}, Fe^{2+}, Cu^{2+}, Cd^{2+}, Ca^{2+}, Ag^{+}, K^{+}, Ni^{2+}, Cr^{3+}, Zn^{2+}, Pb^{2+} and Co^{2+} ions (200 µL of M^{n+}, $1 \cdot 10^{-2}$ M) (λ_{ex} = 250 nm, λ_{em} = 410 nm)

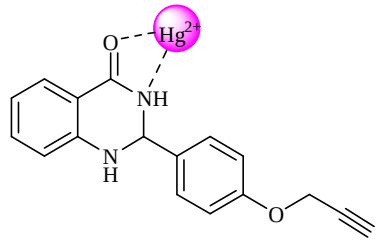

Fig. 3. The proposed sensing mechanism for the chemosensor in the presence of Hg^{2+} ions

Competition study

To further evaluate the 2,3-dihydro-quinazolin-4(1H)-one selectivity to Hg^{2+} ion, a competitive test was performed. The fluorescence spectrum of the sample was recorded by a mixture of Hg^{2+} ions (200 µL · 10^{-2} M) and various metal cations (200 µL of M^{n+} · 10^{-2} M) with excitation at 250 nm. Adding Hg^{2+} ions reduced the fluorescence emission intensity of the corresponding sensor at 420 nm, and other metal ions did not interfere with the mercury ions. Thus, this test indicated that the sample could be applied as a fluorescent sensor for Hg^{2+} ions (Fig. 4).

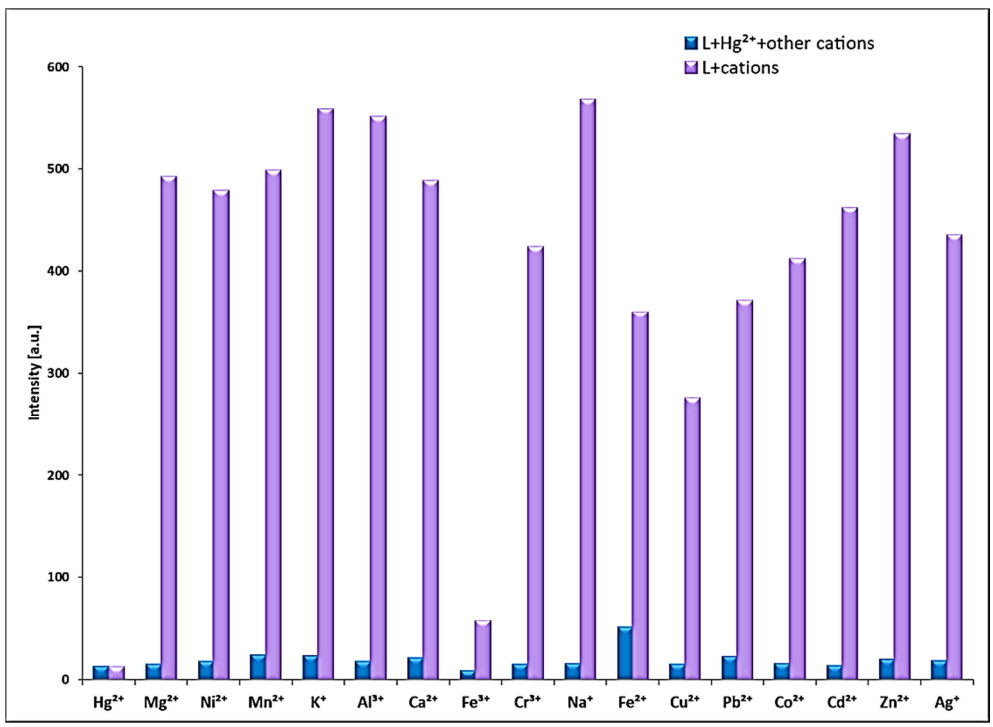

Fig. 4. Fluorescence emission spectrum of the sample dissolved in acetonitrile (10^{-4} M) in the presence of mixture Hg^{2+} ions (200 µL · 10^{-2} M) and various metal cations containing Na^{+}, Mg^{2+}, Al^{3+}, Mn^{2+}, Cd^{2+}, Fe^{2+}, Cu^{2+}, Cd^{2+}, Ca^{2+}, Ag^{+}, K^{+}, Ni^{2+}, Cr^{3+}, Zn^{2+}, Pb^{2+} and Co^{2+} ions (200 µL of M^{n+}, 1 · 10^{-2} M) (λ_{ex} = 250 nm, λ_{em} = 410 nm)

Titration study

To investigate Hg^{2+} concentration and fluorescence emission intensity of this sensor, a titration test was performed at various concentrations of Hg^{2+} ions. As indicated in Figure 5, by adding the concentration of Hg^{2+}, the fluorescence emission intensity gradually decreased. In the next step, according to the titration data, the fluorescence intensity curve against the concentration of Hg^{2+} ion was plotted, which illustrates a suitable linear relation between the fluorescence emission intensity and Hg^{2+} ions with a regression coefficient of 0.9716. The detection limit of this sensor to Hg^{2+} ion was calculated using the equation $DL = 3S_d/m$ and acquired the amount of $3.915 \cdot 10^{-6}$ M (Fig. 5).

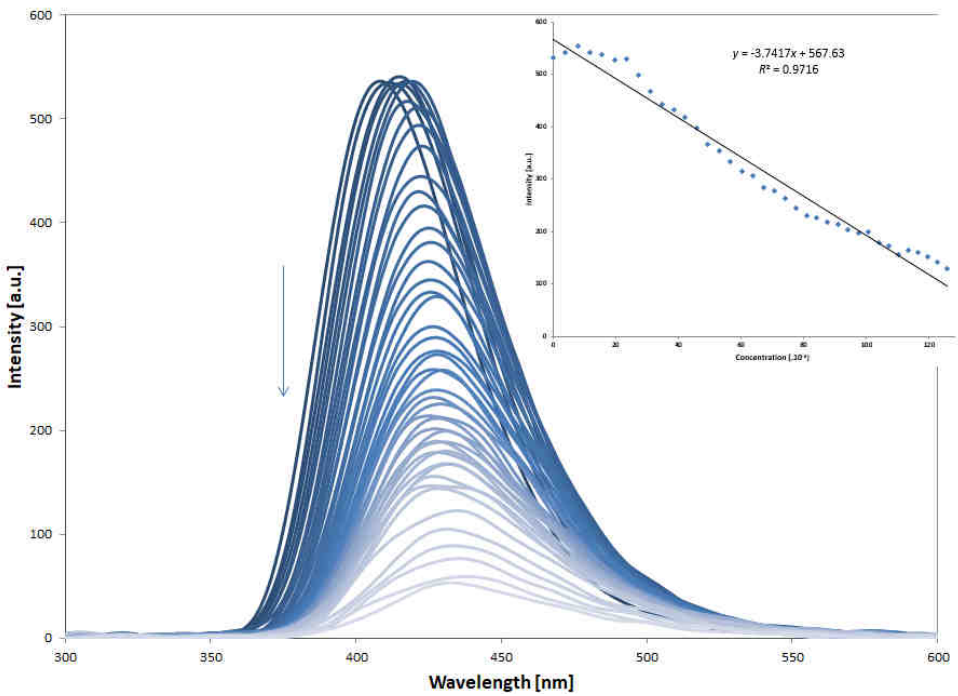

Fig. 5. Fluorescence emission of the sample dissolved in acetonitrile (10^{-4} M) using different concentrations of Hg^{2+} ion from 0 to $125.9 \cdot 10^{-6}$ M (λ_{ex} = 250 nm, λ_{em} = 410 nm)

Docking study for 2,3-dihydro-quinazolin-4(1H)-one

The molecular docking for the 2,3-DHQ was performed against the malignant enzyme, as per our previous report, the scaffold displayed anticancer activity [36, 37]. Based on the previous report, we have performed molecular docking for the 2,3-DHQ 2-(4-(prop-2-yn-1-yloxy)phenyl)-2,3-dihydro-quinazolin-4(1H)-one **B** inhibitor with receptor 5ACC enzyme. The molecular docking has been carried out with Autodock software [32] as described by Dallakyan et al. in 2015. The 5ACC protein is responsible for causing cancer in the mammary gland and can increase tumor growth. The 3D crystal structure was downloaded from the protein data bank [38] in the PDB format. The enzyme 5ACC is a selective estrogen receptor having inner ligand (E)-3-(3,5-difluoro-4-((1R,3R)-2-

(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-B]indol-1-Y1) phenyl)acrylic acid (Azd9496). The active cavity of the protein was identified with the help of (Castro) program. The docking was performed with ligand 2,3-DHQ, the inhibitor is accommodated into the active site of the protein 5ACC with binding energy protein having –9.1 kcal/mol. The inhibitor 2,3-DHQ, displays hydrogen binding with the LEU-346 residues, and the ligand produces van der Waals of interaction with amino acid residues like ARG-394, PHE-404, GLU-353, LEU-349, LEU-387, ASP-351, TRP-383, THR-24, LEU-384, MET-388, and ARG-394 amino acids (Fig. 6). After the modification of the 2-(4-(prop-2-yn-1-yloxy)phenyl)-2,3-dihydro-quinazolin-4(1H)-one ligand could be the best candidate for the finding potential anticancer agent.

a) b)

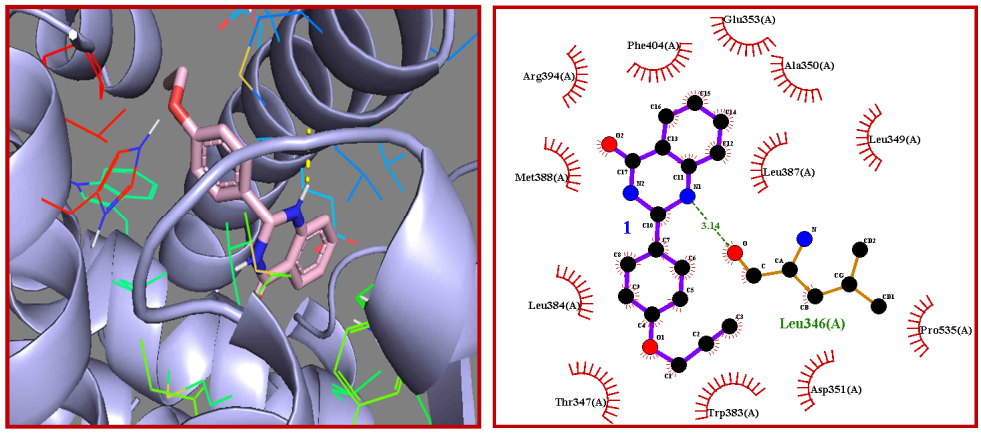

Fig. 6. a) Docking pose of **A** ligand into the binding pocket of PDB: **5ACC** protein, b) 2D interaction of **B** molecule showing interaction with essential amino acid residues

Conclusion

In this work, ligand as chemosensor is synthesised by the reaction of isatoic anhydride, propynyloxy-benzaldehyde, and ammonium acetate by deployment of SBA-Pr-SO_3H. Its fluorescence intensity is significantly quenched in the presence of Hg^{2+} ions, which is a highly toxic and common contaminant. Therefore, this compound functions as an efficient chemosensor for Hg^{2+}. The molecular bonding of inhibitor 2-(4-(prop-2-yn-1-yloxy)phenyl)-2,3-dihydro-quinazolin-4(1H)-one displays excellent binding interaction with the protein PDB: 5ACC.

Nomenclature

PL - Photoluminescence
DL - Detection limit
S_d - The standard deviation of the response
m - The slope of calibration curve
2,3-DHQ - 2,3-dihydro-quinazolin-4(1H)-one
PDB - Protein Data Bank

5ACC-pdb protein - A Novel Oral Selective Estrogen Receptor Down-regulator, AZD9496, drives Tumor Growth Inhibition in Estrogen Receptor positive and ESR1 Mutant Models
LEU-346 - Leucine 346
ARG-394 - Arginine-394
PHE-404 - Phenylalanine-404
GLU-353 - Glutamic acid-353
LEU-349 - Leucine-349
LEU-387 - Leucine-387
ASP-351 - Aspartic acid-351
TRP-383 - Tryptophan-383
THR-24 - Threonine-24
LEU-384 - Leucine-384
MET-388 - Methionine-388
ARG-394 - Arginine-394

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